MOH/P/PAK/391.18(GU)

CLINICAL PRACTICE GUIDELINES

# Management of Hypertension

## 5TH EDITION (2018)


Malaysian Society of Hypertension

Ministry of Health Malaysia

Academy of Medicine of Malaysia

## STATEMENT OF INTENT

This guideline was developed to be a guide for best clinical practice in the management of hypertension. All efforts were made to ensure references quoted were the most current at the time of printing. Specific attempts were made to use local data and publications to ensure local relevance. Adherence to this guideline may not necessarily lead to the best clinical outcome in individual patient care. Every health care provider is responsible for the care of his/her unique patient based on the clinical presentation and treatment options available locally. However, adherence to this guideline is strongly recommended as a starting point in managing patients as it constitute the best available evidence at the time of writing.

## REVIEW OF THE GUIDELINES

This guideline was issued in 2018 and will be reviewed in 2023 or earlier if important new evidence becomes available. This is an update to the Clinical Practice Guideline on Management of Hypertension – 4th Edition (published 2013) and supersedes the previous. Electronic version will be made available on the following websites:

www.moh.gov.my
www.acadmed.org.my
www.msh.org.my

## DISCLOSURE STATEMENT

The panel members had completed disclosure forms. None held shares in pharmaceutical firms or acted as consultants to such firms. Some may have been engaged as speakers in conferences or Continuing Professional Development activities mainly organised by the Malaysian Medical Association, the Malaysian Society of Hypertension, National Heart Association of Malaysia or similar professional non-governmental associations (NGOs). These events may or may not have received financial assistance from pharmaceutical companies as part of an educational grants (details are available upon request from the CPG Secretariat).

## SOURCE OF FUNDING

The development of the CPG on Management of Hypertension (5th Edition) was supported via unconditional educational grant from Servier Malaysia Sdn. Bhd. The funding body was not involved in and has no influence on the development of the guidelines. An independent third party was engaged for all secretarial task and was appointed by and reported directly to the Malaysian Society of Hypertension.

# Key Messages

1. Hypertension is defined as persistent elevation of systolic BP of 140mmHg or greater and/or diastolic BP of 90 mmHg or greater.

2. The prevalence of hypertension in Malaysians aged 18 years and above was 35.3% in 2015, a slight increase from 33.6% in 2011.

3. Hypertension is a silent disease; unfortunately, in 2015, for every two diagnosed patients in Malaysia there are 3 undiagnosed patients. This has not changed since 2011. Blood pressure should be measured at every chance encounter.

4. Untreated or sub-optimally controlled hypertension leads to increased cardiovascular, cerebrovascular and renal morbidity/ mortality and overall mortality.

5. A systolic BP of 120 to 139 mmHg and/or diastolic BP of 85 to 89 mmHg is defined as 'at risk blood pressure' and should be treated in certain high risk groups.

6. Healthy living should be recommended for all individuals with hypertension and 'at risk blood pressure'.

7. Decisions on pharmacological treatment should be based on global vascular risks and not on the level of blood pressure per se.

8. In patients with newly diagnosed uncomplicated hypertension and no compelling indications, choice of first line monotherapy includes ACEIs, ARBs, CCBs, diuretics and ß-blockers.

9. Only 37.4% of Malaysian patients achieved blood pressure control (<140/90 mmHg) while on treatment. Although this is an improvement from 2011 (34.7%) every effort should be made to achieve target blood pressure in all patients. Target blood pressure depends on specific patient groups.

10. Combination therapy is often required to achieve target and may be instituted early in patients with stage II hypertension and in high risk stage I hypertension.

11. A patients whose BP is not controlled on three or more drugs (including a diuretic) is by definition having resistant hypertension.

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# Foreword

In the Name of Allah, the Most Beneficent, the Most Merciful.

In 2015 the Ministry of Health released data from the National Health and Mortality Survey which focused on Non Communicable Diseases. Diseases of the heart and circulatory system (Cardiovascular diseases or CVD) still dominates the national health landscape being the number 1 cause of morbidity and mortality for the last few decades and is projected to do so for years to come. Of all the risk factors contributing to CVD, hypertension confer the greatest risk for both male and female based on the latest national burden of disease in 2008. It is thus pertinent that all health care providers directly or indirectly involved with CVD know what is latest in the management of hypertension.

I will like to record my utmost appreciation to all the members of the Working Group on Hypertension for their tireless effort in coming up with this latest edition of the Hypertension Clinical Practice Guideline. This is the fifth in the series since it was first launched in 1998. This reflects the rapid evolution of knowledge in hypertension driven by major outcome trials for which there were a few since the last edition 5 years ago. There are also more Malaysian studies quoted which is a testimony of the growing research interest in the topic nationally. I am happy to report that in some of the landmark multicentre clinical trials quoted, Malaysian researchers were actively involved. A special thanks to the Health Technology Assessment Unit of the Ministry of Health Malaysia for ensuring that the development of this CPG conforms to the high standards it had laid down.

Although the NHMS 2015 showed some positive developments in important key indicators on hypertension, there is still a lot of scope for improvement. It is hoped that this latest edition of the Hypertension CPG will continue to play an important role in controlling this major CVD risk factor. It is the hope of the Working Group that the release of this new edition will be followed by concerted effort by various stakeholders to implement the recommendations made. By so doing, we will have contributed in a significant way to combat the scourge of CVD particularly pre mature CVD. If that happens, this CPG will have served its purpose, God Willing.

Yours Sincerely,

**Abdul Rashid Abdul Rahman**
Chairman, Working Group on Hypertension CPG 2018

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# Rationale and Process of Guidelines Development

## RATIONALE

The Clinical Practice Guideline on the Management of Hypertension was developed to provide a clear and concise approach to all health care providers on the current concepts in the management of hypertension. Since hypertension is managed by various levels of health care providers in Malaysia, attempts were made to ensure the different stakeholders will benefit from this CPG. This is reflected by the representation of the committee members who developed the guideline. There were four previous guidelines on hypertension; in 1998, 2002, 2008 and 2013.This edition is the fifth in the series and was deemed necessary due to new evidence which has emerged since the last edition. Prior to the publication of this edition, the National Health and Morbidity Survey 2015 was published. The results of the survey showed that the prevalence of hypertension has increased while the awareness has decreased compared to a similar survey done in 2011. However the rate of blood pressure control in the hypertensive population has increased by 10% (now 37.4% of treated patients are controlled). This rate of blood pressure control is still poor when one compares with a large nation like Canada where the control rate was more than 80%. This may reflect the fact that clinicians are still not clear of the target blood pressure to achieve in their patients. It is hoped that this CPG will contribute towards achieving the desired targets.

## GUIDELINE DEVELOPMENT PROCESS

The members of the Development Group (DG) for this Clinical Practice Guideline (CPG) were from the Ministry of Health (MOH), Ministry of Higher Education (MOHE) and private healthcare providers. The membership of the DG was multidisciplinary and most specialties are represented by at least 2 experts. These are Cardiovascular Medicine, Nephrology, Geriatrics, Obstetrics and Gynaecology, Family Medicine and Clinical Pharmacology/Clinical Pharmacy. There are also specialties which are represented by 1 expert. These include Endocrinology, Neurology and Public Health. Where there are at least 2 members, 1 act as the principal author and the other reviewer of the initial draft. Each draft will then be reviewed collectively in every DG meeting.

The CPG update was done based on the CPG Management of Hypertension 4th edition of 2013. In the update, systematic review methodology was used and the scope covered include epidemiology and public health, definition and classification, blood pressure management, diagnostic criteria, investigations, global cardiovascular risk evaluation, general principle of management, non pharmacological and pharmacological management, management of patient sub groups and approach to resistant and refractory hypertension. Emerging areas in hypertension are also covered including Health Economics, Device Based treatment and scope for future research. A literature

search was carried out using the following electronic databases: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network. The search was done on Published English literature focusing mainly but not exclusively on Clinical Trials. Important observation studies, where relevant, were also looked at. Unlike some CPGs, the search was not limited to literature published in the last fifteen years. This is because hypertension management has be powered and driven by good evidence generated over the last thirty years. Some seminal and practice changing trials were conducted a few decades ago and the result so conclusive that repeating the trials will be an act of futility. In addition, the reference lists of all recent Hypertension Guidelines i.e that written over the last 5 years only were retrieved and searched to further identify relevant studies. All searches were conducted from 24 May 2017 to 5 January 2018. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published after January 2018 to be included. Future CPG updates will consider evidence published after this cut-off date.

References were also made to the most recent CPG on Hypertension from the American College of Cardiology / American Heart Association released in full in December 2017. This CPG was evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 23 clinical questions were developed under 13 different sections. Members of the DG were assigned individual questions within these sections (refer to Appendix 5 for Clinical Questions). The DG members met 9 times throughout the development of these Guideline. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon. Where evidence was insufficient, the recommendations were made by consensus of the DG. This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials in particular trials where Malaysia participated. Where evidence are lacking or non existent, local practices are taken into consideration.

The literature used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was done using the principles of Scottish Intercollegiate Guidelines Network (Version 1.0 updated July 2017). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers both nationally and internationally. It was also posted on the Malaysian Society of Hypertension (MSH) official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development methodology by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/index.php/pages/view/117).

# Objectives, Questions and Targets

## OBJECTIVES

This guideline is intended to provide education and awareness on the proper ways to:

1. diagnose hypertension
2. assess and investigate a patient with hypertension

This guideline is intended to provide evidence on the:

1. optimal management of a patient with hypertension
2. latest therapeutics on subgroups of hypertensive patients

## EXCLUSION

This guideline, however, does not cover:

1. strategies for hypertension screening
2. strategies to reduce population blood pressure

## CLINICAL QUESTIONS

The two major clinical questions to be addressed in this guideline include:

1. What are the current best practices in the management of a patient with hypertension?
2. How can hypertension management be done in tandem with the overall strategy to manage global vascular risk of a patient?

For further detail, please refer Appendix 5.

## TARGET POPULATION

This guideline is to be applied to adults (including the elderly and pregnant women) and children with hypertension. It is also applicable to hypertensive patients with various concomitant clinical conditions.

## TARGET GROUP

This guideline is developed for all levels of health care providers involved in the management of hypertension in adults, elderly, pregnant women and children.

## CLINICAL INDICATORS FOR QUALITY MANAGEMENT

**Treatment setting:**

Primary care / Secondary care

**Name of indicator:**

1. Rate of anti-hypertensive prescription for newly diagnosed cases of hypertension
2. Rate of blood pressure control among patients who are treated with antihypertensive drugs

**Definition of control:**

- <140/90 mmHg for all
- <140/80 mmHg for patients with diabetes
- <130/80 mmHg for patients with ischaemic heart disease/ cerebrovascular disease/renal impairment

**Numerator:**

1. Number of newly diagnosed cases of hypertension prescribed anti-hypertensive drugs
2. Number of patients on treatment who achieved blood pressure control

**Denominator:**

1. Total number of newly diagnosed cases of hypertension
2. Total number of patients who are diagnosed and on anti-hypertensive drug treatment

*Rate of treatment = (Numerator/Denominator) x 100%*

*Rate of blood pressure control = (Numerator/Denominator) x 100%*

## LEVEL OF EVIDENCE

| LEVEL | STUDY DESIGN |
|---|---|
| I | Evidence from at least one properly randomised controlled trial |
| II-1 | Evidence obtained from well-designed controlled trials without randomisation |
| II-2 | Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group |
| II-3 | Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence |
| III | Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees |

Source: US/Canada Preventive Services Task Force

## GRADES OF RECOMMENDATION

| | |
|---|---|
| A | At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population |
| B | Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT |
| C | Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality |

Source: Modified from the Scottish Intercollegiate Guidelines Network (SIGN)

Note: The grades of recommendation relate to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

# Summary of Recommendations

| ISSUES | RECOMMENDATIONS | GRADE |
|---|---|---|
| **Measurement of Blood Pressure** | Measure BP at every opportunity as a high number of Malaysians are undiagnosed. | B |
| | Check BP for every adult above age 18 years at least once as part of their annual health screening, and more frequently for those who are at risk (family history, obese and those at-risk of high blood pressure). | B |
| | Use electronic blood pressure measurement devices instead of mercury sphygmomanometers despite the latter being a gold standard for non-invasive measurement. **(NEW)** | C |
| | Before measuring BP, check if patients have stopped smoking, eating, drinking caffeinated drinks, have not been exercising for at least 30 minutes, be seated for at least 1 min in a quiet room, back & arm supported, (e.g. resting on the table), be seated with legs uncrossed, stopped talking and is relaxed. | C |
| | Check and use the correct bladder cuff size with placement at heart level. | C |
| | Encourage patient to do home BP monitoring (HBPM) which helps to empower them and may improve medication adherence. | C |
| | Use ambulatory BP monitoring (ABPM) only in selected clinical situations (e.g. to confirm isolated office, masked and labile hypertension). | C |
| **Diagnosis and Initial Assessment** | Assess initial BP measurement results and global CV risk before deciding on the appropriate follow-up required. **(NEW)** | C |
| **Non-Pharmacological Management** | **BMI or Weight**<br>Achieve a weight loss of as little as 1kg from baseline to reduce blood pressure by 1 mmHg SBP. **(NEW)** | A |
| | **Salt Intake**<br>Reduce salt intake to <2g of sodium or <5g of salt a day (equivalent to 1 teaspoonful of salt). **(NEW)** | A |

| ISSUES | RECOMMENDATIONS | GRADE |
|---|---|---|
| **Non-Pharmacological Management** (Continued) | **Alcohol**<br>Refrain from alcohol intake. Advise patient who insists to continue drinking to consume ≤ two drinks per day. | A |
| | **Exercise**<br>Advise patients to perform physical activity (e.g. moderate intensity aerobic exercise of at least 150 minutes per week). | A |
| | **Diet**<br>Encourage diet rich in fruits, vegetables and dairy products with reduced saturated and total fat. | A |
| | **Smoking**<br>Stop smoking to reduce overall cardiovascular risk. | C |
| | **Relaxation**<br>Encourage patient to manage stress although evidence on relaxation interventions have not been convincing. | C |
| **Pharmacological Management** | Treat most patients with pharmacological agent life-long. | C |
| | Choose mono-therapy in patients with stage 1 hypertension and with no compelling indication from one of the 5 classes of drug (ACEIs, ARBs, CCBs, Diuretics or ß-blockers) based on patient's individual clinical profile. **(NEW)** | C |
| | Choose combination therapy in patients with medium/high/very high risk stage 1 hypertension and stage 2 hypertension. **(NEW)** | A |
| | Treat BP to SBP <140 mmHg and DBP <90 mmHg for most hypertensive patients. | A |
| | Treat SBP to <130 mmHg and DBP <80 mmHg for high/very high risk patients. | A |
| | Use combination therapy (free or single pill) for most patients to achieve BP control. | A |
| | Arrange periodic scheduled visits to assess global CV risk, emerging new risk factors and organ damage/complications. | C |
| | Co-manage patients whose BP are controlled with primary care facilities (Klinik Kesihatan or private General Practice). | C |

| ISSUES | RECOMMENDATIONS | GRADE |
|---|---|---|
| **Management of Severe Hypertension** | **Hypertensive Urgencies** | |
| | Do not reduce BP rapidly (within minutes to hours) in hypertensive urgencies as it may precipitate ischaemic events. | C |
| | For patients whose BP responded with adequate rest (after 2 hours), discharge them with Hypertensive Urgency Discharge Plan. **(NEW)** | B |
| | For patients whose BP do not respond to adequate rest, start with combination oral pharmacotherapy targeting a BP reduction of 25% within 24 hours. | C |
| | **Hypertensive Emergencies** | |
| | Reduce BP by 10%-25% within minutes to hours but not lower than 160/100 mmHg. This is best achieved with parenteral drugs. **(NEW)** | B |
| | Reduce SBP to less than 140 mmHg during the first hour for patients with severe preeclampsia or eclampsia, and pheochromocytoma crisis. Reduce to less than 120 mmHg for patients with aortic dissection. | C |
| | Reduce BP by no more than 25% within the first hour; then, if stable, to 160/100 mmHg within the next 2 to 6 hours; and then cautiously to normal during the following 24 to 48 hours in all other situations. | C |
| **Hypertension and Diabetes Mellitus** | Initiate drug treatment if BP is consistently >140/80 mmHg. | A |
| | Use ACEIs in diabetes without proteinuria. Use ARB for ACEI intolerant patients. | A |
| | Use ACEIs or ARBs in patients with diabetes and proteinuria. | A |
| | Consider CCBs, diuretics or ß-blockers if RAS blockers cannot be used. | C |
| | Aim for BP in the diabetic to be <140/80 mmHg. | A |
| | Consider to lower BP <130/80 mmHg in younger patients. | C |
| **Hypertension and Renal Diseases** | Patients with proteinuria of <1 g/24 hours, lower BP to <140/90 mmHg. **(NEW)** | A |
| | In patients with proteinuria of >1g/24 hours, lower BP to <130/80 mmHg. **(NEW)** | A |

| ISSUES | RECOMMENDATIONS | GRADE |
|---|---|---|
| **Hypertension and Renal Diseases** (Continued) | In patient >50 years, GFR >20 ml/min/1.73m$^2$ and proteinuria <1g/day lower SBP <120 mmHg using Automated Self-measured Office BP to reduce cardiovascular event. **(NEW)** | B |
| | Choose RAS blockers as initial antihypertensive therapy for patients with micro- or macroalbuminuria. | A |
| | Add non-dihydropyridine CCBs if BP goal is still not achieved and there is persistent proteinuria. | A |
| | Consider concurrent diuretic therapy and dietary salt restriction as salt and water retention are important determinants of hypertension in CKD. | B |
| | Avoid dual RAS blockade in patients with CKD. **(NEW)** | A |
| **Hypertension and Heart Diseases** | Use ß-blockers, ACEIs or ARBs in post myocardial infarction patients to reduce recurrent myocardial infarction and death. | A |
| | Initiate ß-blockers, ACEIs and Aldosterone antagonists in patients with systolic heart failure (HFrEF) to reduce morbidity and mortality. | A |
| | Use ARBs or ACEIs and aldosterone antagonist in heart failure patients with preserved ejection fraction (HFpEF) to reduce morbidity including hospitalisation. | A |
| | Use RAS blockers in patients >75 years old with AF to reduce mortality. **(NEW)** | B |
| | Use any antihypertensive except ß-blockers as first choice in patients with PAD. | C |
| | Give ACEI to patients with PAD to prevent vascular events. **(NEW)** | B |
| | Consider cilostazol in the elderly patients with symptomatic CAD and concurrent PAD. **(NEW)** | B |
| | Use ARBs as treatment of choice in hypertensive patients with LVH on ECG. | A |
| | Treat blood pressure to <140 / <90 mmHg in patients with concurrent IHD, peripheral arterial disease (PAD), PAD with/ without AF. **(NEW)** | B |
| | Treat blood pressure to <130/80 mmHg in patients with LVH. **(NEW)** | B |
| | Prescribe antiplatelet agent unless contraindicated. | A |

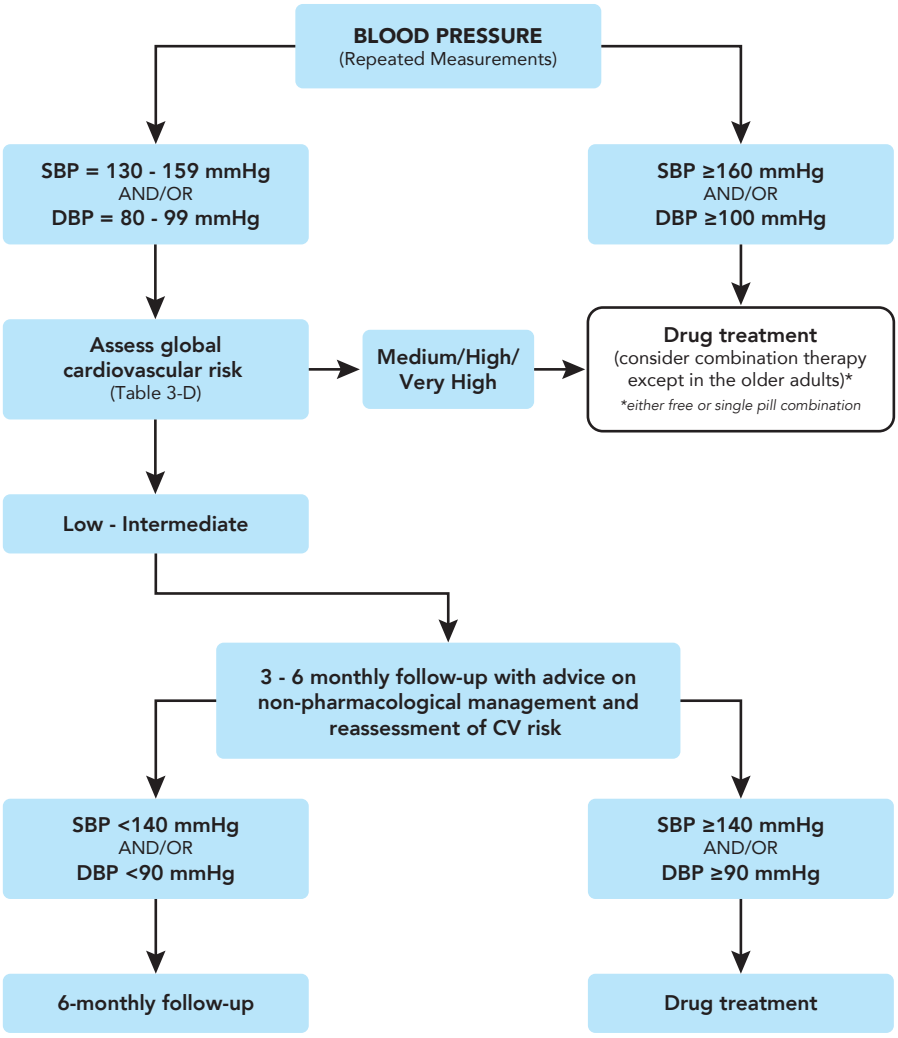
| ISSUES | RECOMMENDATIONS | GRADE |
|---|---|---|
| **Hypertension and Stroke** | Treat BP to prevent both primary and secondary stroke. | A |
| | Treat BP to <140/90 mmHg for primary prevention. | B |
| | Lower BP to be <140/90 mmHg in both normotensive and hypertensive patients for secondary prevention. Combination of ACEI and diuretics is preferred for secondary prevention. | A |
| | Lower BP to <130/80 mmHg for secondary prevention in lacunar stroke. **(NEW)** | A |
| | Do not lower SBP <180 mmHg in the first 2 weeks in acute ischaemic stroke patients unless hypertensive emergencies co-exist. **(NEW)** | C |
| | Avoid lowering BP abruptly with sublingual nifedipine in acute stroke. | C |
| | Do not lower SBP to <140 mmHg in patients presenting within 6 hours of haemoraghic stroke (HS) and presenting SBP of <220 mmHg. | C |
| | Consider aggressive reduction of BP in HS patients presenting with SBP ≥220 mmHg with continuous intravenous infusion of antihypertensive and frequent BP monitoring. **(NEW)** | C |
| **Hypertension in The Older Adults** | Measure standing BP and use it to guide treatment decision. **(NEW)** | C |
| | Assess comprehensively to confirm hypertension. **(NEW)** | C |
| | Assess for frailty, mobility, function, cognition, nutrition, postural hypotension and falls. **(NEW)** | C |
| | Individualised treatment based on clinical scenarios. **(NEW)** | C |
| | Target SBP <150 mmHg for >80 year olds. | A |
| | Target SBP <140 mmHg for 65-80 year olds. **(NEW)** | B |
| | Consider SBP <130 mmHg in fit 65-80 year olds. **(NEW)** | A |
| | Apply less strict targets for the frail, functionally and/or cognitively-impaired, those with multi-morbidities and those with adverse reactions from therapy. Consider de-prescribing in this group of patients. **(NEW)** | C |

| ISSUES | RECOMMENDATIONS | GRADE |
|---|---|---|
| **Hypertension in Women** | Use Korotkoff V to diagnose and monitor treatment of hypertension in pregnant women. **(NEW)** | C |
| | Consider automated BP device instead of mercury sphygmomanometer to diagnose and monitor treatment. **(NEW)** | A |
| | Provide counselling and appropriate management to women with chronic hypertension and who are planning for pregnancy. | C |
| | Avoid RAS blockers in all women of childbearing potential unless adequate precaution has been taken against pregnancy. **(NEW)** | A |
| | Refer pregnant women with hypertension to the obstetrician for further management. | C |
| | Provide low dose calcium supplementation (500-1000 mg daily) from early pregnancy to prevent pre-eclampsia. **(NEW)** | A |
| | Commence aspirin (100-150 mg and taken at bedtime) from 12-16 weeks and continue until delivery in pregnant women with one or more high risk factors or two or more moderate risk factors for pre-eclampsia. **(NEW)** | A |
| | The drugs of choice in pregnancy are still methyldopa (first line) and labetalol (alternative first line) with nifedipine as second line. **(NEW)** | C |
| | In an acute hypertensive crisis, use IV labetalol (20 mg slow bolus over 5 minutes followed by 40mg 10-20 minutes later) or continuous infusion of 1-2mg/minute. IV hydralazine (bolus or infusion) is an alternative but do not use it as first line treatment. **(NEW)** | C |
| | Use oral nifedipine 10 mg stat dose to rapidly control BP in acute hypertensive crisis prior to transfer to hospital. | C |
| | Administer parenteral magnesium sulphate as drug of choice for prevention of eclamptic fit. | A |
| | **Hypertension and Oral Contraceptives** | |
| | Advise woman who develop hypertension whilst on combined oral contraceptives (COC) to stop smoking and offer them alternative forms of contraception. | C |
| | Review BP at least every 6 months. | C |

| ISSUES | RECOMMENDATIONS | GRADE |
|---|---|---|
| **Hypertension in Women** (Continued) | **Hypertension and Hormonal Therapy** | |
| | Monitor BP in normotensive women taking HRT every 6 months | C |
| | Monitor closely hypertensive women on conjugated equine estrogen (CEE) every 3 months. | C |
| **Hypertension in Neonates, Children and Adolescents** | Measure BP at every encounter if the child have risk factors or annually for obese children >7 year old. | C |
| | Once a child is diagnosed with hypertension, he/she should be referred to a paediatrician for further evaluation and management. | C |
| | Start non-pharmacologic management especially weight reduction in obese children and in all children with BP of >90$^{th}$ percentile. | C |
| | Once pharmacologic therapy is initiated, BP must be reduced to <90$^{th}$ percentile (Systolic and Diastolic) and <130/80 mmHg in adolescents ≥13 years old. **(NEW)** | C |
| | In children and adolescent with CKD, lower BP to <50$^{th}$ percentile. **(NEW)** | C |
| **Economic Impact of Hypertension** | Conduct more awareness programmes on clinical and economic benefits in prevention and early treatment of hypertension. | B |
| | Institute behavioral changes especially on medical treatment adherence to reduce complications and long-term healthcare cost. **(NEW)** | A |
| **Resistant and Refractory Hypertension** | Treat patients with at least 3 drugs (inclusive of a diuretic) before diagnosing resistant hypertension. | C |
| | Consider drug non-adherence and secondary hypertension before diagnosing resistant hypertension or refractory hypertension. **(NEW)** | C |
| | Add spironolactone as a fourth drug in resistant hypertension. **(NEW)** | A |
| | Consider referring for device based therapy in patients with true resistant and refractory hypertension. | C |
| **Aspirin in Hypertension** | Treat patients BP to target first before initiating aspirin therapy. | A |
| | Consider using aspirin in patients with higher baseline BP. | B |

# Summary

## ALGORITHM FOR THE MANAGEMENT OF HYPERTENSION



# Summary

## RISK STRATIFICATION

| Co-Existing Condition / BP Levels (mmHg) | No RF No TOD No TOC | TOD or RF (1-2) No TOC | TOC or RF(≥3) or Clinical atherosclerosis or CKD | Previous MI / IHD, Previous stroke or Diabetes or CKD |
|---|---|---|---|---|
| SBP 130 - 139 and/or DBP 80 - 89 | Low | Intermediate | High | Very High |
| SBP 140 - 159 and/or DBP 90 - 99 | Low | Medium | High | Very High |
| SBP 160 - 179 and/or DBP 100 - 109 | Medium | High | Very High | Very High |
| SBP >180 and/or DBP >110 | High | Very High | Very High | Very High |

| Risk Level | Risk of Major CV Event in 10 years | Management |
|---|---|---|
| **Low-Intermediate** | <10% | Healthy living |
| **Medium** | 10 - 20% | Drug treatment and healthy living |
| **High** | 20 - 30% | Drug treatment and healthy living |
| **Very high** | >30% | Drug treatment and healthy living |

TOD = Target organ damage (LVH, retinopathy, proteinuria).
TOC = Target organ complication (heart failure, renal failure).
RF = Additional risk factors (smoking, TC >6.5mmol/L, family history of premature vascular disease).
Clinical atherosclerosis = CHD, carotid stenosis, peripheral vascular disease, transient ischaemic attack, stroke.

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# 1 Epidemiology, Definition and Classification of Hypertension

Hypertension is defined as persistent elevation of systolic blood pressure (BP) of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater, taken at least twice on two separate occasions.

Although there is an attempt to redefine hypertension as >130 and/or 80 mmHg,[1] this Committee recommends that the old recommendation remains. The Committee is of the opinion the proposed lower definition will not change the way we treat our patients, particularly those with cardiovascular complications with BP equal to or more than 130/80 mmHg needs treatment to lower BP regardless.

Non-Communicable Diseases (NCDs) is already the main cause of death in Malaysia (Figure 1-A) and the biggest contributor in terms of disability life-years (DALYs), with high blood pressure the biggest contributor for both males and females[2] (Figure 1-B).

**FIGURE 1-A Mortality Attributable to Risk Factors, Malaysia 2008[2]**

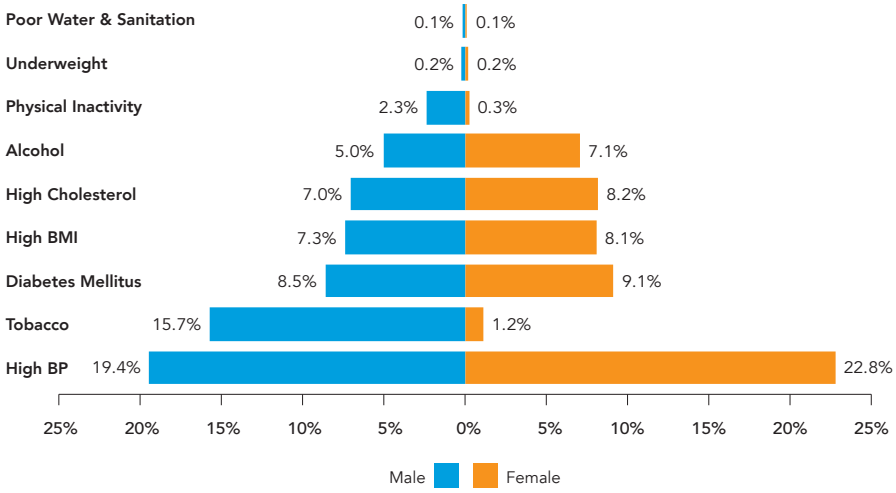
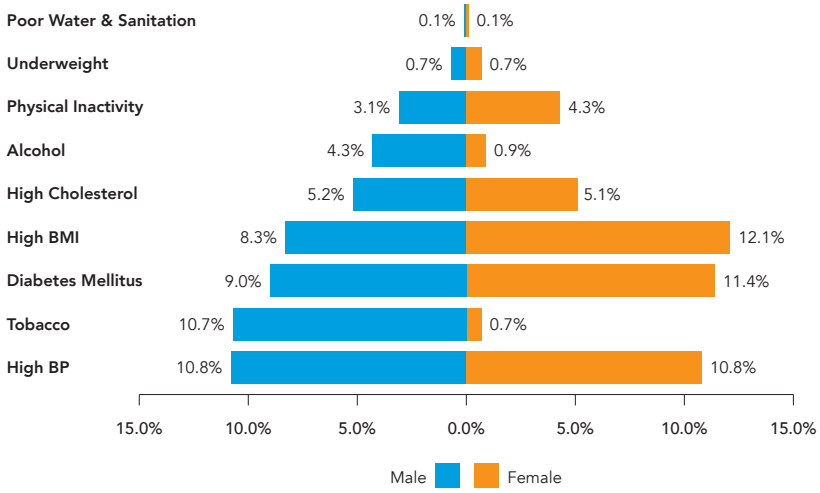


**FIGURE 1-B DALYs Attributable to Risk Factors, Malaysia 2008[2]**




The latest National Health and Morbidity Survey (NHMS) for NCD risk factors in 2015[3] showed an overall prevalence of hypertension of 35.3% among adults 18 years and above. This is an increase from 33.6% in 2011 as compared to 34.6% in 2006. However, in terms of awareness, only 37.5% were aware in 2015 a drop from 40.7% in 2011. In 2006, the awareness rate was 35.6%.[3]

No significant difference between gender was observed. There was a general increasing trend in prevalence with age, from 6.7% in the 18-19 years age group, reaching a peak of 75.4% among the 70-74 years age group. Based on the 2015 survey, prevalence was the highest among other Bumiputras (37.3%) followed by Malays (36.4%), Indian (34.9%) and Chinese (34.2%).[3]

Hypertension was more prevalent in the rural area in all three NHMS: 36.9% versus 32.9% (2006), 36.5% versus 32.6% (2011) and 39.2% versus 34.1% (2015). In terms of gender differences, hypertension was more prevalent among males; 35.3% versus 33.9% (2006), 34.2% versus 33% (2011) and 35.9% versus 34.8% (2015).

The relationship between BP and risk of cardiovascular events is continuous, consistent and independent of other risk factors. The higher the BP, the greater the chance of myocardial infarction, heart failure, stroke and kidney diseases. The presence of each additional risk factor, such as dyslipidaemia, diabetes mellitus or smoking status, compounds the risk. Therefore, the main aim of identifying and treating high BP is to reduce these risks of end organ damage or end organ complications. The classification of clinic BP levels in adults is shown in Table 1-A.

**TABLE 1-A Classification of Clinic Blood Pressure Levels in Adults**

| Classification* | Systolic (mmHg) | | Diastolic (mmHg) | Prevalence in Malaysia[3] |
|---|---|---|---|---|
| Optimal | <120 | and | <80 | 30.7 |
| Normal | 120-129 | and/or | 80-84 | 25.3 |
| At Risk | 130-139 | and/or | 85-89 | 18.6 |
| **Hypertension** | | | | |
| Stage 1 (Mild) | 140-159 | and/or | 90-99 | 17.3 |
| Stage 2 (Moderate) | 160-179 | and/or | 100-109 | 5.7 |
| Stage 3 (Severe) | ≥180 | and/or | ≥110 | 2.4 |
| Isolated Systolic Hypertension | ≥140 | and | <90 | 11.2 |

Home and Ambulatory BP may be used to diagnose and classify elevated blood pressure (Table 1-B) (see section on chapter 2.2 and 2.3).

**TABLE 1-B Criteria for Staging Hypertension Based on Clinic, Home and Ambulatory Blood Pressure Monitoring**

| Category | Clinic BP (mmHg) | Home BP Monitoring Average or Ambulatory BP Daytime Average (mmHg) |
|---|---|---|
| Stage I Hypertension | ≥140/90 | ≥135/85 |
| Stage II Hypertension | ≥160/100 | ≥150/95 |
| Severe Hypertension | SBP ≥180 or DBP ≥110 | - |

Note: Adapted from National Institute for Health and Clinical Excellence (NICE) Hypertension, 2011.[4]

## 1.1 Isolated Systolic Hypertension

Isolated systolic hypertension (ISH) is defined as SBP of ≥140 mmHg and DBP <90 mmHg. It is common after the age of 50, and carries with it a poor prognosis. Clinical trials have demonstrated that control of ISH reduces total mortality, cardiovascular mortality, stroke and heart failure events.[5,6,7]

Changing patterns of BP occur with increasing age. The rise in SBP continues throughout life in contrast to DBP, which rises until approximately age 50, tends to level off over

the next decade, and may remain the same or fall later in life.[8,9] Diastolic hypertension predominates before age 50, either alone or in combination with SBP elevation. The prevalence of systolic hypertension increases with age, and above 50 years of age, systolic hypertension represents the most common form of hypertension. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important.[10]

## 1.2 Isolated Office ("White-Coat") Hypertension

Isolated office hypertension is characterised by an elevation in clinic blood pressure but normal home or ambulatory blood-pressure values. In these subjects the clinic BP is persistently above 140/90 mmHg but the home or daytime ambulatory systolic/diastolic BP measurements are lower than 135/85 mmHg.

## 1.3 Masked Hypertension

Patients with masked hypertension have normal clinic blood pressure but elevated daytime ambulatory or home blood-pressure level (≥135/85 mmHg). Prognosis of masked hypertension is worse than isolated office hypertension.[12]

For both isolated office and masked hypertension, once diagnosed, initial therapeutic interventions should be non-pharmacological and aim for adoption of healthy living. However, drug treatment is indicated, particularly when the patient's cardiovascular risk profile is elevated or when target-organ damage (TOD) is detected.[12] (Refer to chapter 3 on Diagnosis and Initial Assessment).

### SUMMARY

- Hypertension is defined as persistent elevation of systolic BP of 140 mmHg or greater and/or diastolic blood pressure of 90 mmHg or greater, taken at least twice on two separate occasions.

### RECOMMENDATIONS

- Measure BP at every opportunity as a high number of Malaysians are undiagnosed.
- Check BP for every adult above age 18 years at least once as part of their annual health screening, and more frequently for those who are at risk (family history, obese and those at-risk of high blood pressure).

# 2 Measurement of Blood Pressure

Blood pressure should be measured under standardised condition (see section 2.1). It can be measured directly or indirectly. There are four common devices used for the indirect measurement of BP namely:

- electronic devices
- aneroid sphygmomanometer
- automated ambulatory BP devices
- mercury column sphygmomanometer

The mercury sphygmomanometer remains the gold standard for non-invasive measurement.[13(Level III)] However, it is largely being replaced by the electronic blood pressure measurement devices due to environmental and health concerns.[14]

There are many calibrated electronic or ambulatory BP devices available in the market. Only models validated by professional bodies (www.bhsoc.org, www.aami.org) should be used.

An appropriate cuff size should be used. Both the length and width of the inflatable bladder are important. The bladder length should encircle at least 80% of the circumference whilst the width should be at least 40% of the circumference of the arm. The standard cuff size should be 13 cm x 24 cm. Too small a cuff size will give a falsely high reading. Too big a cuff will give a falsely low reading.

Blood Pressure should be measured in both arms on the first visit and the higher reading is taken as the systolic BP.[13] Patient should be rested at least 1 minute before measurement. At least 2 readings preferably 1-2 minutes apart should be taken in the same arm with the patient in the same position. A third reading should be taken if the difference between the first two readings is greater than 10 mmHg. The last two readings should be averaged. In the elderly, BP should be taken sitting & standing. Blood pressure measurements should not be done on the arm with arterio-venous fistula in haemodialysis patients.

If the difference in BP between the two arms is >20/10 mmHg, further evaluation is required to look for the cause. If patients are at high risk of postural hypotension, blood pressure should be taken lying and one minute after standing.

A systolic drop of >20 mmHg after one minute of standing is considered a significant postural drop.[13]

## 2.1 Electronic BP Sets

As mentioned earlier, electronic BP sets are now preferred.

A technical committee assessment by MOH concluded that if electronic BP set is used, it must be confirmed by mercury Sphymomanometer in patients with cardiac illness, artherosclerosis, renal disease and in children. (Digital Blood Pressure Measurement sets, Health Technology Assessment Section, Medical division, Ministry of Health Malaysia. 014-2017 available at http://www.moh.gov.my.)

These electronic machines are generally less accurate in patients with arrhythmias (e.g. atrial fibrillation).

## 2.2 Home BP Measurement (HBPM) Using Electronic Devices

Home BP measurement is a useful adjunct in the diagnosis and management of hypertension especially in selected patients. If properly performed, it has good prognostic value.[15,16 (Level II-2)]

Systematic reviews have shown that HBPM is superior compared to office measurements in diagnosing hypertension, in uncontrolled hypertension, assessing antihypertensive treatment, improving patient's adherence (compliance) and provides potential cost saving.[17 (Level I),18-20]

Additionally, some studies have shown that HBPM measurements can be an alternative to ABPM and may have similar prognostic value.[21,22(Level I)] Home devices that measure the blood pressure in the fingers or the wrists are not recommended.

Situations where HBPM is useful include:[23]

- at initial assessment
- to diagnose hypertension
- to diagnose isolated office hypertension
- to diagnose masked hypertension
- to assess treatment effects
- to diagnose true resistant hypertension
- to encourage adherence to treatment
- to optimise blood pressure control

## RECOMMENDATIONS

**BP Measuring Technique**

**For Clinic BP, patients should:**

- refrain from smoking, eating, caffeine intake or exercise for at least 30 minutes
- be seated for at least 1 min in a quiet room, back & arm supported (e.g. resting on the table)
- be seated with legs uncrossed, not talking and relaxed
- use the correct bladder cuff size placed at heart level

For home measurements, besides the above:

- a minimum measurement for 3 days (ideally 7 days) should be performed
- should be done at about the same time once in the morning (before drug intake if on treatment) and evening (before meal)
- two readings should be taken at each occasion (at least 1 minute apart)
- the readings must be immediately recorded in a specific logbook or stored in a device with memory

The following must be taken into consideration when interpreting HBPM:[23]

- BP values measured on the first monitoring day should be disregarded
- Average the remaining BP measurements (at least 3 days)
- Mean home systolic BP >135 mmHg and/or diastolic BP >85 mmHg should be considered as elevated

## 2.3 Ambulatory Blood Pressure Monitoring (ABPM)

Most of the data upon which estimates of risk are based, as well as benefits of treatment have been accumulated from office BP readings and therefore ABPM is not essential for the diagnosis and management of most patients with hypertension.

The data provided by ABPM does not influence therapeutic decisions in the vast majority of patients. The current cost of ABPM devices will also limit its widespread use.

ABPM is useful in selected clinical situations. These include:[24,25 (Level III)]

- diagnosis of isolated office hypertension
- diagnosis of masked hypertension
- patients with borderline or labile hypertension
- detection of nocturnal hypertension
- evaluation of suspected hypotensive symptoms, especially in the elderly
- fluctuating office BP readings
- confirmation of resistant hypertension

# 3 Diagnosis and Initial Assessment

Evaluation of patients with documented hypertension has three objectives:

1. To exclude secondary causes of hypertension. (Table 3-A)
2. To ascertain the presence of target organ damage or complication. (Table 3-B)
3. To assess lifestyle and identify other cardiovascular risk factors (Table 3-C) or coexisting condition that affect prognosis and guide treatment. (Table 3-D)

Such information is obtained from adequate history, physical examination, laboratory investigations and other diagnostic procedures.

**TABLE 3-A Secondary Causes of Hypertension**

- Parenchymal kidney disease
- Renovascular disease
- Sleep apnoea
- Primary aldosteronism
- Drug-induced or drug-related
  - » Oral contraceptives
  - » Steroids
  - » Non-Steroidal Anti-inflammatory Drugs / COX-2 Inhibitors
  - » Erythropoeitin
- Cushing syndrome
- Phaeochromocytoma
- Acromegaly
- Thyroid disease
- Parathyroid disease
- Coarctation of the aorta
- Takayasu Arteritis

**TABLE 3-B Manifestations of Target Organ Damage (TOD) / Target Organ Complication (TOC)**

| Organ | Manifestations |
|---|---|
| **Heart** | • Left Ventricular Hypertrophy<br>• Coronary Heart Disease<br>• Heart Failure |
| **Brain** | • Transient Ischaemic Attack<br>• Stroke<br>• Dementia |
| **Peripheral vasculature** | • Absence of one or more major pulses in extremities (except dorsalis pedis) with or without intermittent claudication<br>• Carotid bruit<br>• Abdominal aortic aneurysm |
| **Kidney** | • GFR <60 ml/min/1.73m$^2$<br>• Proteinuria (1+ or greater)<br>• Microalbuminuria* (2 out of 3 positive tests over a period of 4-6 months) |
| **Retina** | • Haemorrhages or exudates<br>• Papilloedema |

TOD = Target organ damage (LVH, retinopathy, proteinuria)

TOC = Target organ complication (heart failure, renal failure)

* defined as normal to mildly increased (UACR<30mg/g), moderately increased (UACR 30-300mg/g) and severely increased (UACR >300mg/g)

A complete history should include:

- duration and level of elevated BP if known
- symptoms of secondary causes of hypertension
- symptoms of target organ complications (i.e. renal impairment and heart failure)
- symptoms of cardiovascular disease (e.g. CHD and cerebrovascular disease)
- symptoms of concomitant disease that will affect prognosis or treatment (e.g. diabetes mellitus, heart failure, renal disease and gout)
- family history of hypertension, CHD, stroke, diabetes, renal disease or dyslipidaemia
- dietary history including salt, caffeine, liquorice and alcohol intake
- drug history of either prescribed or over-the-counter medication (NSAIDs, nasal decongestants, OCP/HRT)
- exposure to traditional or complementary medicine
- lifestyle and environmental factors including air pollution that will affect treatment and outcome (e.g. smoking, physical inactivity, substance abuse; recreational & doping, psychosocial stressors and excessive weight gain)
- presence of snoring and/or day time somnolence which may indicate sleep apnoea

Physical examination should include the following:

- General examination including height, weight and waist circumference
- Measure BP appropriately. (refer to Chapter 2)
- Fundus examination
- Examination for carotid bruit, abdominal bruit, presence of peripheral pulses and radio-femoral delay
- Cardiac examination for cardiomegaly, signs of heart failure and aortic regurgitation
- Abdominal examination for renal masses/bruit and aortic aneurysm
- Neurological examination to look for evidence of stroke
- Signs of endocrine disorders (e.g. Cushing syndrome, acromegaly and thyroid disease)
- Ankle brachial index (if available)

The minimum initial investigations aim to screen for presence of secondary causes of hypertension, determine the presence of CV risk factors, target organ damage (TOD) and target organ complication (TOC). They should include the following:[26(Level III)]

- Full blood count
- Blood glucose
- Renal function tests (creatinine, eGFR, serum electrolytes)
- Lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides)
- Uric acid
- Urinalysis (dip stick: albuminuria/microalbuminuria & microscopic haematuria)
- Electrocardiogram (ECG)

If the examination or investigations suggest the presence of a secondary causes, the patient should be referred for specialist evaluation. If there is evidence of TOD or TOC (Table 3-B), further tests should be considered.

**TABLE 3-C Co-existing Cardiovascular Risk Factors for Risk Stratification**

- Diabetes mellitus
- Dyslipidaemia
- Cigarette smoking
- Microalbuminuria/Proteinuria
- Estimated GFR <60 mL/min/$m^2$

According to a study in Malaysia as many as 54% patients with essential hypertension did not have their cardiovascular risks adequately assessed.[27]

Following initial clinical evaluation and investigations, the patient should be risk stratified. Many patients with hypertension have more than one other cardiovascular

risk factor. Each additional risk factor increases cardiovascular risk substantially. Hence, overall global cardiovascular risk of a patient with hypertension should be done.[28,29] There are various ways to assess global cardiovascular risk and this includes using validated risk charts like the Framingham General Cardiovascular Risk Chart which has been validated locally and found to perform quite well[30,31] or using risk stratification tables (Table 3-D) which stratifies the risk of developing major cardiovascular events, which includes stroke, myocardial infarction and total mortality.

**TABLE 3-D Risk Stratification**

| **Co-Existing Condition** / **BP Levels (mmHg)** | No RF<br>No TOD<br>No TOC | TOD or<br>RF (1-2)<br>No TOC | TOC or RF(≥3) or Clinical atherosclerosis or CKD | Previous MI / IHD, Previous stroke or Diabetes or CKD |
|---|---|---|---|---|
| SBP 130 - 139<br>and/or<br>DBP 80 - 89 | Low | Intermediate | High | Very High |
| SBP 140 - 159<br>and/or<br>DBP 90 - 99 | Low | Medium | High | Very High |
| SBP 160 - 179<br>and/or<br>DBP 100 - 109 | Medium | High | Very High | Very High |
| SBP >180<br>and/or<br>DBP >110 | High | Very High | Very High | Very High |

| Risk Level | Risk of Major CV Event in 10 years | Management |
|---|---|---|
| **Low-Intermediate** | <10% | Healthy living |
| **Medium** | 10 - 20% | Drug treatment and healthy living |
| **High** | 20 - 30% | Drug treatment and healthy living |
| **Very high** | >30% | Drug treatment and healthy living |

TOD = Target organ damage (LVH, retinopathy, proteinuria).
TOC = Target organ complication (heart failure, renal failure).
RF = Additional risk factors (smoking, TC >6.5mmol/L, family history of premature vascular disease).
Clinical atherosclerosis = CHD, carotid stenosis, peripheral vascular disease, transient ischaemic attack, stroke.

**TABLE 3-E Recommendations for Follow-Up Visit Based on Initial Blood Pressure Measurements for Adults**

| Initial BP (mmHg) | | | Recommended follow-up |
|---|---|---|---|
| Systolic | | Diastolic | |
| <120 | and | <80 | Recheck in one year |
| 120 – 139 | and | 80 – 89 | Assess global CV risk & Recheck within 3 – 6 months |
| 140 – 159 | and/or | 90 – 99 | Assess global CV risk & Confirm within two months |
| 160 – 179 | and/or | 100 – 109 | Assess global CV risk & Evaluate within one month and treat if confirmed |
| 180 – 209 | and/or | 110 – 119 | Assess global CV risk & Evaluate within one week and treat if confirmed |
| ≥210 | and/or | ≥120 | Assess global CV risk & Initiate treatment after repeated measurement during the same encounter |

Modified from JNC-VII [32(Level III)]

# 4 Non-Pharmacological Management

Non-pharmacological management (healthy living) plays an important role in the management of hypertension and in improving overall cardiovascular health.[33-35] When recommending healthy living, it is important to know that these interventions require a joint effort from patient, family and healthcare providers.

## 4.1 Weight Reduction

Dietary interventions to lower body weight are often recommended for overweight people with mild hypertension. In people with hypertension, weight reducing diet has been shown to reduce blood pressure and body weight.[36] A 4kg reduction in body weight would achieve a BP reduction of 4.5/3.2 mmHg. There is evidence that showed a reduction of 1kg in weight relates to 1 mmHg reduction in SBP.[37] However, the long term effect of weight loss on mortality and morbidity in people with hypertension is unknown.[36,37]

## 4.2 Sodium Intake

High salt intake is associated with increased risk of stroke, stroke mortality, and coronary heart disease mortality.[38,39] Reducing sodium intake significantly reduces blood pressure in adults.[38-41] WHO recommends a reduction of sodium intake to <2 g/day or <5 g/day of salt (about one teaspoon of salt) in adults.[42] A recent Cochrane review has shown that a reduction of sodium intake from a high average of 201 mmol/day (11.6g of salt) to an average level of 66 mmol/day (3.8g of salt), resulted in a decrease in BP of 7.8/2.7 mmHg in Asian people with hypertension.[40] However there is inadequate evidence assessing the effect of reduced sodium intake on cardiovascular disease mortality and morbidity.[38,39,43-45] In Malaysia, the estimated mean sodium excretion of normotensive people was 3.4 to 3.8 g, equivalent to 8.7 to 9.5 g of salt intake per day.[46,47] This exceeds the recommended salt intake and hence salt reduction is recommended for most people especially the hypertensive population.[48]

## 4.3 Alcohol Consumption

Alcohol consumption elevates BP. Previous meta-analysis has shown that reducing alcohol consumption reduced BP by 3.3/2 mmHg.[49(Level I)] A recent meta-analysis has shown that reducing alcohol intake lowers BP in a dose-dependent manner with an apparent threshold.[50(Level I)] People who drink are advised to limit alcohol consumption to < two drinks per day.[50(Level I)]

## 4.4 Regular Physical Activity

Increased physical activity has been shown to reduce BP. However, there is a lack of data on its effect on cardiovascular events and mortality.[51] Meta-analyses have shown that dynamic aerobic endurance,[52-53] dynamic resistance,[54] and isometric resistance training[55-57] lower BP. All patients with hypertension benefit from any form of these physical activities.[58] Cumulative moderate intensity aerobic exercise of at least 150 minutes per week is advised.[59,60]

## 4.5 Healthy Eating

A diet rich in fruits, vegetables and low fat dairy products with reduced saturated and total fat can substantially lower BP (11/6 mmHg in hypertensive patients and 4/2 mmHg in patients with high normal BP).[60(Level I)] A recent meta-analysis suggests that healthy dietary patterns such as the Dietary Approaches to Stop Hypertension (DASH), Nordic, and Mediterranean diet significantly lowered BP by 4.26/2.38 mmHg.[61] These diets are rich in fruit, vegetables, whole grains, legumes, seeds, nuts, fish and dairy products and low in meat, sweets, and alcohol. A recent cohort study that included Malaysian population without cardiovascular disease has shown that higher fruit, vegetable, and legume consumption was associated with a lower risk of non-cardiovascular and total mortality.[62]

## 4.6 Cessation of Smoking

Smoking can raise BP acutely. However the effect of chronic smoking on BP is less clear. Nevertheless smoking cessation is important in reducing global cardiovascular risk.

## 4.7 Relaxation Therapy

Stress management is useful but evidence on relaxation interventions on BP reduction has not been convincing.[60,63] Yoga had been shown in a systematic review to reduce blood pressure by 4.2/3.6 mmHg but the quality of evidence is poor.[64]

## 4.8 Dietary Potassium Intake

A meta-analysis has shown that increased dietary potassium intake reduces BP in adults with hypertension without adverse effect on blood lipid concentrations, catecholamine concentrations, or renal function.[65] For adults with normal renal function and not at risk of hyperkalaemia, increasing dietary potassium can reduce BP by 3.49/1.96 mmHg.[65] Higher dietary potassium intake was associated with a 24% lower risk of stroke.[65] This can be achieved by eating fruits, vegetables, nuts and legumes.

## 4.9 Others

Evidence for beneficial effect of micronutrient alterations, caffeine reduction and dietary supplementation with fish oil, calcium, magnesium, garlic and fibre on BP is limited.[34,35,66-73] Meta-analyses have suggested that regular consumption of black tea and green tea can reduce BP but the sample size was small and quality of studies varied.[74,75(Level 1)]

### RECOMMENDATIONS

- Healthy Living must be instituted as an integral part in managing hypertension. (Grade A)
- Reduce salt intake, do regular physical activity, limit alcohol intake to < 2 drinks per day for those who drink, increase dietary potassium and lose weight to reduce BP. (Grade A)

# 5 Pharmacological Management

## 5.1 General Guidelines

All patients must be risk stratified to guide management. Decision to initiate pharmacologic treatment depends on the global cardiovascular risk (Table 3-D). It is the reduction of BP which provides the main benefits in the general hypertensive population.[76 (Level I)] The choice of drug should be individualised.

### 5.1a Initiating Treatment

For patients with Stage I (mild) hypertension with low cardiovascular risk, advice should be given on healthy living for a period of three to six months. Pharmacological treatment has not been shown to prevent cardiovascular outcome in this group of patients.[77,78] Patients should be seen at least twice (ideally monthly) during this period to assess the efficacy of the non-pharmacological intervention. Stage I patients with medium or higher risk[79-84] should be offered drug treatment upon diagnosis (Figure 5-A).[(Level I)]

### 5.1b Choosing Antihypertensive Drug Treatment

In patients with newly diagnosed uncomplicated hypertension and no compelling indications, choice of first line monotherapy includes ACEIs, ARBs, CCBs and diuretics which have all been shown to reduce cardiovascular morbidity and mortality.[85-89(Level I)] Beta-blockers are not recommended as first line monotherapy in this group of patients according to some guidelines.[4(Level III),90,91] This was based on an earlier meta-analysis which showed that it is not as effective in lowering blood pressure and in the prevention of stroke compared to the other anti-hypertensive agents.[92-95] However more recent meta-analyses including updated versions of earlier meta-analyses[95,99(Level I)] and an analysis[100] have suggested ß-blockers (especially ß1 selective) can be given as first line agent. Other guidelines continue to recommend ß-blockers as first line agent even in uncomplicated newly diagnosed hypertension.[26,101,102] However, almost all guidelines recommend that ß-blockers should be considered in younger patients in particular:

- those with an intolerance or contraindication to ACEIs and ARBs or
- women of child-bearing potential or
- patients with evidence of increased sympathetic drive.

Ideally, individualisation should be based on scientific evidence of reduction in clinical outcomes and co-morbidities (Table 5-C). Contraindications to the use of these drugs must also be considered.

In patients with stage I hypertension, treatment should be started with monotherapy at low dose. Monotherapy can lower BP to <140/90 mmHg in approximately 20–50% of patients with mild to moderate hypertension[103] If after a sufficient period of treatment (up to six weeks) with monotherapy BP is still not controlled, three options are available;

- the dose of the initial drug can be increased
- the drug can be substituted with another class of drug
- a second drug can be added

Choices of combination therapy is as shown in Table 5-A & 5-B.

If target BP is not achieved despite showing some blood pressure lowering effect with monotherapy, either increase the dose of the initial anti-hypertensive agent or add a second anti-hypertensive. The former may however give rise to dose-related adverse effects. Properly selected antihypertensive combinations may also mitigate the adverse effects of each other. If the patient does not show response or does not tolerate the initial drug, substituting with a drug from another class is recommended. (Level III) In patients presenting with stage II hypertension or beyond, combination therapy as first line is recommended.(Level III) (Refer to Figure 5-A). Combination therapy can be considered as first line in high risk stage 1 hypertension especially for secondary prevention [83,84] (Level 1)

Single Pill Combinations (SPC) is very convenient to use and promote treatment adherence by reducing pill burden and simplifying the treatment regimen.[104,105,106] (Level 1) In addition, it takes less time to achieve BP control using a combination than monotherapy.[107,108,109] (Level I)

It should be emphasized that simplification of the treatment regimen using SPC is only one strategy for improving adherence. For many patients, cost is a critical issue. In Malaysia, generic SPC are generally not available. Patented SPC are available but are more expensive. This may adversely affect adherence especially for self-paying patients. Free drug combination is the obvious choice in such circumstances. It is however worth emphasizing that available evidence showed SPC is associated with not only improved adherence, but also lower overall healthcare cost.[110](LevelII-2)

It is important to be reminded that the beneficial effects of BP lowering with pharmacotherapy is demonstrated from medium to very high CV risk. The absolute benefit in terms of CV event reduction is greater the higher baseline risk.[111] (Level 1)

## TABLE 5-A Effective Anti-Hypertensive Combinations Used in Outcome Trials

| Effective combination | Patients studied |
|---|---|
| ACEI + thiazide-like diuretics | Post stroke[79], diabetes[83] |
| ARB + thiazide[82,112] | Hypertensive with Left Ventricular Hypertrophy. High risk hypertensives |
| CCB + ACEIs or ß-blocker + thiazide[80] | Patients with Coronary Artery Disease |
| CCB + thiazide[82] | High risk hypertensives |
| CCB + ACEI[110] | Medium risk hypertensives with no overt vascular diseases |
| ACEI + CCB[84] | High risk hypertensives |
| Thiazide-like diuretics + ACEI[113] | Very elderly (>80 years old) |
| CCB + thiazide or thiazide diuretics[114] | Medium risk hypertensives |
| CCB + ARB[114] | Medium risk hypertensives |
| CCB + ß- blocker[114] | Medium risk hypertensives |

## TABLE 5-B Drug Combinations in Hypertension

**Preferred** (based on outcome trials)[79,80,82-84,112-115]

- ACEI / thiazide or thiazide-like diuretics
- ARB / thiazide diuretics
- ACEI / CCB
- ß-blocker / thiazide diuretics
- CCB / thiazide diuretics
- Thiazide diuretics / K+ sparing diuretics
- CCB/ thiazide or thiazide-like diuretics
- CCB/ARB
- CCB / ß-blocker

**Acceptable** (no outcome trial evidence yet)

- ß-blocker / thiazide-like diuretics
- DRI/diuretic

ARB = angiotensin receptor blocker
ACEI = angiotensin-converting enzyme inhibitor
CCB = calcium channel blocker
DRI = direct renin inhibitor

### 5.1c Target Blood Pressure

Efforts must be made to achieve target BP. For patients <80 years old, the target SBP should be <140 mmHg and DBP <90 mmHg.[88,100] For patients aged 80 years and above, aim for a target of <150/90 mmHg[115] (Refer to chapter 7.5 on Hypertension in Older Adults). For high/very high risk individuals the target is <130/80 mmHg[116,117] (Refer to chapter 7 on Hypertension in Special Groups).

If BP is still >140/90 mmHg with three drugs, including a diuretic at optimal tolerated doses, there is a need to exclude medication non-adherence and isolated office hypertension. After excluding these causes of uncontrolled hypertension, the patient is then defined as having resistant hypertension[118] (Refer to chapter 10 on Resistant Hypertension). A quick check on the possible causes of resistant hypertension is required. These include:

- secondary hypertension
- excessive sodium intake, excessive liquorice intake, drugs and drug interactions. (see chapter 4 Non-pharmacological Management)
- complications of long standing hypertension such as nephrosclerosis, loss of aortic distensibility and atherosclerotic renal artery stenosis

## 5.2 Follow–Up Visits

Follow up intervals should be individualised based on global CV risk, pre-treatment BP levels and drugs used. For high and very high risk patients, it is advisable to bring the BP to target within 3 to 6 months.[82] Once target BP is achieved, follow-up at three to six-month intervals is appropriate. As a rule, once the BP is controlled, most patients will require life-long treatment. Patients must be counseled to have at least six monthly follow ups even though the BP is well controlled and not to resort to merely going for repeat prescription without seeing a doctor. During these visits, doctors should assess persistence of BP control, adverse reaction to treatment, global vascular risk (including new onset and pre-existing CV risk factors) and complications of hypertension with may have developed since the last visit.

## 5.3 When To Refer

Most patients can be effectively managed by primary care practitioners. Patients with the following conditions should be referred to the appropriate specialists including Family Medicine Specialists for further assessment. Indications for referral to the appropriate specialists include:

- severe hypertension (>180/110 mmHg) - refer to chapter 6 on Management of Severe Hypertension
- suspected secondary hypertension
- resistant and refractory hypertension

- recent onset target organ damage
- pregnancy
- office hypertension with additional CV risk
- children and adults <30 years
- secondary prevention with multiple co-morbidities/risk factors

## 5.4 Step-Down Therapy

Step-down therapy is discouraged in the vast majority of patients. However in patients who insist on it, the following criteria must be considered first:

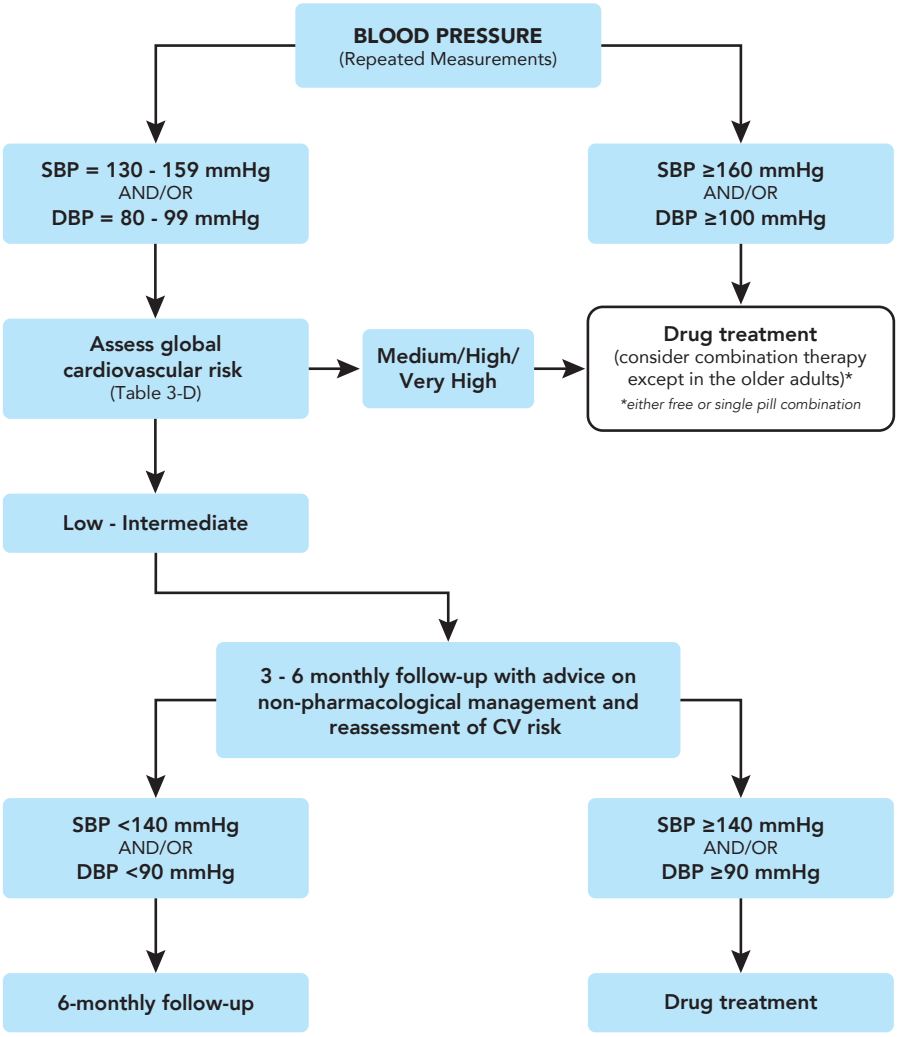
- Patients' BP must not be higher than stage I (mild) hypertension with low global CV risk
- BP well-controlled for at least 1 year on the same medication at the same dosage
- Must agree to be followed-up at least 3-6 monthly
- Must be motivated to adopt healthy living

A recent systematic review supports this recommendation.[119] This review of studies done between 1975 to 2013 showed that a trial of treatment withdrawal in well controlled hypertensives followed by subsequent regular blood pressure monitoring is safe with minor adverse events. Predictors of successful withdrawals were patients on prior monotherapy and lower blood pressures before withdrawal.

### RECOMMENDATIONS

- Treat most patients with pharmacological agent life-long. (Grade C)
- Choose mono-therapy in patients with stage 1 hypertension and with no compelling indication from one of the 5 classes of drug of agents (ACEIs, ARBs, CCBs, Diuretics or ß-Blockers) based on patient's individual clinical profile. (Grade C)
- Choose combination therapy in patients with medium/high/very high risk stage 1 hypertension and stage 2 hypertension. (Grade A)
- Treat BP to SBP<140 mmHg and DBP<90 mmHg for most hypertensive patients. (Grade A)
- Treat SBP to <130mmHg and DBP <80 mmHg for high/very high risk patients. (Grade A)
- Use combination therapy (free or single pill) for most patients to achieve BP control. (Grade A)
- Arrange periodic scheduled visits to assess global CV risk, emerging new risk factors and organ damage/complication. (Grade C)
- Co-manage patients whose BP are controlled with primary care facilities (Klinik Kesihatan or private general practice). (Grade C)

**FIGURE 5-A Algorithm for the Management of Hypertension**



## TABLE 5-C Choice of Anti-Hypertensive Drugs in Patients with Concomitant Conditions

| Concomitant Condition | Diuretics | ß-blockers | ACEIs | CCBs | Peripheral ∂-blockers | ARBs |
|---|---|---|---|---|---|---|
| Diabetes mellitus (without nephropathy) | + | +/- | +++ | + | +/- | ++ |
| Diabetes mellitus (with nephropathy) | ++ | +/- | +++ | ++ | +/- | +++ |
| Gout | +/- | + | + | + | + | ++ |
| Dyslipidaemia | +/- | +/- | + | + | + | + |
| Coronary heart disease | + | +++ | +++ | ++ | + | +++ |
| Heart failure | +++ | +++[#] | +++ | +[@] | + | +++ |
| Asthma | + | – | + | + | + | + |
| Peripheral vascular disease | + | +/- | ++ | + | + | + |
| Non-diabetic renal impairment | ++ | + | +++ | ++ | + | ++ |
| Unilateral Renal artery stenosis | + | + | ++[$] | + | + | ++[$] |
| Older Adults with no co-morbid conditions | +++ | + | + | +++ | +/- | + |
| Very Elderly (>80 yrs) with no co-morbid conditions | +++ | + | +++ | ++ | +/- | ++ |

The grading of recommendation from (+) to (+++) is based on increasing levels of evidence and/or current widely accepted practice.

+/- Use with care
– Contraindicated
[#] Metoprolol, bisoprolol, carvedilol, nebivolol – dose needs to be gradually titrated
[@] Current evidence available for amlodipine and felodipine only
[$] Contraindicated in bilateral renal artery stenosis

# 6 Management of Severe Hypertension

Severe hypertension is defined as persistent elevated SBP >180 mmHg and/or DBP >110 mmHg.

These patients may present with:

- incidental finding in an asymptomatic non-previously diagnosed patient
- treated hypertension on follow-up who are asymptomatic
- patients with symptoms which may include:
  - » non-specific symptoms like headache, dizziness, lethargy
  - » symptoms and signs of acute target organ damage/complication. These include acute heart failure, acute coronary syndromes, acute renal failure, dissecting aneurysm, subarachnoid haemorrhage, hypertensive encephalopathy and preeclampsia/eclampsia (Refer to chapter 7.4 Hypertension and Stroke, chapter 7.6 Hypertension in Women)

Patients are then categorised as having:

a. hypertensive urgencies (urgency), or

b. hypertensive emergencies (emergency)

(a) and (b) are also referred to as hypertensive crises.

In a recent large series, only a minority of patients admitted (5.1%) had hypertensive crises. Of those, more than three quarters (76.6%) constitute hypertensive emergencies.[120(Level II)]

Management of these patients depends on the clinical presentation and laboratory investigations. The evaluation of these patients should include a thorough history and physical examination, particularly looking for signs of acute target organ damage/complication and causes of secondary hypertension. (Table 6-A)

The commonest reason of severe hypertension is long-standing poorly controlled essential hypertension. Other causes are as listed in Table 6-A.

**TABLE 6-A Common Causes of Severe Hypertension**

| Causes | Example |
|---|---|
| **Parenchymal renal disease** | Chronic Kidney Disease<br>Primary glomerulonephritis |
| **Renovascular disease** | Atherosclerotic disease<br>Fibromuscular dysplasia<br>Polyarteritis nodosa |
| **Systemic disorders with renal involvement** | Systemic lupus erythematosus<br>Systemic sclerosis<br>Vasculitides |
| **Endocrine** | Conn syndrome (primary hyperaldosteronism)<br>Phaeochromocytoma<br>Cushing syndrome |
| **Drugs** | NSAIDs<br>COX-2 inhibitors<br>Oral Contraceptives<br>Amphetamines / Metamphetamines<br>Cyclosporin<br>Cocaine<br>Other Illicit Drugs<br>Phencyclidine<br>Clonidine withdrawal |
| **Congenital disease** | Coarctation of Aorta<br>Polycystic kidney disease |
| **Pregnancy related** | Preeclampsia / eclampsia |

# 6.1 Specific Management

The aim of management is to reduce BP in a controlled, predictable and safe manner, to avoid provoking or aggravating acute coronary syndrome, cerebral or renal ischaemia.

## 6.1.1 Hypertensive Urgency

Hypertensive urgency is defined as severe increase in BP which is not associated with acute end organ damage/complication and these include patients with grade III or IV retinal changes (also known as accelerated and malignant hypertension), but no overt symptoms and signs of acute target organ damage/complication. These patients may be admitted.

Blood pressure measurement should be repeated after 30 minutes of bed rest.[121,122(Level II)] Initial treatment should aim for about 25% reduction in BP over 24 hours but not lower than 160/100 mmHg.[123,124(Level II)] Oral drugs proven to be effective are outlined in Table 6-B. Combination therapy may be necessary. Importantly, there is no role for intravenous BP lowering drugs. Many of these patients have withdrawn from or are not adhering to antihypertensive therapy and do not have clinical or laboratory evidence of acute target organ damage.[125] Possible precipitating factors for hypertensive urgency include non-adherence to anti-hypertensive medications, less effective outpatient blood pressure control, acute pain, herbal supplement and emotional stress.[125,126]

Therapeutic strategies for previously undiagnosed patients include (Figure 6-A: Flowchart in management of hypertensive urgency):

1. Rest in quiet room for at least 2 hours[121,122,127]
2. Initiate oral anti-hypertensive agents if BP remains >180/110 mmHg[121]
3. Hypertensive urgency discharge plan (Figure 6-B)

**FIGURE 6-A Flowchart in Management of Hypertensive Urgency**

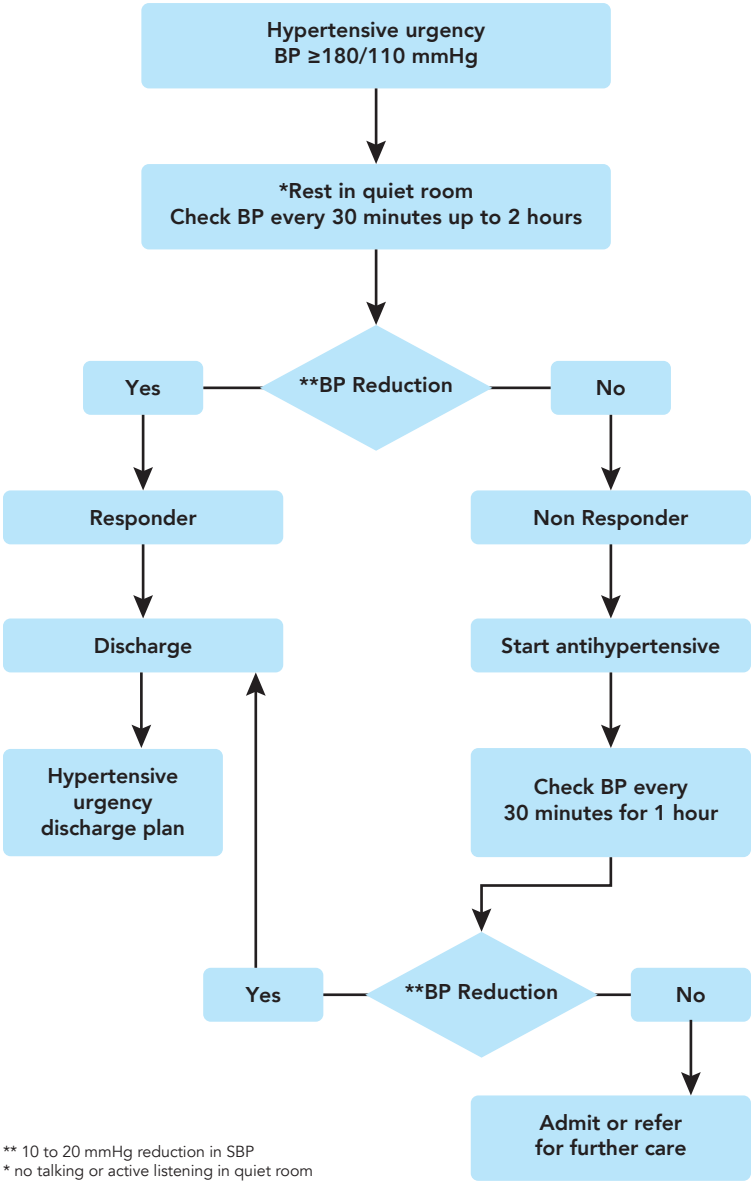


**TABLE 6-B Oral Treatment for Hypertensive Urgencies**

| Drug | Starting Dose (mg) | Onset of action (hr) | Duration (hr) | Frequency (prn) |
|---|---|---|---|---|
| **1. Captopril** | 12.5 mg | 0.5 | 6 | 1 - 2 hrs |
| **2. Nifedipine** | 10 mg | 0.5 | 3 - 5 | 1 - 2 hrs |
| **3. Labetalol** | 200 mg | 2.0 | 6 | 4 hrs |

**FIGURE 6-B Hypertensive Urgency Discharge Plan**

**Blood pressure monitoring**
- Home BP monitoring **OR** check by healthcare provider at least 3 times per week
- If BP >180/110 mmHg, repeat after 5 minutes; **IF** second BP higher or same as the first one **OR** have symptoms, seek medical help.

**Medication**
- Take anti-hypertensive as prescribed

**Follow up care**
- Adhere to clinic follow up appointment

**When to call 999**
- symptoms such as chest pain, difficulty in breathing or altered mental status occurs

## 6.1.2 Hypertensive Emergency

Hypertensive emergency is defined as severe elevation of blood pressure associated with new or progressive end organ damage/complication such as acute heart failure, dissecting aneurysm, acute coronary syndromes, hypertensive encephalopathy, acute renal failure, subarachnoid haemorrhage and/or intracranial haemorrhage. These may occur in patients with BP <180/110 mmHg, particularly if the BP has risen rapidly.

These patients:

- should be admitted for immediate intervention and monitoring.
- need to be reduce their BP rapidly based on clinical scenarios - refer also to chapter 7.4 Hypertension and Stroke, and chapter 7.6 Hypertension in Women.
- should have their BP reduced by 10%-25% within certain minutes to hours but not lower than 160/90 mmHg.[128,129(Level III)]

This is best achieved with parenteral drugs. (Table 6-D)

**TABLE 6-C Common Clinical Scenario of Hypertensive Emergencies with Treatment Goals**

| Clinical scenario | BP reduction | Additional consideration |
|---|---|---|
| **Acute heart failure** | BP lowering until symptom resolution.<br><br><25% within 1 hour, then ≤160/100 mmHg over 2 to 6 hours. | ß-blocker or CCB use could cause exacerbation of symptoms. |
| **Acute coronary syndrome** | Reduce BP to reduce cardiac workload and improve coronary perfusion.<br><br><25% within 1 hour, then ≤160/100 mmHg over 2 to 6 hours.[128]<br><br>An alternative is to reduce DBP by 10% to 15% or to approximately 110 mmHg in 30 to 60 minutes, if the patient is clinically stable, further gradual reductions toward a normal BP can be implemented over the next 24 to 48 hours. | Consider type A aortic dissection as cause of acute coronary syndrome; avoid selective ß-blockers if cocaine abuse suspected.[125,130,131] |
| **Acute aortic dissection** | Reduce SBP to ≤120 or BP ≤120/80 mmHg (lower if tolerable) and HR to <60 bpm within 1 hour. | Beta blockade should precede vasodilator (e.g., nicardipine or nitroprusside) administration, if needed for BP control or to prevent reflex tachycardia or inotropic effect; SBP ≤120 mmHg should be achieved within 20 min.[1]<br><br>Avoid ß-blockers if severe aortic regurgitation is noted.[131] |

continued on next page...

| Clinical scenario | BP reduction | Additional consideration |
|---|---|---|
| **Hypertensive Encephalopathy** | Reduce BP 20% –25% within 1 hour to reduce intracranial pressure. | Avoid nitroprusside because it can lead to intracranial oedema. |
| **Acute renal failure** | Reduce BP to around 25% within 3 to 24 hours.[132] | |
| **Preeclampsia and Eclampsia** | Reduce SBP to <140 mmHg within the first hour.<br><br>*Refer Chapter 7.6 Hypertension in Women* | Definitive treatment is delivery of foetus.<br><br>ACE inhibitors, ARBs, renin inhibitors, and nitroprusside contraindicated.[1] |
| **Sympathetic crises** | Rapid BP lowering until symptom resolution. | Avoid ß-blocker monotherapy (except for labetalol). |
| **Phaeochromocytoma** | Rapid BP lowering until symptom resolution. | Avoid ß-blocker monotherapy (except for labetalol). |
| **Acute ischemic stroke** | *Refer Chapter 7.4 Hypertension and Stroke* | |
| **Haemorrhagic stroke** | *Refer Chapter 7.4 Hypertension and Stroke* | |

There has been very few head to head comparative trials on the management of hypertensive crises especially hypertensive emergencies. A recent meta-analysis showed that IV labetalol have comparable efficacy and safety compared to nicardipine with the later showing more predictable and consistent BP control.[133,134 (Level 1)]

Specific clinical scenarios requiring rapid lowering of SBP, usually to at least <140 mmHg, in the first hour of treatment include aortic dissection, severe preeclampsia or eclampsia, and pheochromocytoma with hypertensive crisis.[1,131]

In summary, the selection of an antihypertensive agent should be based on the drug's pharmacology, pathophysiological factors underlying the patient's hypertension, degree of progression of target organ damage, the desirable rate of BP decline, and the presence of comorbidities. The therapeutic goal is to minimise target organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.[1,129]

**TABLE 6-D Treatment Options for Hypertensive Emergencies[123,129,135]**

| Drugs | Dose | Onset of action | Duration | Remarks |
|---|---|---|---|---|
| **Labetalol** | Adult*<br>20 mg injected slowly for at least 2 min; followed by 40-80 mg every 10 min.<br>Max: 200 mg<br><br>Children**<br>1 month - 11 years:<br>IV 0.25-0.5mg/kg (Max 20mg).<br>IVI 0.5-1.0 mg/kg/hr initially.<br>Maintenance: 0.25-3.0 mg/kg/hr. | ≤5 min | 3 - 6 hrs | Patient should remain supine during and 3 hr after the procedure.<br><br>Caution in heart failure. |
| **Nitroglycerine** | Adult*<br>Initial: 5-25 mcg/min.<br>Usual range: 10-200 mcg/min; up to 400 mcg/min in some cases. | 2 - 5 min | 3 - 5 min | Preferred in acute coronary syndrome and acute pulmonary oedema. |
| **Isosorbide Dinitrate** | Adult*<br>IV infusion 2-20 mg/hr, titrate based on target BP. | 3 - 15 min | 1 hour | Preferred in acute coronary syndrome. |
| **Hydralazine#** | Adult*<br>Initial: 5-10 mg via slow inj, may repeat after 20-30 min. Alternatively, as a continuous infusion, initial dose of 0.2-0.3 mg/min.<br>Maintenance: 0.05-0.15 mg/min.<br><br>Children**<br>1 month - 11 years:<br>IV 0.1-0.5 mg/kg (Max 10 mg) may be repeated after 4-6 hr.<br>IVI 12.5–50 mcg/kg/hr<br>Max 3 mg/kg/day. | 10 - 30 min | 3 - 8 hrs | Caution in acute coronary syndromes, cerebrovascular accidents and dissecting aneurysm.<br><br>Unpredictable BP-lowering effects. |

continued on next page...

| Drugs | Dose | Onset of action | Duration | Remarks |
|---|---|---|---|---|
| **Nicardipine** | Adult*<br>Slow IVI at an initial rate of 5 mg/hr. Increase infusion rate as necessary, up to max 15 mg/hr. Consider reducing to 3 mg/hr after response is achieved.<br><br>Children**<br>IV bolus 0.5-5 mcg/kg over 1 minute.<br>IVI 1- 4 mcg/kg/min. | 5 - 10 min | 1 - 4 hrs | Caution in acute heart failure and coronary ischaemia. |
| **Esmolol** | Adult*<br>Loading dose of 80 mg over 15-30 sec, followed by an infusion of 150 mcg/kg/min, may increase to 300 mcg/kg/min if necessary.<br><br>Children**<br>IV bolus 250-500 mcg/kg over 1 min.<br>IVI 50-200 mcg/kg/min for 4 min.<br>May repeat sequence. | 1 min | 10 - 20 min | Used in peri-operative situations and tachyarrhythmias. |

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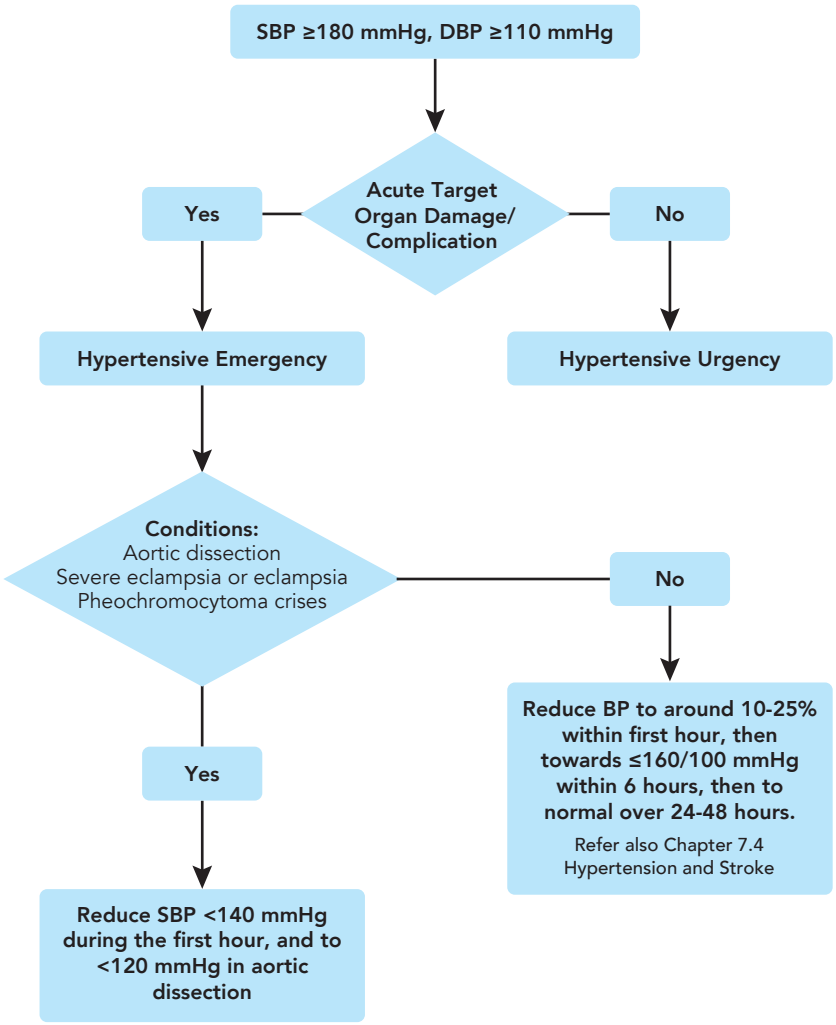
| Drugs | Dose | Onset of action | Duration | Remarks |
|---|---|---|---|---|
| **Sodium Nitroprusside** | Adult*<br>Initial: 0.3-1.5 mcg/kg/min, adjust gradually as needed. Usual: 0.5-6 mcg/kg/min. Max rate: 8 mcg/kg/min, discontinue if there is no response after 10 mins. May continue for a few hr if there is response.<br><br>Children*<br>IV 0.25-0.5 mcg/kg/min, may be repeatedly double at interval of 15-20 min. Max 6 mcg/kg/min. | seconds | 1 - 5 min | Caution in heart failure.<br>Require intra-arterial blood pressure monitoring.<br><br>Lower dosing adjustment required for elderly and those already receiving antihypertensives. |

* Referenced from 153rd Edition, MIMS, 2018.
** British National Formulary for Children (BNFC) 2018-2019.
# In pregnancy refer to chapter 7.6 Hypertension in Women.

**TABLE 6-E Differences Between Hypertensive Emergency and Urgency**

| Variable | Emergencies | Urgencies |
|---|---|---|
| Symptoms | Yes | No or minimal |
| Acute target organ damage/complication | Yes | No |
| BP reduction rate | Minutes to hours | Hours to days |
| Evaluation for secondary hypertension | Yes | Yes |

**FIGURE 6-C Flowchart in Management of Hypertensive Emergency***




* Flowchart adopted from Whelton, et al 2017, pg 139 [1]

## 6.2 Dangers of Rapid Reduction in Blood Pressure

Rapid reduction of BP (within minutes to hours) in hypertensive urgencies should be avoided as it may precipitate ischaemic events.[136]

Oral or sublingual drugs with rapid onset of action can result in an uncontrolled BP reduction. Several serious side effects have been reported with the administration of sublingual fast-acting nifedipine and therefore this is no longer recommended.[137(Level III)] However oral nifedipine retard can be used and has been recommended as first line therapy for hypertensive urgencies.[124(Level III)]

Following stabilisation of patient's BP, subsequent management is tailored towards achieving optimal control.

For management of patients with severe hypertension and stroke, refer to chapter 7.4 Hypertension and Stroke.

### RECOMMENDATIONS

- In hypertensive urgencies, aim for 10-20 mmHg SBP reduction after 2 hours of rest. Failing this, pharmacotherapy should be initiated. (Grade B)
- Treat hypertensive urgencies with combination oral therapy targeting BP to reduce by around 25% within 24 hours. (Grade C)
- Treat hypertensive emergencies with intravenous drugs with specific targets based upon clinical scenarios. (Grade B)
- Reduce SBP to less than 140 mmHg during the first hour for patients with severe preeclampsia or eclampsia, and pheochromocytoma crisis. For patients with aortic dissection reduce SBP to less than 120 mmHg. (Grade C)
- Reduce SBP by no more than 25% within the first hour; then, if stable, to 160/100 mmHg within the next 2 to 6 hours; and then cautiously to normal during the following 24 to 48 hours in all other situations. (Grade C)

# 7 Hypertension in Special Groups

## 7.1 Hypertension and Diabetes Mellitus

From the Malaysian National Health and Morbidity Survey (NHMS) 2015, the prevalence of diabetes in those 18 years and above was 17.5%, and in the 18-19 years age group the prevalence was 5.5%, indicating that diabetics in Malaysia are generally younger.

Hypertension is common in patients with diabetes mellitus. Its presence increases the risk of morbidity and mortality. In 2016 the prevalence of hypertension in Malaysian diabetics was 76%.[138] Hypertension should be treated early in diabetes to prevent both microvascular and macrovascular complications and CV death.

### 7.1.1 Threshold for Treatment

Pharmacological treatment should be initiated in patients with diabetes when the BP is persistently ≥140 mmHg systolic and/or ≥90 mmHg diastolic.

The presence of microalbuminuria or overt proteinuria should be treated even if the BP is <140/90 mmHg. An ACEI or ARB is preferred.[139-147 (Level I)] In a proportion of patients, microalbuminuria may be normalised by high doses of ACEIs[143 (Level 1)] or ARBs[144,145 (Level I)] even if the BP is already optimally controlled. Normalisation of microalbuminuria is associated with a reduction in the rate of decline in glomerular filtration rate.[148]

### 7.1.2 Target Blood Pressure

Tight BP control should take precedence over the class of anti-hypertensive drug used.[149,150 (Level I)] This will often require combination therapy.

Prior to the ACCORD study, it was generally accepted that for diabetics, the lower the BP the better the outcomes. However, in the ACCORD Study, diabetic patients at high risk of cardiovascular events who were randomised to a target systolic blood pressure (SBP) of <120 mmHg, did not show a reduction in the composite outcome of CV death, myocardial infarct and stroke, as compared with <140 mmHg.[151 (Level I)] This could possibly be due to the J-curve phenomenon seen in this particular cohort of patients who had underlying cardiovascular disease at baseline. This is supported by a more recent population based analysis.[152]

In diabetics with CKD, the recommended target BP is <130/80 mmHg.

Other reports[153,154] emphasise that major trials like ACCORD incorporate elderly patients (mean age 62 years) with established CVD or with multiple CV risk factors. These trials may not be relevant to younger diabetics with few or no risk factors, in whom continued benefits are derived from lowering the SBP to below 140 mmHg. In Malaysia, diabetics are younger and more aggressive BP targets may confer greater benefits.

The targets recommended by Malaysian CPG have been consistent over the years; and the studies above confirm that generally the target BP should be aimed at <140/80 mmHg,[83,155] with a target of <130/80 mmHg in younger patients and those at higher risk of cardiovascular disease.[139,155,156] However, in diabetics with established CAD further lowering of the BP beyond 120/80 mmHg does not confer additional cardiovascular benefit.

### 7.1.3 Management

The management of the hypertensive diabetic will involve healthy living changes as well as drug treatment.

### 7.1.4 Principles of Pharmacological Management

The use of certain classes of anti-hypertensive drugs may be detrimental to the diabetic patient because of their modes of action or adverse effects. Diabetes control may be compromised and diabetic complications aggravated, for example:

- decreased insulin responsiveness with higher doses of diuretics
- masking of the early symptoms of hypoglycaemia with ß-blockers and slower recovery from hypoglycaemia with non-selective ß-blockers
- aggravation of the symptoms of peripheral vascular disease with ß-blockers
- dyslipidaemia with most ß-blockers and diuretics
- worsening of orthostatic hypotension with peripheral ∂-blockers or centrally acting drugs

Angiotensin-converting enzyme inhibitors (ACEIs) are the drugs of choice based on extensive data attesting to their cardiovascular benefits and reno-protective effects in patients with diabetic kidney disease.[157 (Level I)] They have also been reported to prevent the onset of nephropathy in normoalbuminuric diabetic patients with or without hypertension.[155,158,159 (Level II)] In addition they do not have adverse effects on lipid and carbohydrate metabolism. However, its routine use in normotensive

normoalbuminuric diabetic patients is currently not recommended. If an ACEI is not tolerated, an angiotensin receptor blocker (ARB) should be considered.

For type 1 diabetes with nephropathy, ACEIs are the recommended agent.[140] For type 2 diabetes, both the ACEIs & ARBs may be used.

Thiazide and thiazide-like diuretics can be added on when monotherapy is inadequate. Single Pill Combination of a thiazide-like diuretic (indapamide) with perindopril has been reported to reduce overall mortality.[83(Level I)]

CCBs do not have significant adverse metabolic effects. They do not compromise glycaemic control in diabetic patients. They can be effectively combined with a RAS blocker to lower blood pressure in hypertensive diabetics. The combination of benazepril with amlodipine was superior to the combination of benazepril with hydrocholothiazide, leading to a reduction of cardiovascular events in the overall study population as well as the diabetic subgroup.[84(Level 1)]

Beta-blockers may be used when ACEIs, ARBs or CCBs cannot be used or when there are concomitant compelling indications. However, they should be used with caution, especially in patients with type 1 diabetes.[160(Level III)]

The SGLT2 inhibitors are a new class of oral anti-diabetic agents. In addition to lowering blood sugar levels, they lower the BP modestly but consistently.[161] However, the mechanism by which BP is lowered is unknown. In the EMPA-REG trial[162(Level 1)] and the CANVAS Program,[163(Level 1)] the SBP was lowered by a mean of 5.0 and 3.9 mmHg respectively. In the two trials, the composite endpoints of CV death, myocardial infarct and strokes was also reduced. The reduction in the composite endpoints may however, not be related to BP reduction and the underlying mechanism in improving CV outcome is also unknown.

## RECOMMENDATIONS

- Initiate ACEIs in diabetes without proteinuria. Use ARB for ACEI intolerant patients. (Grade A)
- Initiate ACEIs or ARBs in patients with diabetes and proteinuria. (Grade A)
- Consider CCBs, diuretics or ß-blockers if RAS blockers cannot be used. (Grade B)

# 7.2 Hypertension and Renal Diseases

## 7.2.1 Hypertension and Non-Diabetic Chronic Kidney Disease

Hypertension may be a cause or consequence of chronic kidney disease (CKD).[164,165] CKD is one of the commonest causes of secondary hypertension. Hypertension in CKD is often associated with an elevated serum creatinine, proteinuria and/or haematuria. The prevalence of hypertension increases with increasing levels of renal impairment, and approximately 50-75% of individuals with GFR <60 ml/ min/1.73m$^2$ (CKD stages 3–5) have hypertension.[166] Hypertension accelerates the progression of CKD and may lead to end stage renal disease (ESRD). In addition, CKD is associated with an increased risk of cardiovascular disease. There are proven benefits of blood pressure lowering for prevention of cardiovascular events in patients with moderately reduced kidney function[167] as well as those on dialysis.[168,169(Level 1)]

Tight control of BP in patients with CKD is therefore important. BP goals depend on urinary protein excretion. The target BP should be <140/90 mmHg for patients with CKD[170-172 (Level I)] and <130/80 mmHg for those with proteinuria ≥1g/24hours.[173(Level I)] Where well tolerated, aiming towards an Automated Office Systolic BP of 120mmHg in patients aged >50 years with nondiabetic nephropathy, GFR>20 ml/min/1.73m$^2$ and proteinuria <1g/day has shown cardiovascular benefits.[174,175(Level II-2)] When aiming towards <120 mmHg systolic, close monitoring is recommended to detect treatment-related adverse effects including hypotension, syncope, electrolyte abnormalities and acute kidney injury.[175] All anti-hypertensive drug classes can be used to achieve this goal.[167]

In the management of hypertension in CKD, control of BP and proteinuria are the most important factors in terms of retarding CKD progression. Anti-hypertensive agents that reduce proteinuria have an advantage in patients with nondiabetic proteinuric nephropathy. Meta analyses of comparative trials concluded that ACEI conferred an anti-proteinuric effect greater than other anti-hypertensive drugs.[176(Level 1)] Overall 30% reduction in incidence of ESRD with ACEI can be expected.[177] The anti-proteinuric effect and reduction in ESRD was beyond that attributable to the BP lowering effect.[172,178(Level I)] This anti-proteinuric effect of ACEI was most prominent in patients on a low sodium diet or those treated with diuretics. Patients with proteinuria >3g/24 hours benefit the most.[172,178] The advantage of ACEI is most apparent in patients with rapid progression of renal disease associated with proteinuria. ARBs are similar to ACEI in lowering BP and reducing proteinuria.

Combined RAS blockade can reduce proteinuria more than monotherapy.[179] However this is associated with an increased risk of hyperkalaemia, hypotension and renal failure.[180(Level 1)] Hence, this approach is not recommended in patients with CKD.

Renal insufficiency should not be a contraindication to starting ACEI or ARB therapy, nor should it be a reason for discontinuing therapy. Serum creatinine level should be checked within the first two weeks of initiation of therapy and also after every increase in dose. If there is a persistent rise (at least 2 occasions) of serum creatinine

of >30% from baseline within two months, ACEIs[181(Level II-3)] or ARBs should be reduced or stopped after excluding other precipitating factors. These patients should be referred to a nephrologist or physician.

In patients with GFR <30 ml/min/1.73m$^2$, thiazide diuretics may not be effective antihypertensive agents and therefore loop diuretics are preferred.[182(Level III)] Concurrent diuretic therapy will often be necessary in patients with renal insufficiency since salt and water retention is an important determinant of hypertension in this setting.

Calcium channel blockers may be used in renal disease. In those with proteinuria, the non-dihydropyridine group of CCBs namely diltiazem or verapamil are preferred, as they have an additional anti-proteinuric effect.[176(Level I)] Dihydropyridine CCBs can be considered if optimal BP is not achieved but should not be used as monotherapy in patients with proteinuria. The combination of an ACEI and a non-dihydropyridine CCB is more antiproteinuric than either drug alone.[183(Level II-2)]

## SUMMARY

- BP goals depend on urinary protein excretion.
- Anti-hypertensive agents that reduce proteinuria have an advantage in patients with nondiabetic proteinuric nephropathy.
- ACEI and ARBs confer an anti-proteinuric effect greater than other anti-hypertensive drugs.

## RECOMMENDATIONS

- Patients with proteinuria of <1g/24 hours, lower BP to <140/90 mmHg. (Grade A)
- In patients with proteinuria of >1g/24 hours, lower BP to <130/80 mmHg. (Grade A)
- In patient >50 years, GFR >20 ml/min/1.73m$^2$ and proteinuria <1g/day lower SBP <120 mmHg using Automated Self-measured Office BP to reduce cardiovascular event. (Grade B)
- Choose RAS blockers as initial antihypertensive therapy for patients with micro- or macroalbuminuria. (Grade A)
- Consider concurrent diuretic therapy and dietary salt restriction as salt and water retention are important determinants of hypertension in CKD.
- Add non-dihydropyridine CCBs if BP goal is still not achieved and there is persistent proteinuria. (Grade A)
- Avoid dual RAS blockade in patients with CKD. (Grade A)

## 7.2.2 Renovascular Hypertension

Renovascular hypertension (RVH) is defined as a rise in arterial pressure attributable to reduced perfusion of the kidney(s).[184] It is important to diagnose renovascular hypertension as it is potentially reversible. Treatment also has the potential to restore or preserve renal function. The aetiology of renovascular hypertension includes the following:

- Atherosclerotic renovascular disease
- Fibromuscular dysplasia
- Takayasu's arteritis
- Transplant renal artery stenosis

Atherosclerotic renal artery stenosis (ARAS) is an important cause as it can lead to ESRD.[185] It is also associated with coronary heart disease, cerebrovascular disease and peripheral vascular disease. In patients with ARAS older than 60 years, the five-year-survival is 45% in patients with bilateral ARAS and 18% in those requiring dialysis therapy.[186]

The presence of a stenotic renal vessel in a patient with hypertension does not necessarily equate to RVH. Some clinical features suggestive of RVH include:

- onset of hypertension before 30 years, especially without family history
- recent onset of hypertension after 55 years or deterioration in BP control in a previously well-controlled patient
- resistant hypertension
- abdominal bruit; particularly if associated with a unilateral small kidney
- flash pulmonary oedema
- renal failure of uncertain cause in the presence of normal urine sediment
- renal failure induced by ACEIs or ARBs
- coexisting diffuse atherosclerotic vascular disease

Renal angiography including measurement of the pressure gradient remains the gold standard in the diagnosis of RVH.[187] Non-invasive investigations include doppler sonography, captopril-enhanced isotope scan, spiral CT angiography (CTA), and magnetic resonance angiography (MRA) in patients with normal renal function.[188]

All patients with ARAS require intensive medical therapy. ACEIs or ARBs are recommended to control blood pressure and reduce clinical events in those with known cardiovascular disease. Medical treatment includes statins, low dose aspirin, cessation of smoking and management of diabetes when present. This approach can be considered for patients with stenosis less than 70% or those with stable renal function and good BP control despite radiological evidence of stenosis >70%. These lesions should be monitored for progression using colour duplex sonography and the renal function of patients must be carefully monitored. A persistent rise in creatinine

of >30% over 2 months warrants cessation of ACEI/ARB drug therapy. This is best done under specialist's supervision.

If revascularisation is required, it is usually achieved by percutaneous angioplasty with stenting or surgical revascularisation in patents with complex anatomic lesions. Revascularisation should be considered under the following circumstances:[188]

- A short duration of blood pressure elevation prior to the diagnosis of RVH
- Recurrent flash pulmonary oedema or refractory heart failure
- Resistant hypertension
- Intolerance to optimal medical therapy e.g. deterioration of renal function during antihypertensive therapy
- Otherwise unexplained progressive deterioration in renal function

Where indications for revascularisation are uncertain, 3 prospective randomised trials have not demonstrated compelling benefits either with endovascular stents or surgery when added to effective medical therapy.[189-191(Level 1)]

Patients with fibromuscular dysplasia (FMD) rarely have excretory dysfunction, and hypertension in these patients generally responds to ACEIs.[192(Level II-2)] Given the typical patient with FMD (young female with lower angioplasty-related risks, the need for many years of anti-hypertensive treatment plus limitations of RAS blockers during pregnancy), most clinicians would probably favour angioplasty for patients with FMD.[193(Level III)] However, the benefits of angioplasty may be limited. The chance of achieving normal BP without anti-hypertensive agents is less than 30%, although some improvement in BP may be expected in an additional 50% or more.[193]

## SUMMARY

- Optimal medical management of ARAS includes ACEI or ARB for blood pressure control and reduction of CV events, statins, low dose aspirin and glycaemic control.

## RECOMMENDATIONS

- Patients with RVH due to ARAS should be primarily medically managed because renal angioplasty and stenting has not shown any advantage over optimal medical therapy alone. (Grade B)
- Patients with RVH due to FMD should be considered for revascularisation. (Grade B)

# 7.3 Hypertension and Heart Disease

## 7.3.1 Hypertension and Coronary Heart Disease

Hypertension is the major risk factor for atherosclerosis, driving overall CV risk, thus sustained good control is important. This is especially important in the presence of other risk factors. Multiple CHD risk factors combine as multipliers, to increase CHD risk that is greater than the sum of its individual components. Management of patients with hypertension should consider the individual's absolute CHD risk. (Refer Table 3-D Risk Stratification) The decision to initiate drug treatment should take this into consideration.

Although the recommended target is <140/90 mmHg, in those at high CV risk in whom it is deemed safe on clinical grounds, and in whom drug therapy is well tolerated, aiming for a lower blood pressure may be considered.[116,117,194(Level 1)]

Clinical studies have also shown that coronary events in hypertensive patients with CHD are reduced in those whose blood pressure is controlled.[195(Level 1)] Based on many studies using different groups of antihypertensives, the benefits are achieved predominantly by lowering the blood pressure rather than the use of any specific class of antihypertensive agent.[96,196,197(Level 1)]

There are clinical trials showing morbidity and mortality benefits of anti-hypertensive agents such as ß-blockers, ACEIs and ARBs,[198-200(Level 1)] following myocardial infarction. Following any coronary event, patients will be at high risk of subsequent events, especially if the hypertension is not controlled. In the first 2 weeks after an MI, ß-blockers have been shown to reduce re-infarctions and mortality in the short term (30 days).[201-204(Level 1)]

Cardio-selective ß-blockers are preferred. In CHD patients with symptomatic & stable angina, the treatment of choice should be a ß-blocker or a CCB. Short-acting nifedipine should not be used.

Combination therapies, with suitable drugs should be considered to reduce adverse effects and improve adherence (refer Chapter 5 Pharmacological Management).

**The blood pressure target in patients with hypertension and CHD is <130 / <80 mmHg.[116(Level 1)]**

## 7.3.2 Hypertension and Heart Failure

Hypertension is the most frequent underlying cause of heart failure. Chronic, uncontrolled hypertension can cause heart failure with reduced ejection fraction (≤40%) (HFrEF).[205]

In hypertensive patients with HFrEF, hypertension aggravates heart failure by increasing left ventricular afterload, promoting left ventricular remodeling and progression of myocardial damage. Hypertension treatment is important for improving the long-term prognosis.

Anti-hypertensive agents including ß-blockers,[206-208] ACEIs,[209] and aldosterone antagonist,[210] have shown mortality benefits and reduction in the number of hospitalisations, in patients with HFrEF. In these patients, ACE inhibitors and ß-blockers are recommended for initial therapy. ß-blockers are contraindicated in the presence of acute heart failure. Careful monitoring for hyperkalaemia is recommended when combining an aldosterone antagonist with an ACEI or ARB. The evidence for ARB is less convincing[211] but they may be used for ACEI intolerant patients.[212-218]

In patients with heart failure with preserved ejection fraction >50% (HFpEF), blood pressure control is important. For these patients, results with ARBs have been mixed.[213,215] Several randomised control trials evaluating the efficacy of ARBs found no effect on prognosis including all-cause mortality. In these patients spironolactone has been shown to reduce hospitalisation with HF.[219]

A meta-analysis with ACEI has shown a modest effect on HFpEF.[220(Level 1)] However, a large-scale, prospective study (Swedish Heart Failure Registry) indicated that the total mortality rate was lower in patients taking RAS blockers.[221]

Should hypertension be persistent in spite of ACEI / ARB, aldosterone antagonist and/or ß-blocker, CCBs which are not negatively inotropic, such as amlodipine and felodipine, can be added. These patients should also be on loop diuretics for symptomatic relief.

### RECOMMENDATIONS

- Use ß-blockers, ACEIs or ARBs in post myocardial infarction patients to reduce recurrent myocardial infarction and death. (Grade A)
- Initiate ß-blockers, ACEIs and Aldosterone antagonists in patients with systolic heart failure to reduce morbidity and mortality. (Grade A)
- Use ARBs or ACEIs and aldosterone antagonist in heart failure patients with preserved ejection fraction to reduce morbidity including hospitalisation. (Grade A)
- Treat blood pressure to <140 / <90 mmHg.

## 7.3.3 Hypertension and Atrial Fibrillation

Hypertension is the most important risk factor for new onset of atrial fibrillation (AF)[222,223] of which it increases the risk of cardiogenic cerebral embolism. In the presence of AF, the incidence of cardiovascular events and mortality increases by 2.5-fold[224-226] In particular, left ventricular hypertrophy and left atrial enlargement are independent risk factors for new onset of atrial fibrillation. When antihypertensive treatment leads to the regression of left ventricular hypertrophy, the incidence of atrial fibrillation decreases.[227]

Hypertension further increases the risks of stroke and arterial embolism in patients with chronic atrial fibrillation.[228,229]

Although anticoagulants are used to reduce the risk of stroke in patients with AF, it also increases the incidence of hemorrhagic complications, especially intracranial hemorrhage.[230] Strict blood pressure control is necessary in patients taking antithrombotic drugs.[231]

A few small studies [232,233] and subgroup analyses of larger trials [234,235] have reported that ARB can reduce the incidence of recurrent atrial fibrillation or help maintain patient in sinus rhythm.[236]

For elderly patients (>75 years old) who are on anticoagaulation for atrial fibrillation, both ACEI and ARB reduce mortality.[237(Level II-2)]

For rate-control of permanent atrial fibrillation, ß-blockers or non-dihydropyridine CCBs (verapamil and diltiazem) should be considered.[238]

**The blood pressure target is <140/90 mmHg.[239]**

## 7.3.4 Hypertension and Peripheral Arterial Disease

Hypertension and peripheral arterial disease (PAD) can co-exist. The risk factors for PAD include hypertension, diabetes, current smoking and dyslipidaemia.[240] As atherosclerosis is a systemic vascular disease; diffuse atherosclerosis, CAD, and renovascular disease often coexist in these patients. 2-5% of patients with hypertension have intermittent claudication and 25-55% of patients with peripheral arterial disease present with hypertension.[241]

Patients with PAD have almost three times the risk of a cardiovascular event and death.[242] They should be screened for atherosclerotic disease of the other systems. Control of hypertension in patients with PAD is poor.[243] The aim of treatment in PAD is

both symptom relief and prevention of cardiovascular events. There is no consensus on the treatment of choice for hypertensive patients with PAD,[244] although sub-analysis of major trials showed benefits of ACEI in patients with PAD.[245] ß-blockers may cause vasoconstriction and worsen frequency of intermittent claudication. They may be used with caution in patients with compelling indications (CHD and/or HF). Should patients present with Raynaud's phenomenon, consider CCBs which have vasodilating properties. Cilostazol has been shown to be useful especially in the elderly with disabling peripheral arterial disease.[246] In addition to these medications, patients should stop smoking. Other therapies including LDL-cholesterol lowering and better control of diabetes are also recommended.

**The blood pressure target is <140/90 mmHg[247(Level II-2)]**

## RECOMMENDATIONS

- Treat blood pressure in hypertensives with peripheral arterial disease (PAD) to <140/90 mmHg. (Grade B)
- Use any antihypertensive except ß-blockers as first choice. (Grade C)
- Give ACEI to patients with PAD to prevent vascular events. (Grade B)
- Consider cilostazol in the elderly patients with symptomatic CAD or PAD. (Grade B)
- Counsel patients to stop smoking. (Grade B)
- Ensure other concurrent risk factors (especially diabetes, dyslipidaemia) are optimally managed.
- Prescribe antiplatelet agent unless contraindicated. (Grade A)

### 7.3.5 Hypertension and Left Ventricular Hypertrophy (LVH)

Left Ventricular hypertrophy is caused by pressure load and often regresses through long-term antihypertensive treatment. Those with LVH are at risk of premature cardiovascular events or death.

The most important factor in the regression of cardiac hypertrophy is good BP control. Hence all antihypertensives currently used can reduce cardiac hypertrophy through sustained control of blood pressure.[248,249] Regression of LVH can also be achieved by weight reduction and salt restriction. Echocardiography is more sensitive than ECG for detection of LVH.[250] Several studies have suggested that BP lowering leads to regression of LVH.[251,252] To reduce clinical outcome, ARBs are preferred in hypertension with LVH on ECG.[112(Level 1)]

**RECOMMENDATIONS**

- Target BP <130/80 mmHg. (Grade A)
- Use ARBs as treatment of choice in hypertensive patients with LVH on ECG. (Grade A)

## 7.4 Hypertension and Stroke

Hypertension is the most important modifiable risk factor for ischaemic stroke (IS) and haemorrhagic stroke (HS).[254] Blood Pressure levels are consistently shown to be associated with the risk for stroke.[255,256] Although both SBP and DBP are associated with stroke, SBP is more predictive.[257] Data from the Malaysian National Stroke Registry (NSR) showed that more than 75% out of the 1018 patients included in the registry has hypertension as its major risk factor.[258]

Worldwide, 15 million people suffer from stroke annually. Of these, 5 million die and another 5 million are left permanently disabled.[254] It is presently among the top four leading causes of death in ASEAN countries.[259] In Malaysia, stroke is the leading cause of death and disability in adults. Its incidence has alarmingly increased annually by 29.5% (ischaemic stroke) and 18.7% (haemorrhagic stroke).[258]

### 7.4.1 Primary Prevention of Stroke

Systematic reviews of 17 primary prevention trials involving a total of 47,000 participants showed that lowering SBP by 10–12 mmHg and DBP by 5–6 mmHg leads to a 38% reduction in the risk of stroke.[260(Level 1)]

The benefits have been shown in both systolic-diastolic hypertension and in isolated systolic hypertension.[261,262, (Level 1)] All classes of antihypertensives have the potential to prevent stroke. Calcium channel blockers in particular, provided significantly better protection against stroke compared with diuretics and/or ß-blockers in Asian[263(Level 1)] and Caucasian[115(Level 1)] populations. In the elderly[264(Level 1)] and very elderly[113(Level 1)] hypertensives, diuretics has been shown to prevent stroke.

### 7.4.2 Treatment of Hypertension in Acute Stroke

Treatment of elevated BP in acute stroke is controversial.[265] Stress-related high BP values (>140/90 mmHg) are present in up to 80% of patients with acute stroke while almost 25% of patient presents with markedly raised SBP values >180 mmHg.[266,267] In a majority of patients, a decline in blood pressure without any specific medical treatment will occur within days or weeks.[268,269] A slightly higher systemic BP is required to maintain the cerebral perfusion in the situation of increased intracranial pressure, partial thrombosis and disturbed cerebral perfusion (See Figure 7.4-A).

### 7.4.2.1 Ischaemic Stroke (IS)

Current guidelines recommend that treatment of hypertension in acute IS should be delayed for several days or up to 2 weeks after an IS unless there is hypertensive encephalopathy, severe left ventricular failure, acute renal failure, acute myocardial infarction, aortic dissection, acute pulmonary oedema or repeated BP readings reveal SBP values >220 mmHg and DBP >120 mmHg.[270] (Table 7.4-A). Existing antihypertensive medications during the acute phase of stroke should be deferred until patients have suitable enteral access and are medically and neurologically stable.[265 (Level III)]

In cases where acute BP reduction is indicated, BP lowering should be done cautiously targeting BP reduction of 10 to 20% from the baseline BP over 24 hours. More profound BP reductions (>20%) have been associated with neurological and functional worsening.[270] BP management in patients for thrombolysis/thrombectomy will not be discussed in this guideline (Discussed in the ischaemic stroke CPG).

### 7.4.2.2 Haemorrhagic Stroke (HS)

Current recommendations for treatment of elevated BP levels in patients with acute HS are more aggressive than those with IS[271(Level III)] (Table 7.4-A). Both the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial,[271(Level 1)] a 4-tier dose-escalation study of intravenous nicardipine-based BP lowering in 80 patients within 3 hours of ICH, and the pilot phase Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT1)[272(Level 1)] trial in 404 mainly Chinese patients within 6 hours of ICH found rapid reduction of SBP to <140 mmHg to be safe. The INTERACT2 trial has shown no increase in death or serious adverse events from early intensive BP lowering in eligible patients with elevated SBP. INTERACT2[273(Level 1)] trial and subsequent meta-analysis[274] have suggested that acute aggressive lowering of SBP to ≤140 mmHg within 3-6 hours of onset provide some evidence to indicate improved functional recovery. The more recent ATACH-II trial enrolled patients within 4.5 hours of ICH onset. They were randomly assigned to blood pressure reduction with intravenous nicardipine to achieve systolic pressures in the range of 140 to 179 mmHg (standard care) or 110 to 139 mmHg (intensive blood pressure lowering). This trial took more aggressive and faster approach in BP lowering. Unfortunately, it did not show any significant outcome in mortality and functional recovery. There were significantly more renal adverse events within 7 days after randomisation in the intensive-treatment group.[275]

Parenteral agents, such as labetalol or nicardipine that are easily titrated and have minimal vasodilatory effects on cerebral blood flow are preferred. Otherwise, easily titratable intravenous medications can also be used. The use of sublingual nifedipine should be avoided because of the risk of abrupt BP reduction and possible worsening ischaemia.[270,273(Level III)]

**TABLE 7.4-A Current Guideline for the Management of Blood Pressure in Acute Phase of Ischaemic and Haemorrhagic Stroke***

| Acute phase of ischaemic stroke [270,273,276] | |
|---|---|
| **BP level, mmHg** | **Treatment** |
| **SBP ≤220 or DBP ≤120** | Defer anti-hypertensive therapy |
| **SBP >220 or DBP >120** | i. Labetolol. 20 mg injected slowly for at least 2 min; followed by 40-80 mg every 10 min. Max: 200 mg.<br>ii. Nitroglycerine. Initial: 5-25 mcg/min. Usual range: 10-200 mcg/min; up to 400 mcg/min in some cases.<br>iii. Nicardipine. Slow IVI at an initial rate of 5 mg/hr. Increase infusion rate as necessary, up to max 15 mg/hr. Consider reducing to 3 mg/hr after response is achieved.<br>iv. Sodium Nitroprusside. Initial: 0.3-1.5 mcg/kg/min, adjust gradually as needed. Usual: 0.5-6 mcg/kg/min. Max rate: 8 mcg/kg/min, discontinue if there is no response after 10 mins. May continue for a few hours if there is response.<br>v. Target: 10–20% reduction from baseline BP over 24 hours. |
| **Acute phase of haemorrhagic stroke[276]** | |
| **SBP 150 – 220 mmHg** | Avoid aggressive SBP lowering to <140 mmHg. |
| **SBP >220 mmHg** | Consider aggressive BP lowering within 6 hours with continuous intravenous infusion and close BP monitoring.<br>Target: SBP lowering towards 140 mmHg. |

* Referenced from 153rd Edition, MIMS, 2018.

## 7.4.3 Secondary Prevention of Stroke

Patients who have had a stroke or a Transient Ischaemic Attack (TIA) are at increased risk of future stroke, especially in the following few months.[277] Annual recurrence rate is 12.5% per year.[278] Survival rates decreased from 63.7%, 42.8% and 24% at 1, 5 and 10 years respectively. Of those who survived at 10 years, almost a third had poor range of clinical outcomes.[279]

Lowering BP has been shown to reduce the risk of subsequent strokes.[280,281] Meta analyses of randomised controlled trials confirm approximately 30–40% reduction in stroke risk with blood pressure lowering.[282]

Combination of ACEI and thiazide-like diuretic has been shown to reduce stroke recurrence in both normotensive and hypertensive patients when treatment was started at least two weeks after the stroke.[79(Level 1)]

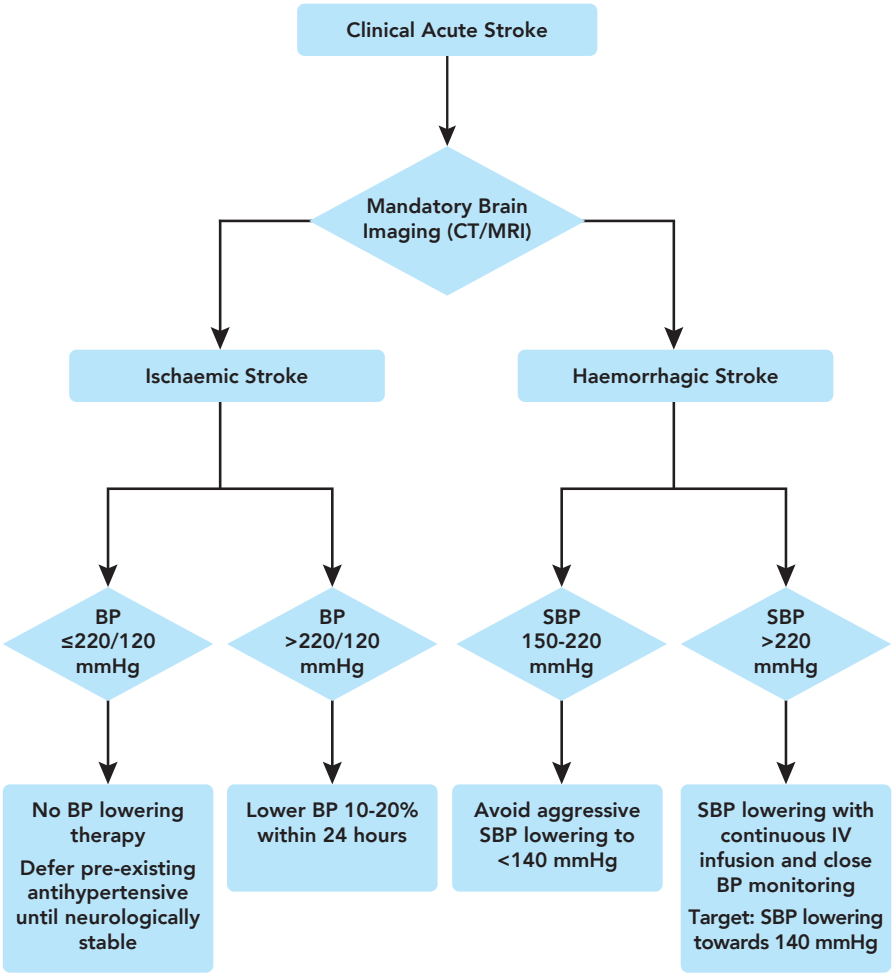
Three additional large-scale randomised trials of antihypertensive medications after stroke have been published. In one such trial, patient with hypertension and a stroke or TIA within 2 years of the event were randomised to an ARB or CCB. Despite similar BP reductions, recurrent total strokes and TIAs were less frequent among those randomised to ARB. There was a reduction in primary composite events which were significantly lower with ARB, with reduction in TIAs accounting for most of the benefit of ARB.[283(Level 1)] However in a bigger trial, patients with Ischaemic stroke were randomised to ARB or placebo within 90 days of an event with no clear benefits of ARB in preventing recurrent stroke after 2.5 years of follow-up.[284(Level 1)] In another placebo control trial involving ARB, patients with IS were randomised within 30 hours following onset of symptoms.[285(Level 1)] At 6 months follow-up, there were no significant difference in the composite primary endpoint (stroke, myocardial infarction, or vascular death). Taken together, a specific role for ARB in secondary stroke prevention cannot be confirmed.[286(Level 1)]

The target BP after a stroke is less clear. More recent guidelines suggested a target of <140/90 mmHg[26(Level III)] but the most recent major outcome trial suggest that for patients with recent lacunar stroke, a target of <130/80 mmHg is beneficial[287(Level 1)] especially for prevention of intracranial haemorrhage.

## RECOMMENDATIONS

- Treat blood pressure to prevent both primary and secondary stroke.(Grade A)
- Do not lower SBP <180 mmHg in the first 2 weeks in acute ischaemic stroke patients unless hypertensive emergencies co-exist. (Grade C)
- Do not lower SBP to <140 mmHg in patients presenting within 6 hours of haemoraghic stroke (HS) and BP of <220 mmHg. (Grade C)
- Consider aggressive reduction of BP in HS patients presenting with SBP >220 mmHg with continuous intravenous infusion of antihypertensive and frequent BP monitoring. (Grade C)
- Avoid lowering BP abruptly with sublingual nifedipine in acute stroke. (Grade C)
- Lower BP to be <140/90 mmHg in both normotensive and hypertensive patients for secondary prevention. (Grade A)
- Lower BP to <130/80 mmHg for secondary prevention in lacunar stroke. (Grade A)

**FIGURE 7.4-A Treatment Algorithm for Acute Stroke**



## 7.5 Hypertension in the Older Adults

Hypertension is a very common modifiable risk factor for cardiovascular morbidity and mortality in older people. The definition of hypertension in the older adult (>65 years old) is the same as that of the general adult population. Hypertension is an increasingly important public health concern as our population ages. The prevalence of hypertension in adults >65 in Malaysia has been reported to be 71.7%,[288] and the proportion of older adults in Malaysia is expected to increase from 9.0% in 2017 to 15% of the total population by 2030.[289]

Hypertension magnifies the risk for cardiovascular disease, with each 20 mmHg increase in systolic blood pressure and 10 mmHg increase in diastolic BP associated with a doubling in risk of death from stroke and coronary artery disease.[255] In older adults, the risk of cardiovascular events and death is twice as that observed in younger individuals at same levels of BP.[4] SBP increases linearly with age, leading to an increase in prevalence of isolated systolic hypertension in the older adult. SBP is a better predictor of cardiovascular events than DBP.[290]

Treatment of hypertension in the older adult, particularly of high SBP, significantly reduces the risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (myocardial infarction, heart failure and stroke).[6,79,83,113,117,151,253,262,263,287,291-295(Level 1)] There is evidence that this benefit extends to even the very elderly (>80 years old).[113(Level1)]

Despite the profusion of published data, there remains ongoing debate regarding optimal management of BP in the older adults, with various guidelines espousing different targets and treatment recommendations. The term 'hypertension in older adults' itself causes some difficulty as it encompasses the age groups of the 'young-old' (65-70 years) to the 'old-old' (>80 years). This group of patients is extremely heterogeneous with regards to comorbidities, frailty, and physical and cognitive functioning. Hypertension trials are also widely variable in terms of age cut-offs, inclusion and exclusion criteria, patient cardiovascular risk profiles, treatment regimens and method of BP measurement.

Current evidence supports treating the older adult to a target SBP of <150 mmHg to improve all cardiovascular outcomes.[6,113,262,293(Level 1)] There is some evidence that targeting a SBP of <140 mmHg may be beneficial, especially in reducing risk of stroke,[296,297] whilst a recent trial supports even stricter targets (SBP <130 mmHg).[117(Level 1)]

### 7.5.1 Considerations in the Older Adults

Hypertension management in older adults are often complicated by the various pathologies associated with aging. There are numerous challenges including multiple comorbidities, postural hypotension, falls, functional and cognitive impairment and frailty. These conditions frequently overlap. The absolute benefit of aggressive BP treatment in older adults with multiple comorbidities and frailty is not well known.

### 7.5.1.1 Multiple Comorbidities

Multiple morbidity increases with age and its prevalence is estimated to be about 65% and 82% for those aged 65-84 and 85 years and above respectively.[298] Multimorbidity is defined as the presence of 2 or more long term conditions.[299] At least two-thirds of hypertensive patients have another chronic disease.

There is limited evidence from randomised controlled trials to guide management of hypertension in this group of patients.[300] Observational studies imply that a SBP of 140-160 mmHg is associated with better mortality outcomes in older adults with impaired physical or cognitive functioning.[301-307(Level II- 2)] Observational data have also found that treating to lower targets (SBP <120 mmHg and DBP <70 mmHg) may increase the risk of death and cardiac events in older high-risk individuals (those with CAD, LVH and diabetes mellitus),[308-314(Level II-2)] supporting a J-curve association between both SBP and DBP and adverse outcomes in older persons.

### 7.5.1.2 Polypharmacy and Adverse Drug Reactions

Polypharmacy is another feature associated with older adults and has been shown to be related to poor outcomes including postural hypotension, falls, electrolyte disturbances, heart failure, hospitalisation and mortality.[315] Antihypertensives commonly contribute to polypharmacy in older adults.[316] Adverse drug reactions are more frequent and often more severe in older adults due to physiological changes affecting drug pharmacokinetics and pharmacodynamics, presence of multiple comorbidities, and polypharmacy. Therefore, it is important to critically evaluate the need for each medication.

### 7.5.1.3 Postural Hypotension and Falls

Advancing age is associated with an independent increase in prevalence of postural hypotension. Postural hypotension is defined as a sustained reduction in SBP of at least 20 mmHg or DBP of 10 mmHg from lying to standing position.[317] In symptomatic older adults it is recommended to check BP up to 3 minutes of standing. Both uncontrolled hypertension, especially ISH, and aggressive BP treatment have been associated with postural hypotension.[318-322(Level II-1)] Postural hypotension, symptomatic or not, is associated with falls in older adults.[318,323,324(Level II-2)] Less strict BP targets may therefore be acceptable in the very elderly, the frail, those with multimorbidities and previous fallers.[322(Level III)]

### 7.5.1.4 Cognition

In addition to cardiovascular disease, another pertinent health concern for the ageing Malaysian population is cognitive decline and dementia. Dementia has a devastating impact on quality of life, and is associated with significant escalation

of healthcare expenditure. Hypertension in midlife (40-65 years old) has been found in longitudinal studies to be a risk factor for developing cognitive decline in later life. Hypertension predisposes mainly to development of vascular cognitive impairment, but has also been found to be a risk factor for Alzheimer's pathology.[325,326(Level II-2)]

Evidence from randomised controlled trials on the effect of antihypertensive treatment on incident cognitive decline and dementia in older adults has largely been negative, due to most trials being of insufficient duration,[6,295,327-329] although observational studies of up to 20 years suggest a benefit.[301] Conversely, observational data suggest that aggressive treatment of hypertension (to <130 mmHg SBP and <70 mmHg DBP) in older adults is associated with increased risk of new-onset cognitive impairment,[301,325,326] and more rapid cognitive decline in individuals with established dementia.[330]

#### 7.5.1.5 Frailty

Frailty increases in the older adult, especially in those over 80.[331] It is defined as increased vulnerability to physical stressors as a result of reduced physiological reserve.[332] The HYVET trial showed benefit of treating hypertension in adults >80 years of age and did not find any effect of frailty on the benefit of hypertensive treatment. However, it should be noted that HYVET excluded the very frail. Post-hoc analysis of the SHEP trial[333(Level II-1)] found that the benefit of treatment on cardiovascular and all-cause mortality disappeared in those with functional impairment. Observational studies have also demonstrated the importance of frailty status on hypertension and outcomes.[301,303(Level II-2)] Therefore, results from the HYVET and SPRINT trials which support treatment in the very elderly and intensive therapy respectively need to be interpreted with caution. Goals should be driven by patients' functional status and comorbidities.

### 7.5.2 Assessment

Recommendations for BP measurements in older adults are similar to those for the general population. If there is presence of postural hypotension, the standing BP is used to guide treatment decisions.

It is very important to ascertain hypertension and the true level of BP before commencing or adding pharmacological therapy. We advocate multiple readings using an automated office blood pressure monitor after up to 3 minutes of quiet rest.

Evaluation of older patients with hypertension should not differ from that of younger adult populations. In cases of resistant hypertension, secondary causes such as atheromatous renal artery disease should similarly be ruled out.

Where appropriate, one should consider a formal frailty assessment using one of the validated tools.[334(Level II)] At a minimum, one should observe for a reduction in mobility, decreased functional ability and impaired cognition.

## 7.5.3 Treatment

The >65's are the most medically heterogeneous population and a simple 'one size fits all' approach would not be appropriate. Individualised decision in the context of comorbidities and patient tolerance to medication(s) is important.

Therapy should be started cautiously with monotherapy at a low dose and titrated upwards slowly. The patient should be reviewed frequently in the initial stage (2 – 4 weeks). Initiation with combination therapy is not encouraged and considered only after failure of initial therapy.

In the presence of ADRs such as postural hypotension and falls, de-prescribing should be considered. There is evidence that de-prescribing does not result in an increase in mortality in this group of patients.[335] This will also improve pill burden for the patient and address polypharmacy.

Treat the older adult when SBP is >160 mmHg. Treatment targets are as stated below:

**TABLE 7.5-A Treatment SBP Targets for Older Adults**

| Older Adult Population | Target SBP (mmHg) |
|---|---|
| >80 years old | <150 |
| 65-80 years old | <140 |
| Multiple comorbidities<br>Functional and cognitive impairment<br>Frail<br>Institutionalized<br>Experiencing ADRs | Consider less strict targets<br>Limit number of antihypertensive agents |

For fit* 65-80 years old patients consider target SBP <130 mmHg.

* free from health conditions that limit mobility and/or functional ability with good nutrition and cognitive status.

### Non-pharmacological Management (refer to chapter 4)

Non-pharmacological interventions, particularly sodium restriction and weight loss, have been proven to be efficacious in the older adults.[336(Level 1)] Refer to chapter 4 for more on non-pharmacological methods.

## 7.5.4 Conclusion

There are many challenges in treating hypertension in the older adult. Managing blood pressure in isolation is not conducive to achieving a patient-centered approach. BP targets depend on many factors unique to each patient. Healthcare providers must be mindful that in older adults, additional aspects must be considered before starting therapy. These include frailty, physical and cognitive functioning, and tolerance to treatment. Less strict BP targets may be considered in certain situations.

### SUMMARY

- Treatment of hypertension in the older adult, particularly of high SBP, significantly reduces the risk of all-cause mortality, cardiovascular mortality, and cardiovascular events (myocardial infarction, heart failure and stroke), even in the very elderly.
- There is strong evidence of benefit for treating to target SBP <150 mmHg.
- There is some evidence for treating to even lower target SBPs in certain subgroups of older adults.
- Older patients with multimorbidities, cognitive or functional impairment and frailty are under represented in randomised control trials for hypertension. Observational studies suggest worse outcomes in these patients.

### RECOMMENDATIONS

- Measure standing BP and use it to guide treatment decision. (Grade C)
- Assess comprehensively to confirm hypertension. (Grade C)
- Assess for frailty, mobility, function, cognition, nutrition, postural hypotension and falls. (Grade C)
- Individualised treatment based on clinical scenarios. (Grade C)
- Target SBP <150 mmHg for >80 year olds. (Grade A)
- Target SBP <140 mmHg for 65-80 year olds. (Grade B)
- Consider SBP <130 mmHg in fit 65-80 year olds. (Grade A)
- Apply less strict targets for the frail, functionally and/or cognitively-impaired, those with multi-morbidities and those with adverse reactions from therapy. Consider de-prescribing in this group of patients. (Grade C)

# 7.6 Hypertension in Women

## 7.6.1 Hypertension in Pregnancy

Hypertension in pregnancy is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg.[337] An increase of SBP of 30 mmHg and DBP of 15 mmHg above baseline BP is no longer recognised as hypertension if absolute values are below 140/90 mmHg. Nevertheless, this warrants close observation, especially if proteinuria and hyperuricaemia are also present.[338] Korotkoff V should be used as the cut-off point for DBP, and Korotkoff IV utilised only when Korotkoff V is absent.[337(Level III)] The gold standard tool to measure blood pressure in preeclampsia is still the mercury sphygmomanometer.[337] In the absence of a mercury sphygmomanometer, an automated blood pressure measuring device can be used provided it is calibrated annually against the mercury sphygmomanometer. Automated devices are acceptable for BP measurement in pregnancy based on a prospective study, which showed that there was no difference in the maternal and fetal outcomes despite lower DBP reading using the automated device.[339]

### 7.6.1.1 Proteinuria

Significant proteinuria in pregnancy is defined as ≥300 mg protein in a 24-hour urine sample, or a spot urine protein-creatinine ratio ≥30 mg/mmol.[337] If the dipstick is the only test available, 2+ is approximated to ≥300 mg/day proteinuria.[337] Significant proteinuria reflects advanced disease and is associated with poorer prognosis.

### 7.6.1.2 Classification

There are various classifications for Hypertension in Pregnancy. The most recent is by the International Society for the Study of Hypertension in Pregnancy (ISSHP). [337]

1. Preeclampsia (PE): de novo or superimposed on chronic hypertension
    a. PE is clinically diagnosed in the presence of de novo hypertension after 20 weeks gestation, with one or more of the following:
        i. Significant proteinuria
        ii. Renal insufficiency: serum creatinine ≥90 micromol/l or oliguria
        iii. Liver disease: raised transaminases and/or severe right upper quadrant or epigastric pain
        iv. Neurological problems: convulsions (eclampsia), hyperreflexia with clonus or severe headaches, persistent visual disturbances (scotoma)

v. Haematological disturbances: thrombocytopenia, coagulopathy, haemolysis
vi. Fetal growth restriction

b. PE superimposed on chronic hypertension is diagnosed in the presence of any of the following, in a woman with chronic hypertension:
   i. De novo proteinuria after 20 weeks gestation
   ii. A sudden increase in the severity of hypertension
   iii. Appearance of features of PE-eclampsia, and
   iv. Worsening proteinuria in a woman with pre-existing proteinuria early in gestation

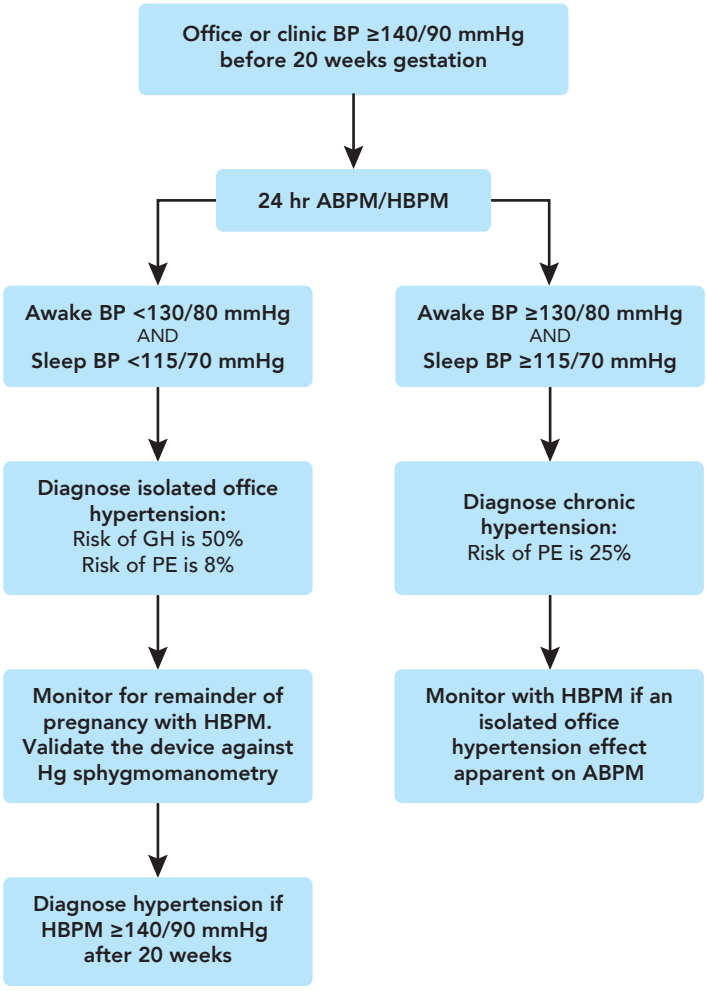
This is followed by normalisation of the BP by three months postpartum. Oedema is no longer part of the definition of PE.[340] Excessive weight gain or failure to gain weight in pregnancy may herald the onset of PE.[341]

2. Gestational hypertension is defined as hypertension detected for the first time after 20 weeks gestation. Although it usually runs a benign course, it can progress into PE in 25% of cases, more so if it presents before 34 weeks.[337]

3. Isolated office hypertension is defined as elevated BP of 140/90 mmHg only in the clinic with normal BP demonstrated by ambulatory BP monitoring (ABPM) either awake or during sleep. In the absence of ABPM device, HBPM can be used. Studies in non-pregnant population showed that they are comparable.[342] Women in this group should not be considered low risk as they may progress to gestational hypertension (50%) or PE (8%).[337,343]

4. Chronic hypertension is hypertension diagnosed prior to 20 weeks gestation or presence of hypertension preconception, or de novo hypertension in late gestation that fails to resolve three months postpartum.

**FIGURE 7.6-A ABPM to Diagnose and Manage Isolated Office Hypertension in Pregnancy.***




ABPM = Ambulatory Blood Pressure Monitoring
HBPM = Home Blood Pressure Monitoring
* adapted from Brown MA 2014.[344]

### 7.6.1.3 Key Points in Primary Care Practice

The primary care physician plays an important role in the prevention and early detection of PE and its complications. An obstetrician should lead the joint management of women with hypertensive disorders in pregnancy.

1. **Preconception counseling and adjustment of treatment in women with chronic hypertension.**

   Women with chronic hypertension may require a change in the type of anti-hypertensive agent used pre-pregnancy.[345(Level III)] The drugs of choice in pregnancy are methyldopa and labetalol (Table 7.6-A). Atenolol has been shown to lead to fetal growth restriction. The use of ARBs, ACEIs and thiazide diuretics are associated with fetal anomaly and are therefore contraindicated in pregnancy.[346] Women in the reproductive age group requiring these drugs should be on effective contraception. In the event of unplanned pregnancy, the drugs must be stopped.[347]

   It should be noted that the treatment of hypertension in pregnancy is solely for maternal safety particularly for prevention of intracranial bleeding. It does not reduce the risk of development of preeclampsia or perinatal mortality, nor improve fetal growth.[348] There is still no clear evidence on the target BP that should be achieved prior to or during pregnancy. A recent study comparing less tight (target DBP of 100 mmHg) against tight (target DBP 85 mmHg) control of BP in women with non-proteinuric chronic hypertension or gestational hypertension showed no significant differences between these two groups with regard to both maternal and perinatal complications.[349]

2. **Recognition of women at risk of preeclampsia for commencement of prophylaxis.**

| Risk | Risk Factors |
|---|---|
| **Moderate**[349] | • primigravida<br>• age >40 years<br>• pregnancy interval >10 years<br>• body mass index of >35 kg/m$^2$ at first visit<br>• family history of PE<br>• multiple pregnancy |
| **High**[349] | • hypertensive disease during previous pregnancy<br>• chronic kidney disease<br>• autoimmune disease such as Systemic Lupus Erythematosus (SLE) or anti-phospholipid syndrome (APS)<br>• type 1 or type 2 diabetes mellitus, and<br>• chronic hypertension |

**3. Prophylactic therapy**

**a. Aspirin**

Women with ≥2 moderate or one high risk factor should be started on low dose aspirin from 12 weeks up to 16 weeks of gestation until delivery.[350] The dosage should be 100-150 mg and taken at bedtime in order to significantly reduce the incidence of PE.[351-353]

**b. Calcium**

A systematic review showed that low dose calcium supplement (generally 500-1000mg daily) commenced before 20 weeks gestation reduces the risk of PE.[354]

**c. Vitamin D**

There is no proven role of vitamin D in reducing the risk of PE.[355]

**d. Others**

Other supplements in pregnancy such as marine oil, garlic, and pyridoxine have no proven benefits.[356-358] Combined vitamin C and E (i.e. tocopherol from soybean) should be avoided because they significantly increase the incidence of low birth weight without any preventive effect against PE.[359]

**4. Prediction of the incidence of preeclampsia**

A predictive test that is available locally, measuring serum sFlt-1/PlGF ratio from 20 weeks of gestation onwards has good negative predictive value for a week. It is useful in identifying which patients require admission and close monitoring. It will also help to decide on the need for antenatal corticosteroids in anticipation of pre-term delivery.[360]

**5. Fetal anomaly screening**

Women with chronic hypertension have about 20-30% increased risk for fetal congenital cardiac anomaly.[361] These women are to be referred to the Maternal-Fetal Medicine (MFM) specialist in the tertiary centre to be recommended to undergo nuchal translucency (NT) scan at 12-14 weeks followed by a detailed ultrasound scan at 22-24 weeks of gestation. If a cardiac anomaly is detected, cardiology referral is recommended.

**6. Prevention of eclampsia and other complications of preeclampsia**

Patient and healthcare provider education on the importance of signs and symptoms of preeclampsia for early diagnosis and referral for further management may prevent progression to eclampsia.[362,363(Level II-2)]

### 7.6.1.4 Severe Preeclampsia

Severe preeclampsia must be promptly identified so that the patient can be urgently admitted to hospital for close observation and timely delivery. The American College of Obstetricians and Gynecologists defines severe preeclampsia based on the following features:[364]

a. Systolic BP ≥160 mmHg or diastolic BP ≥110 mmHg on two occasions at least 4 hours apart while the patient is resting
b. Thrombocytopenia – platelet count below 100,000/cm$^3$
c. Abnormal liver enzymes (elevated AST/ALT), severe persistent right upper quadrant or epigastric pain unresponsive to treatment
d. Pulmonary oedema
e. New onset of cerebral or visual disturbances

Diagnosis of severe preeclampsia should not depend solely on the above criteria. If in doubt, it is better to over rather than under diagnose. This will prevent delay in referral. Any patient with preeclampsia should be closely monitored, as the progression to severe preeclampsia is unpredictable and rapid.

In the event of an acute hypertensive crisis, IV hydralazine, IV labetalol, or oral nifedipine, may be used to lower the BP.[365,366(Level I)] Sublingual nifedipine is no longer recommended (Table 7.6-B).[367(Level III)] Diuretics are generally contraindicated as they reduce plasma volume, may cause Intrauterine Growth Restriction (IUGR) and may possibly increase perinatal mortality. Their only use is in the treatment of acute pulmonary oedema.[341(Level III)] In order to reduce the risk of maternal stroke, the blood pressure should be reduced within 30-60 minutes.[368]

### 7.6.1.5 Anticonvulsants in Preeclampsia-Eclampsia

Parenteral magnesium sulphate is currently the drug of choice for the prevention of eclampsia and to abort an eclamptic fit (Table 7.6-C).[367,369(Level 1)] The alternative is intravenous diazepam, bearing in mind that it is inferior in efficacy compared to magnesium sulphate. Magnesium sulphate also provides fetal neuroprotection following preterm birth with a significant reduction in the incidence of cerebral palsy.[370]

### 7.6.1.6 Postpartum Care

Postpartum, women with hypertensive disorders in pregnancy are advised to have their BP checked regularly at local clinics if there is a significant delay in their scheduled hospital follow-up. In these patients, the dose of anti-hypertensive should be tailed down gradually and not stopped suddenly.

On average, anti-hypertensive agents are required for longer in women with preeclampsia (approximately two weeks) compared with those with gestational hypertension (approximately one week) although there is substantial variability among women that cannot be predicted reliably.[371]

De novo onset of hypertension or aggravation of BP levels during the postpartum period can occur.[372] These patients should be promptly referred to hospital especially if there is significant proteinuria.(Level III) Eclampsia may occur in the postpartum period. Chronic hypertension is diagnosed when the hypertension and/or proteinuria persist after three months postpartum.[337,338]

### 7.6.1.7 Long Term Follow-Up

Evidence suggests that up to 13% of women with preeclampsia will have underlying essential hypertension that was not suspected antenatally.[373] In addition, following severe preeclampsia, there is an increased risk of ischaemic heart disease, thromboembolism and stroke.[374] Long-term follow-up of patients with a history of hypertension in pregnancy is therefore advisable. (Level III)

### 7.6.1.8 Reducing Mortality

A substantial reduction in preeclampsia/eclampsia related mortality could be achieved by widespread screening for hypertension and proteinuria. Early referral and delivery is indicated for severe PE.[375]

**TABLE 7.6-A Anti-Hypertensive Drugs Commonly Used in Pregnancy**

| Drug | Remarks |
|---|---|
| **Methyldopa (first line)** | Oral 250 mg tds, doubling every 48 hrs (up to 1 gm tds) until BP well controlled. Oldest anti-hypertensive agent used in pregnancy, with best safety profile. |
| **Labetalol (alternative first line)** | Oral 100 mg bd, doubling every 48 hrs (up to 400mg bd) until BP well controlled. |
| **Nifedipine (second line)** | Oral 10 mg tds, up to 20 mg tds, when BP poorly controlled despite maximum doses of methyldopa ± labetalol. |

**TABLE 7.6-B Anti-Hypertensive Drugs for Severe Preeclampsia with Acute Hypertensive Crisis[376]**

| Drug | Administration | Remarks |
|---|---|---|
| **Labetalol** | In IV bolus:<br>• 20 mg then 40 mg 10–20 mins later<br>• 80 mg every 10–15 mins up to 200 mg<br><br>Infusion:<br>continuous infusion of 1–2 mg/min until BP stabilises, then stop or reduce to 0.5 mg/min. | May cause fetal bradycardia. |
| **Nifedipine** | Oral 5–10 mg stat (repeat in 30 mins if necessary).<br>After the initial emergency dose, 10–20 mg can be given every 3–6 hrs until BP stabilises. | Especially prior to transferring a patient from a peripheral clinic to hospital. |
| **Hydralazine** | Initial: 5-10 mg via slow inj, may repeat after 20-30 min. Alternatively, as a continuous infusion, initial dose of 0.2-0.3 mg/min.<br>Maintenance: 0.05-0.15 mg/min. | No longer recommended as first line treatment for acute hypertensive crisis in pregnancy.[374] |

**TABLE 7.6-C Anti-Convulsant for Eclampsia (and Severe Preeclampsia)**

| Drug | Administration | Remarks |
|---|---|---|
| **Magnesium Sulphate[377,378]** | IV:<br>• 4g slow bolus over 10 mins<br>• followed by 1-2 g/hr maintenance infusion given via a controlled infusion pump<br><br>IM (deep):<br>• 10g loading dose<br>• Followed by 5 g every 4 hrs in alternate buttock* | Clinical monitoring is important looking for signs of toxicity:<br>• loss of deep tendon reflexes<br>• respiratory depression with rate <16/min)<br>• renal impairment (hourly urine output <30 ml/hr) |
| **Diazepam[378]** | • 10 mg IV bolus, followed by 40 mg in D5% slow infusion so that patient remains sedated | • Only when magnesium sulphate is contraindicated or not available |

## RECOMMENDATIONS

- Use Korotkoff V to diagnose and monitor to treatment of hypertension in pregnant women. (Grade C)
- Consider automated BP device instead of mercury sphygmomanometer to diagnose and monitor treatment. (Grade A)
- Provide counselling and appropriate management to women with chronic hypertension and who are planning for pregnancy. (Grade C)
- Avoid RAS blockers in all women of childbearing potential unless adequate precaution has been taken against pregnancy. (Grade A)
- Refer pregnant women with hypertension to the obstetrician for further management. (Grade C)
- Provide calcium supplementation from early pregnancy to prevent PE. (Grade A)
- Commence aspirin from 12-16 weeks and continue until delivery in pregnant women with one or more high risk factors or two or more moderate risk factors for PE. (Grade A)
- Use oral nifedipine 10 mg stat dose to rapidly control BP in acute hypertensive crisis prior to transfer to hospital. (Grade C)

### 7.6.2 Hypertension and Oral Contraceptives

Combined oral contraceptives (COC) can induce significant increases in BP with chronic use, which is nearly always reversible after 4 weeks of discontinuation.[379] Hypertension has been reported even with low-dose-oestrogen monophasic pills.[380] A woman who develops hypertension while using COC should be advised to stop taking them and should be offered alternative forms of contraception.[381(Level III)] Low dose combined hormonal contraceptives should only be used if no other method is suitable, even for women with controlled hypertension.[382]

Drospirenone (a progestin), has anti-mineralocorticoid diuretic effects, and can lower BP when combined with oestrogen in COCs.[383] It is a recommended alternative for patients with hypertension or who developed hypertension but wish to continue oral contraception. All progestogen-only methods are appropriate except in women whose BP is higher than 160/100 mmHg. In these patients, the injectable depot medroxyprogesterone acetate (DMPA) is contraindicated, along with all oestrogen-containing contraceptives.[381]

Baseline BP must be assessed before initiating hormonal contraceptives. Blood pressure should then be measured at least every six months.[(Level III)] The same applies to usage of the combined contraceptive patch and the vaginal ring.

## 7.6.3 Hypertension and Menopausal Hormonal Therapy

The presence of hypertension is not a contraindication to oestrogen-based menopausal hormonal therapy (MHT). It is recommended that all women treated with MHT should have their BP monitored every six months.[(Level III)] The decision to continue or discontinue hormonal therapy in these patients should be individualised.

Two large trials on women aged 50-79 years, concluded that the use of MHT increased cardiovascular events.[384,385 (Level I)] Conjugated equine estrogen (CEE), alone or in combination with medroxyprogesterone acetate, was used in the study. In view of this, greater caution and closer monitoring is required for hypertensive patients on CEE. Drospirenone when used as progestin in HRT, showed improvement in BP control.[379,386]

**TABLE 7.6-D COC and Hormonal Therapy Preparations Containing Drospirenone***

| Hormonal Preparation | Trade Name | Active Ingredients | |
|---|---|---|---|
| | | Oestrogen | Progestin |
| COC | Yasmin® / Liza® | Ethinyl oestradiol 0.03 mg | Drospirenone 3 mg |
| | Yaz® / Liz® / Lizelle® | Ethinyl oestradiol 0.02 mg | Drospirenone 3 mg |
| MHT | Angeliq® | Estradiol 1 mg | Drospirenone 2 mg |

* Referenced from 153rd Edition, MIMS, 2018.

# 7.7 Hypertension in Neonates, Children and Adolescents

## Hypertension in Neonates and Infants

The incidence of hypertension in neonates admitted to Neonatal Intensive Care Unit was 1.3%.[387]

It is more common in neonates and infants with antenatal steroids, maternal hypertension, postnatal acute renal failure, chronic lung disease, patent ductus arteriosus or in those with indwelling umbilical arterial catheters.[387] Catheter related hypertension is related to thrombus formation at the time of line placement.[388]

## Measurement of BP

Healthy term neonates rarely have hypertension. Routine BP measurements are not advocated in this group. The gold standard of BP measurement in neonates is by direct measurement of arterial pulse pressure wave form.

## Standardised Protocol for BP Measurement in Neonates:[389,390]

- measure by oscillometric device
- lie prone or supine
- use appropriate sized BP cuff
- use right upper arm
- measured when infant is asleep or in quiet awake state
- 3 successive BP reading at 2 min intervals

A reference table for BP values after two weeks of age in infants from 26 to 44 weeks has been derived after taking into consideration gestational age at birth, postconceptional age and size for gestational age. The 95$^{th}$ and 99$^{th}$ percentile values are intended to serve as reference to identify infants with persistent hypertension that may require treatment.[389] (Refer to Appendix 1)

Treatment is recommended when BP is consistently above the 99$^{th}$ percentile. There are few published case series that used diuretics, ACEI, ß-blockers and CCB.[389(Level II-2)]

There is concern over the use of ACEI in preterm neonates.[391] It has been reported to cause an exaggerated fall in BP and may impair the final stages of nephron maturation and it use is best avoided until 44 weeks postconceptional age.[389,392(Level III)]

## Hypertension in Children and Adolescents

In Malaysia, the prevalence of hypertension in primary school children in one study was 13.4%.[393]

Prevalence of hypertension in children and adolescents is increasing in tandem with the increasing prevalence of obesity in this group.[394,395]

The NHMS 2016 has shown that the prevalence of obesity among children below 5 years was 6% (Weight for Height >+2SD).[396] In 2011, the prevalence of obesity among children below 10 years was 5.3%.[397]

## Measurement of BP: Who and when[398]

1. Children ≥7 years old
    - Healthy children: Measure annually if obese
    - Children with diabetes, renal disease, aortic arch obstruction, coarctation or on medications known to increase BP: Measure at every medical encounter

2. Children <7 years who are at risk of developing hypertension

    Measure at every medical encounter for those with:
    - history of complications requiring neonatal intensive care
    - congenital heart disease
    - recurrent urinary tract infections, hematuria or proteinuria
    - known renal disease or urological malformation
    - family history of congenital renal disease
    - solid-organ transplant
    - treatment with drugs known to raise BP
    - other systemic illness associated with hypertension (neurofibromatosis, tuberous sclerosis)
    - evidence of raised intracranial pressure

Although the latest guidelines from the US Task force recommends the age cut off to be 3 years, we recommend 7 years taking into consideration the current state of resources in the primary health centre.(Level III)

## BP Measurement Technique

1. The initial BP measurement may be oscillometric.[399] (On a calibrated machine that has been validated for use in the pediatric population.)
2. If BP level >90$^{th}$ percentile on oscillometric devices, confirmatory measurement should be obtained by auscultation. Re-measure BP twice by using auscultatory technique and average these two.
3. Measurement of BP in children follows the same principles as set out in the section on BP measurement. Special attention needs to be paid in selection of an appropriate cuff size in relation to the child's right upper arm.

### SUMMARY

- **The diagnosis of hypertension in children and adolescents is made when the auscultated BP values on three repeated and different visits are greater than the 95$^{th}$ percentile for age, sex, and height of the patient, or is ≥130/90 mmHg (whichever is lower).[398]**

Height and gender are important determinants of pediatric BP. BP levels are interpreted based on gender, age and height. In the 2017 American Academy of Pediatrics guidelines, normative table were revised by using data from–normal-weight children only. **(Refer to Appendix 2 & 3)**

**TABLE 7.7-A Definitions of BP Categories, Stages, Patient Evaluation and Management (0-18 years)**

| Category | Children Aged 1-13 years | Children Aged ≥13 years | Frequency of BP measurement | Patient Management |
|---|---|---|---|---|
| **Normal** | <90th percentile | <120 / <80 mmHg | Opportunistic | Lifestyle counselling |
| **Stage 1 Hypertension** | ≥95th to <95th percentile +12 mmHg or 130/80 mmHg to 139/89 mmHg (whichever lower) | 130/80 to 139/89 mmHg | Initial<br><br>Recheck in 1-2 week Check upper & lower extremity BP<br><br>Recheck in 3 months | Lifestyle counselling<br><br>Lifestyle counselling<br><br>Diagnostic evaluation Initiate treatment Specialist referral |
| **Stage 2 Hypertension** | ≥95th percentile +12 mmHg or ≥140/90 mmHg (whichever is lower) | ≥140/90 mmHg | Initial Check upper & lower extremity BP<br><br>Recheck within 1 week | Lifestyle counselling<br><br>Diagnostic evaluation Initiate treatment Specialist referral in 1 week |

If the patient BP is symptomatic or >30 mmHg above the 95th percentile (or >180/120 mmHg in an adolescent), send to an emergency department.

Once a child is diagnosed with hypertension, he should be referred to a paediatrician for further evaluation and management.[400]

The healthcare provider should obtain a perinatal, nutritional, physical activity, psychosocial and family history and perform a physical examination to identify finding suggestive of secondary causes of hypertension.

## Primary Hypertension

Children and adolescents ≥6 years of age do not require an extensive evaluation for secondary causes of hypertension if they have a positive family history of hypertension, are overweight or obese, and/or do not have history or physical examination findings suggestive of a secondary cause of hypertension.

## Secondary Hypertension

Causes of secondary hypertension in children:

- Renal parenchymal disease and renal structure abnormality (most common)
- Renovascular disease
- Coarctation of the aorta
- Endocrine hypertension
- Drug induced (corticosteroids)

## Screening test and relevant population

1. Routine investigations to be performed in all patients
   - Urinalysis
   - Chemistry panel (electrolytes, urea, and creatinine)
   - Lipid profile
   - Renal ultrasonography in those <6 years of age or those with abnormal urinalysis or renal function

2. Investigations to assess comorbidities (the obese child)
   - Fasting blood sugar
   - Haemoglobin A1c
   - AST, ALT

3. Optional tests to be obtained on the basis of history and initial study

## Isolated Office Hypertension

A patient with BP levels >95$^{th}$ percentile in a doctor's office but who is normotensive outside a clinical setting has "Isolated Office Hypertension".

Ambulatory blood pressure measurement is necessary to confirm hypertension in otherwise healthy children. ABPM levels should be interpreted with appropriate paediatric normative data for children >5 years of age or height of ≥120 cm. Isolated

office hypertension is diagnosed by ABPM when the mean SBP and DBP <95th percentile and SBP and DBP load <25%.[401]

Isolated office hypertension does not require treatment but may need repeat ABPM in one- to two-year intervals to detect development of sustained hypertension.

## Treatment of Paediatric Hypertension

Goals of therapy for children with hypertension:

- To achieve a BP level that reduces the risk of target organ damage.
- To reduce risk of premature atherosclerosis and early development of cardiovascular disease.
- To reduce risk of developing adult hypertension and metabolic syndrome.[402-404]

## Goals of Therapy[398](Level III)

| | |
|---|---|
| Children and adolescents with hypertension | BP (Systolic and Diastolic) to <90th percentile and <130/80 mmHg in adolescents ≥13 years old |
| Children and adolescents with both chronic kidney disease and hypertension | BP <50th percentile |

## Lifestyle and Non-Pharmacologic Treatment

Non-pharmacologic management including dietary changes, exercise and weight reduction (if obese) is recommended in all children with hypertension.[398]

## Pharmacologic Treatment

Definite indications for initiating pharmacotherapy include:[398]

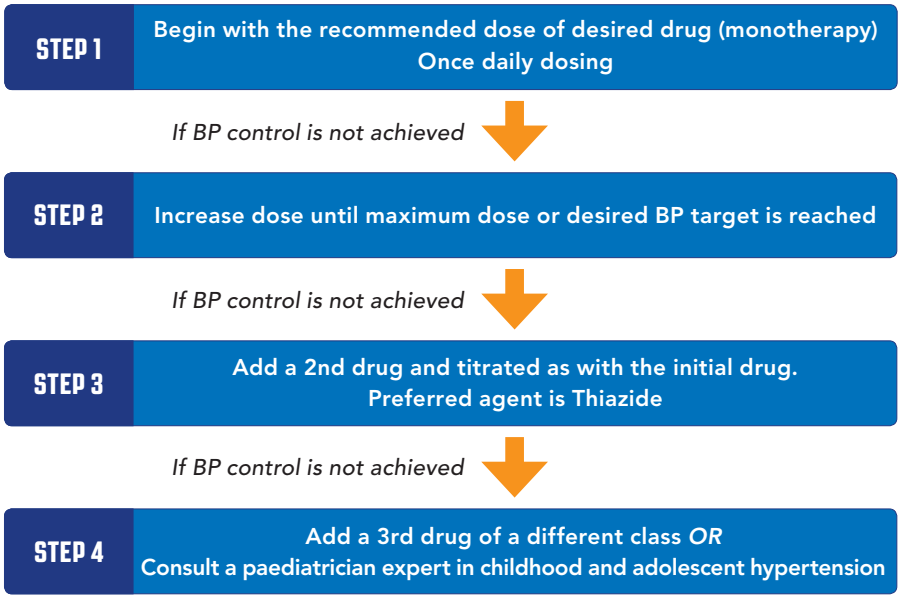
- hypertension with failed lifestyle modification
- stage 2 hypertension without a clearly modifiable factor (e.g. obesity)
- any stage of hypertension associated with chronic kidney disease or diabetes mellitus
- hypertension with target organ damage

Clinicians should initiate pharmacologic treatment with an ACEI, ARB, long-acting calcium channel blocker, or thiazide diuretic.

## Stepped Care Approach

An individualised stepped care approach to the use of anti-hypertensive drugs has been recommended by the Management of High Blood Pressure in Children Clinical Practice Guideline.[398]

**Stepped care approach:**




**Appendix 4** Dosing recommendations for the initial prescription of antihypertensive drugs for outpatient management of chronic hypertension in children and neonates.

## Proteinuric Chronic Kidney Diseases[398]

ACEI or ARBs are preferred in children with proteinuric CKD.

## Obese Hypertensive Children[398]

Diuretics and ß-blockers are potentially diabetogenic and hence should be avoided as initial therapy in children who are obese and hypertensive.

## RECOMMENDATIONS

- For children with risk factors: measure at every encounter.
- For obese children >7 years old: measure annually.
- Once a child is diagnosed with hypertension, he should be referred to a paediatrician for further evaluation and management.
- At the time of diagnosis of hypertension, clinician should provide advice on diet and recommend moderate to vigorous physical activity to help to reduce BP.
- Once pharmacologic therapy is initiated, BP must be reduced to <90$^{th}$ percentile (Systolic and Diastolic) and <130/80 mmHg in adolescents ≥13 years old.

# 8 Economic Impact of Hypertension

Hypertension and its sequelae results in a huge healthcare burden. It is the major risk factor for stroke, MI, HF and end-stage renal disease.[258,406-408] More than half of hypertensives are unaware and almost two thirds of patients on treatment are not controlled.[288]

The cost of treating hypertension consists of direct and indirect cost. Direct cost includes the cost of treatment (drugs, investigations, healthcare providers time and transportation) whereas indirect cost measures the income lost due to hypertension and its complications. A difficult to measure indirect cost would be the cost to society in managing patients with sequelae of hypertension (e.g. managing patients with a hypertensive bleed, hypertensive heart and renal failure).

A study in a primary care setting showed that more than half of treatment cost is driven by antihypertensive medications. This cost increases as the severity of hypertension increases.[409,410] The direct cost to the Ministry of Health for antihypertensive medication has steadily increased from RM570.3 million in 2014 to RM608.8 million in 2016.[411]

The direct and indirect cost for hypertensive complications is not available for Malaysia. A study in Malaysia showed that the estimated direct cost for complications in patients with diabetes for the outcomes of stroke, myocardial infarction and heart failure to be as high as RM12,685 per admission. The estimated cost of diabetes complication to the country annually may be as high as RM3.52 billion based on the highest estimate sensitivity analysis. It is likely that hypertension complication with its higher prevalence would cost more than this. [412]

Patients with hypertension have a significantly higher risk of developing CKD which is associated with a high socioeconomic burden. The annual cost of chronic haemodialysis was RM40,557 and peritoneal dialysis was RM38,138 per patient per year in 2009. The average cost of adult living kidney transplant was RM29,482.[413] The total estimated cost for Renal Replacement Therapy (RRT) was RM1.7 billion. Hypertension contributed to at least 20% of this cost (RM340 million).

Treating hypertension is cost effective.[414] A recent study showed that screening and treating hypertension even for primary prevention has a high health impact (equivalent to RM50,925 per QALY adjusted for purchasing parity).[415] The impact on treating hypertension for secondary prevention is expected to be even higher.

Community-based interventions such as education, screening and self-monitoring have been shown to be cost effective in preventing and controlling hypertension. These initiatives targeted health behavioural changes and medication adherence. They may even reduce the cost of complications and long-term healthcare cost.[415,416]

The vast majority of antihypertensive drugs are now off patent, making generics more affordable. For example, amlodipine became more affordable when its generic form was introduced in 2009. This was evident in the public sector as the expenditure for amlodipine dropped 10-fold, from RM85.8 million in 2008 to RM8.2 million in 2010 making hypertension treatment more cost effective.[417]

Hypertension is responsible for at least 45% and 51% of deaths from heart disease and stroke respectively.[418] A more concerted effort should be taken for the early diagnosis and better control of hypertension. This will reduce the direct and indirect cost of treating hypertension and its complications to the patients, family, society and the government as a whole.

## SUMMARY

- Treating hypertension is cost effective especially with the widespread availability of generic drugs.

## RECOMMENDATIONS

- Conduct more awareness programmes on clinical and economic benefits in prevention and early treatment of hypertension.

# 9 Types of Antihypertensive Agents

## 9.1 DIURETICS

Diuretics, specifically thiazide diuretics, have been the mainstay of hypertension treatment, alone or in combination with other anti-hypertensive agents. Diuretics work via inducing natriuresis which alter long term sodium balance, leading to reduced peripheral vascular resistance and sustained blood pressure reduction. Diuretics provide synergistic effect to almost all anti-hypertensive agents, particularly renin-angiotensin system (RAS) blockers. There were also outcome data that supported the potential cardiovascular benefits of thiazide diuretics, particularly in those with preserved renal function.[419 (Level 1)]

Thiazide diuretics are classified into thiazide (e.g. hydrochlorothiazide) and thiazide-like diuretics, e.g. chlorthalidone (CTD) and indapamide. Locally, hydrochlorothiazide (HCTZ) is the most commonly used thiazide diuretic. Most positive outcome studies used thiazide-like diuretics, i.e. chlorthalidone[5,89] and indapamide.[113] Even though there were no head to head trials comparing HCTZ and CTD, a systematic review and network meta-analyses reported superiority of CTD to HCTZ in preventing cardiovascular events. This difference might be attributed to the pleomorphic effects of CTD or to the shorter duration of action of HCTZ.[420(Level II-1)]

HCTZ is effective in the range of 12.5mg – 50mg daily dose.[421(Level II-1)] However a dose above 25mg per day is more likely to cause electrolyte and metabolic adverse effects. The major out come data for the use of thiazide-like diuretics (CTD) was from ALLHAT study.[89(Level II-1)] Chlorthalidone-based regimen was equally effective in reducing clinical outcome as lisinopril and amlodipine. In chronic kidney disease with eGFR<30ml/min/1.73m$^2$, thiazide diuretics are less effective and a switch to loop diuretics is recommended.

A recent case-control study highlighted a significant increase in the risk of skin and lip squamous cell carcinoma among thiazide diuretics users.[422,423 (Level II-2)] There was a clear dose-response effect with the highest cumulative dose of HCTZ having the highest risk. There was more than 7-fold increased risk of squamous cell carcinoma for a cumulative use of ≥200,000 mg HCTZ (equivalent to 50mg daily for a duration of more than 11 years). Even though this is an observational study, the risk is not negligible.

**TABLE 9.1-A Recommended Dosing for Diuretics**

| Diuretics | Starting Dose* | Recommended Maximum Daily Dose* |
|---|---|---|
| **Hydrochlorothiazide** | 12.5 mg od | 25 mg od |
| **Amiloride/hydrochlorothiazide 5 mg/50 mg** | 1 tablet od | 1 tablet od |
| **Indapamide SR** | 1.5 mg od | 1.5 mg od |

* Referenced from 153rd Edition, MIMS, 2018.

## 9.2 Beta-Blockers (ß-Blockers)

Beta-blockers have long been used in the treatment of hypertension. They are particularly useful in hypertensive patients with effort angina, tachyarrhythmias or previous myocardial infarction where they have been shown to reduce cardiovascular morbidity and mortality. Certain ß-blockers have been shown to be beneficial in patients with heart failure. (Table 5-C)

Beta-blockers are absolutely contraindicated in patients with uncontrolled asthma and relatively contraindicated in other forms of obstructive airways disease (including controlled bronchial asthma). It is also absolutely contraindicated in patients with severe peripheral vascular disease and heart block (2nd and 3rd degree).

They are generally well tolerated. Adverse effects reported include dyslipidaemia, masking of hypoglycaemia, and increased incidence of new onset diabetes mellitus. Despite that, a long-term follow-up of a study in newly diagnosed type 2 diabetes showed that the benefit of ß-blocker persisted and is even better than an ACEI.[424(Level II-2)] Other reported adverse events include erectile dysfunction, cold extremities and nightmares (especially for lipophilic ß-blockers), increased triglyceride levels and reduced HDL levels (especially for non-selective ß-blockers). Use of ß-blockers during pregnancy is cautioned.

In a major landmark study, an ARB was shown to be superior than ß-blocker in patients with high risk hypertension and ECG LVH[112 (Level 1)] This prompted a meta-analysis on the use of ß-blockers in the treatment of hypertension.[92] Beta-blocker therapy did not reduce the risk for first myocardial infarction compared to other drugs but was associated with a significant 16% higher risk for stroke when compared to non- ß-blocker therapy and that atenolol in particular was associated with a significant 26% increase in the risk of stroke when compared to other anti-hypertensive agents. Beta-blockers lower brachial systolic blood pressure but not the aortic pressure compared to other drugs. Heart rate is reduced but peripheral resistance is increased, thus increasing the arterial wave reflection during systole rather than diastole.[425 (Level II-1)] Similarly, another meta-analysis[94]

and a systematic review also showed that ß-blockers were associated with a significant increase in their withdrawal due to side effects.[426]

Caution is necessary in the interpretations of negative findings from earlier analysis on ß-blocker as:

- most of the studies involved atenolol (hence the comparative outcomes of other newer vasodilatating ß-blockers are not well established as there has been no comparative studies between the ß-blocker sub-classes.
- almost all the studies were carried out in the West, hence the comparative outcomes of other ethnic groups are not well established.

However, more recent meta analysis showed that ß-blocker is as effective as other drugs in improving clinical outcome.[95-98] The latest Cochrane Review[95] however indicates that as first line treatment, they are:

- inferior to CCB for total mortality outcomes.
- better than placebo for total CVD (primarily driven by decrease strokes) but no better than other classes of anti-hypertensive agents.
- better than placebo for strokes but worse than CCB and no better than other classes of anti-hypertensive agents for total coronary heart disease outcome.

It is thus reasonable for ß-blockers to be used as single first line therapy to initiate anti-hypertensive therapy for patients with hypertension especially if there are specific compelling needs for its use such as those with post-MI or heart failure. Some guidelines like The National Institute for Clinical Excellence (NICE) UK Guideline,[4] JNC VIII[90] and the ACC/AHA[1] did not recommend ß-blockers as first line anti-hypertensive agent. It is however still recommended as first line by other guidelines.[26,101] including guidelines from this region. [102,427,428]

**TABLE 9.2-A Recommended Dosing for ß-blockers**

| ß-blockers | Starting Dose* | Recommended Maximum Daily Dose* |
|---|---|---|
| **Acebutolol** | 200 mg bd | 1.2 g in divided doses |
| **Atenolol** | 50 mg od | 100 mg od |
| **Betaxolol** | 10 mg od | 20 mg/day |
| **Bisoprolol** | 5 mg od<br>CrCl <40, 2.5 mg/day | 20 mg/day |
| **Metoprolol** | 50 mg bd | 200 mg bd |
| **Nebivolol** | 5 mg od | 40 mg od |
| **Propranolol** | 40 mg bd | 320 mg bd |

* Referenced from 153rd Edition, MIMS, 2018.

## RECOMMENDATIONS

- Consider ß-blocker as single first-line anti-hypertensive agent especially when there are compelling indications for their use. (Grade A)
- Choose vasodilating over non-vasodilating ß-blockers as a preference. However there had not been extensive head-to-head comparison between ß-blockers. (Grade C)

# 9.3 Calcium Channel Blockers

Calcium channel blockers (CCBs) are a structurally and functionally heterogenous class of drug. The main mechanism of action is vasodilation, which decreases peripheral resistance. Certain subtypes of dihydropyridine (DHP) CCBs, e.g. T-type CCBs have been shown to dilate both the afferent and efferent arterioles, reduce glomerular capillary pressure and proteinuria. This may play a role in prevention of kidney damage and preservation of renal function.

In view of the effective BP lowering property and excellent safety profile, CCBs especially dihydropyridine (DHP) type have been recommended as first-line anti-hypertensive agents. A metanalysis showed that CCBs reduced stroke in hypertensive patients more than placebo and ß-blockers but were not different than ACE inhibitors and diuretics.[429] (Level 1) However, there is no evidence that dihydropyridine CCBs are superior to other antihypertensive agents in Asian populations for the treatment of hypertension in reducing cardiovascular death, major cardiovascular events, stroke, congestive heart failure, and coronary revascularisation.[430] (Level 1)

Metanalyses have shown that RAS blockers and CCBs combinations are superior to other combinations in lowering cardiovascular events, in addition to a better safety profile.[431,432] (Level 1)

**TABLE 9.3-A Recommended Dosing for CCBs**

| Dihydropridines | Starting Dose* | Recommended Maximum Daily Dose* |
|---|---|---|
| **Amlodipine** | 5 mg od | 10 mg od |
| **Felodipine** | 5 mg od | 10 mg od |
| **Isradipine** | 2.5 mg bd | 10 mg bd |
| **Lercanidipine** | 10 mg od | 20 mg od |
| **Nifedipine** | 5 mg tid | 20 mg tid |
| **Non-dihydropridines** | | |
| **Diltiazem** | 90 mg bd | 180 mg bd |
| **Diltiazem SR** | 100 mg od | 200 mg od |
| **Verapamil** | 80 mg tid | 160 mg tid |
| **Verapamil SR** | 120 mg od | 480 mg od |

* Referenced from 153rd Edition, MIMS, 2018

## 9.4 Renin-Angiotensin-System (RAS) Blockers

The RAS is implicated at all stages of the "CV continuum" that links hypertension with other risk factors and major CV events. Therefore, it represents a rational and established therapeutic target when lowering blood pressure.[433]

### 9.4.1 Ace Inhibitors (ACEIs)

ACEIs are effective antihypertensive agents which can lower cardiovascular risk, reducing mortality and morbidity in hypertensives and those at high cardiovascular risk.[245,434 (Level 1)] They are more effective in preventing coronary artery disease in patients with hypertension.[435 (Level 1)] ACEIs are generally well tolerated and do not have adverse effects on lipid and glucose metabolism. Their safety profile is good. ACEIs have also been shown to reduce mortality and morbidity in patients with congestive heart failure[436-438 (Level 1)] and in post myocardial infarction patients with reduced left ventricular ejection fraction.[439-444 (Level 1)]

In patients with established vascular disease but normal left ventricular function, ACEIs reduce mortality, myocardial infarction, stroke and new-onset congestive heart failure.[245]

In the diabetic patient, ACEIs have been shown to reduce cardiovascular mortality.[155] (Level 1) These agents prevent the onset of microalbuminuria, reduce proteinuria and retard progression of diabetic and non-diabetic renal disease.[445,446] (Level1)

Adverse effects include cough and, rarely, angioedema. In patients with renovascular disease or renal impairment, deterioration in renal function may occur. Serum creatinine and potassium should be checked before initiation and within 2 weeks after starting. If there is hyperkalemia (>5.6 mmol/L) or a persistent rise of serum creatinine of more than 30% from baseline within two months, the dose of the ACEI should be reduced or discontinued.

This class of drug may increase foetal and neonatal mortality and therefore are contraindicated in pregnancy and breast feeding. Counselling should be given to women of child bearing age before initiation of RAS blockers. Pregnant patients should seek immediate medical advice.

**TABLE 9.4-A Recommended Dosing for ACEIs**

| ACEIs | Starting Daily Dose* | Recommended Maximum Daily Dose* |
|---|---|---|
| **Captopril** | 25 mg bd | 50 mg tds |
| **Enalapril** | 10 mg od | 40 mg daily |
| **Lisinopril** | 10 mg od | 80 mg daily |
| **Perindopril** | 4 mg (as erbumine) or<br>5 mg (as arginine) od | 8 mg (as erbumine) or<br>10 mg (as arginine) od |
| **Ramipril** | 2.5 mg od | 10 mg daily |
| **Imidapril** | 5 mg od | 20 mg daily |

* Referenced from 153rd Edition, MIMS, 2018.

## Combination Therapy with ACEI

The combination of an ACEI and a dihydropyridine CCB is preferred over the combination of an ACEI and a thiazide diuretic in patients with hypertension and high CV risk.[84] (Level 1)

## 9.4.2 Angiotensin Receptor Blockers (ARBs)

ARBs are drugs which specifically block angiotensin II receptors. Unlike ACEIs, persistent dry cough is less and as such ARBs are recommended for risk reduction in ACEI intolerant patients.[447,448(Level 1)]

ARBs are effective in preventing progression of diabetic nephropathy[145,449(Level 1)] and may reduce the incidence of major cardiac events in patients with heart failure,[450,451 (Level 1)] hypertensive LVH[452 (Level 1)] and diastolic heart failure.[213 (Level 1)] In patients with LV dysfunction post MI, ARBs have also been shown to be non-inferior to ACEIs.[453 (Level 1)]

The cardioprotective effects of ARBs when compared to ACEIs especially for prevention of myocardial infarction, CV and all cause mortality were recently called into question.[454(Level 1)] An earlier large meta-analysis of ARBs showed that although it did not increase the risk of myocardial infarction compared to placebo or active control, unlike ACEIs, it seem not to have special cardio protective effects.[455 (Level 1)] A more recent meta-analysis however concluded that that ARBs do reduce CV events including the risk of myocardial infarction.[456 (Level 1)]

Despite conflicting findings from various meta analyses, it is important to look at the original studies, especially "head to head" trials on these drugs. In high risk CV patients with or without hypertension, the evidence showed that ARB is non-inferior to ACEI for CV protection.[457 (Level 1)] However in patients with left ventricular dysfunction, ACEI have more evidence including reducing mortality and ARB is used for ACEI intolerant patients.[451,458(Level 1)] As for diabetics patients with or without hypertension, ACEI improves CV outcome including total mortality especially in combination with thiazide-like diuretics.[83 (Level)] The same is true for non-diabetic nephropathy[178(Level 1)] and type 1 diabetes mellitus with nephropathy.[140,141(Level 1)] However for type 2 diabetic nephropathy, both ACEI[155(Level 1)] and ARB[144-146(Level 1)] improve renal outcome although only ACEI has the added advantage in improving CV and renal outcomes. In hypertensives with ECG left ventricular hypertrophy, CV protection (especially stroke reduction) have been demonstrated with ARB.[112 (Level 1)] On the other hand for secondary stroke prevention, the evidence favour ACEI especially in combination with thiazide-like diuretics.[79(Level 1)] Table 9.4-C summarises the available evidence on the therapeutics of RAS blockers in patients with various comorbidities.

**TABLE 9.4-B Recommended Dosing for ARBs**

| ARBs | Starting Dose* | Recommended Maximum Daily Dose* |
|---|---|---|
| **Candesartan** | 8 mg od | 32 mg od |
| **Irbesartan** | 150 mg od | 300 mg od |
| **Losartan** | 50 mg od | 100 mg od |
| **Telmisartan** | 40 mg od | 80 mg od |
| **Valsartan** | 80 mg od | 320 mg od |
| **Olmesartan** | 20 mg od | 40 mg od |

* Referenced from 153rd Edition, MIMS, 2018.

The safety profile of ARB is very similar to ACEI except for a lower incidence of cough.

## Combination of ACEI and ARB

The combination of ACEI and ARB is not recommended and is to be avoided.

**TABLE 9.4-C RAS Blockers Use in Co-Morbidities** [116,133,136,137,140-147,459,460]

| Condition | ACEIs | ARBs |
|---|---|---|
| **Diabetes mellitus** *(CV protection)* | Preferred | If ACEI intolerant |
| **Diabetes mellitus (eGFR>60) + proteinuria** *(Renal protection)* | Either | Either |
| **Diabetes mellitus type 1 (eGFR <60) +/- proteinuria** *(Renal protection)* | Preferred | If ACEI intolerant |
| **Diabetes mellitus type 2 (eGFR <60) +/- proteinuria** *(Renal protection)* | Either | Either |
| **Non-diabetic proteinuria/renal impairment** | Preferred | If ACEI intolerant |
| **Heart failure (HFrEF)** | Preferred | If ACEI intolerant |
| **Stroke** | Preferred | If ACEI intolerant |
| **Coronary heart disease High CV risk patients** | Either | Either |
| **Coronary heart disease Post MI** | Preferred | If ACEI intolerant |
| **Left ventricular hypertrophy** | | Preferred |

# 9.5 Miscellaneous Drugs

## 9.5.1 The ∂-Blockers and the Combined ∂, ß-Blockers

The peripheral ∂1-adrenergic blockers lower BP by reducing peripheral resistance. They also reduce prostatic and urethral smooth muscle tone and provide symptomatic relief for patients with early benign prostatic hyperplasia (BPH).[461] Unless there are other compelling reasons, they should be the treatment of choice for hypertensive patients with BPH. The use of non-specific ∂-blockers like phentolamine and phenoxybenzamine has been restricted to the treatment of phaechromocytoma.

In addition, ∂-blockers have favourable effects on lipid metabolism. However postural hypotension is a known side effect, especially at initiation of therapy.[462,463] They should be used with care in the elderly.

Combined ∂ and ß-blockers offer enhanced neurohormonal blockade. Labetalol has been in use for over 20 years and is safe in pregnancy **(Refer to chapter 7.6 on Hypertension in Pregnancy)**. The intravenous formulation is useful in hypertensive emergencies, including pre-eclampsia and eclampsia.[464]

Carvedilol has been shown to be effective in hypertension and also to improve mortality and morbidity in patients with heart failure.[465-467 (Level 1)] In addition, it has no adverse effects on insulin resistance and lipid metabolism.[468] However, its safety in pregnancy has not been established.

**TABLE 9.5-A Recommended Dosing for ∂-blockers**

| ∂-blockers | Starting Dose* | Recommended Maximum Daily Dose* |
|---|---|---|
| **Doxazosin** | 1 mg od | 16 mg od |
| **Prazosin** | 0.5 mg bd-tds | 20 mg in divided doses |
| **Terazosin** | 1 mg nocte | 20 mg od |

* Referenced from 153rd Edition, MIMS, 2018.

**Table 9.5-B Recommended Dosing for ∂, ß-blockers**

| ∂, ß-blockers | Starting Dose* | Maximum Dose* |
|---|---|---|
| **Labetolol **** | 100 mg bd | 2.4 gm per day in 2-4 divided doses |
| **Carvedilol ***** | 12.5 mg od | 50 mg od or in divided doses if necessary |

* Referenced from 153rd Edition, MIMS, 2018.
** In the elderly start with 50 mg bd.
*** The dosage of carvedilol for patients with heart failure and angina pectoris is different from the doses indicated.

## 9.5.2 Centrally Acting Agents

The centrally acting agents available in this country are alpha-methyldopa, clonidine and moxonidine. The common side effects of the centrally acting agents include drowsiness, dry mouth, headache, dizziness and mood change. Moxonidine is less likely to cause these reactions. The side-effects may decrease after a few weeks of continued treatment. In general, treatment should begin with the lowest possible dose to minimise the side-effects.

Alpha-methyldopa has been in use for many years. It is the drug of choice for hypertension in pregnancy. It may be considered for resistant hypertension in combination with other classes of anti-hypertensive agents.[469]

Clonidine should **NOT** be withdrawn suddenly because rebound hypertension may occur.[470] The use of clonidine is discouraged because safer and more potent drugs are available.

Moxonidine is an orally administered imidazoline compound with selective agonist activity at imidazoline II receptors. It can be used as monotherapy in patients with mild to moderate hypertension or in combination with other anti-hypertensive agents. Studies have suggested that it may improve the metabolic profile of patients with impaired glucose tolerance or diabetes. Rebound hypertension on cessation of the drug is less likely compared to clonidine but abrupt withdrawal is not recommended. It has been shown to increase mortality in patients with heart failure and is therefore contraindicated in patients with heart failure or at risk of heart failure.[471]

**TABLE 9.5-C Recommended Dosing for Centrally Acting Agents**

| Drug | Starting dose | Maximum dose |
|---|---|---|
| **∂-methyldopa*** | 250 mg bd-tds | 3000 mg daily |
| **Clonidine** | 50 mcg tds | 2400 mcg daily |
| **Moxonidine**** | • 200 mcg od<br>• To be avoided if GFR <30 | • 600 mcg in 2 divided doses<br>• 400 mcg daily (GFR 30–60)<br>• To be avoided if GFR <30 |

* For dosage in pregnancy, refer to chapter 7.6 on Hypertension in Pregnancy.
** Referenced from 153rd Edition, MIMS, 2018.

## 9.5.3 Direct Vasodilators

The only direct vasodilators available in Malaysia are hydralazine and minoxidil. Hydralazine is only available in parenteral formulation for hypertensive emergencies. Minoxidil may be considered for refractory hypertension. The usefulness of this class of drugs is limited by their side-effects, including headache, compensatory tachycardia, salt and water retention. Hirsutism is a troublesome side-effect with long-term use of minoxidil. These drugs should only be prescribed by physicians familiar with their usage.

**TABLE 9.5-D Recommended Dosing for Minoxidil**

| Drug | Starting Dose | Maximum dose |
|---|---|---|
| **Minoxidil*** | 5 mg per day | 100 mg per day |

* Referenced from 153rd Edition, MIMS, 2018.

## 9.5.4 Drugs In Development

As the pathophysiology of hypertension becomes clearer, compounds are being developed to interrupt the pathways leading to an elevated blood pressure and to normalise it.

Among the compounds being tested are:

1. Those targeting aldosterone (anti-aldosterone agents). The strategy is to either block aldosterone production (aldosterone synthase inhibitors) or to block its receptor (mineralocorticoid receptor antagonists).

   The prototypes of mineralocorticoid receptor antagonists would be spironolactone and eplerenone. Finerenone is the latest in this class and is currently undergoing phase III trials, not only for hypertension but also for diabetic nephropathy and heart failure. Because it has low affinity for steroid receptors, there is a lower incidence of gynaecomastia, erectile dysfunction, and reduced libido.
2. Those targeting the classical RAS. These would include angiotensin converting enzyme 2 activators, angiotensin type 2 receptor agonists and vaccines against the angiotensin type 1 and type 2 receptors.
3. Centrally acting aminopeptidase inhibitors to inhibit excessive sympathetic outflow from the brain.
4. Vasopeptidase inhibitors which degrade natriuretic peptides.
5. Dual-acting angiotensin receptor–neprilysin Inhibitors. The combination of valsartan and sacubitril is already in clinical use. However this combination has found its niche in the management of heart failure rather than hypertension.

6. Dual-Acting Endothelin Converting Enzyme–Neprilysin Inhibitors
7. Natriuretic Peptide Receptor Agonists
8. Vasoactive Intestinal Peptide Receptor Agonist
9. Intestinal Na+/H+ Exchanger 3 Inhibitor
10. Dopamine ß-hydroxylase (DßH) Inhibitor

**TABLE 9.5-E New Drugs for Hypertension (adapted from Oparil S. and Schmieder RE. 2015)[472]**

| Drug | Mechanism of action | Status |
|---|---|---|
| **BAY 94–8862 (finerenone)** | Mineralocorticoid receptor antagonist | Phase III |
| **LCZ696** | Dual-acting angiotensin receptor-neprilysin inhibitor | Phase III |
| **SLV-306 (Daglutril)** | Dual acting endothelin-converting enzymes-neprilysin inhibitor | Phase II |
| **PL-3994** | Natriuretic peptide A agonist | Phase II |
| **Vasomera (PB1046)** | Vasoactive intestinal peptide receptor 2 (VPAC2) agonist | Phase II |
| **Vaccines CYT006-AngQß** | Vaccine against angiotensin II | Phase II |
| **Preeclampsia drugs DIF** | Anti-digoxin antibody fragment | Phase II expedited |
| **ATryn** | Recombinant antithrombin | Phase III |

DIF = Digoxin-immune Fab.

# 9.6 Traditional Herbal Medicine and Hypertension

## 9.6.1 Traditional Medicine for Hypertension

In 2000, the WHO in a key paper, (http://who.int/medicines/areas/traditional/definitions/en/) clearly outlined the definition and scope of traditional medicine as follows:

### Traditional medicine

Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether

explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

## Complementary/alternative medicine (CAM)

The terms "complementary medicine" or "alternative medicine" are used interchangeably with traditional medicine in some countries. They refer to a broad set of health care practices that are not part of that country's own tradition and are not integrated into the dominant health care system.

## Herbal medicines

Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations.

In most countries including Malaysia, the traditional treatment of hypertension will consist of:

- oral, usually herbal medication
- various forms of relaxation exercises, including yoga and qigong

## Herbs used in hypertension

There are few publications in the English literature on the treatment of hypertension with herbs. The most quoted is by Tabassum and Ahmad[473], the "Role of Natural Herbs in the Treatment of Hypertension". They comprehensively describe almost 50 herbal remedies for hypertension, including garlic, ginger, roselle, black plum, mistletoe, wheat bran, cocoa, wild tomato, sesame, radish, pomegranate, basil, cork wood, tomato, linseed, flaxseed, black mangrove, French lavender, pima cotton, soybean, carrot, swamp or river lily, Chinese hawthorn, black bean, coffee weed, tea, green oat, breadfruit, celery and prickly custard apple.

An extensive online review on Medscape[474] showed that herbal medicines for hypertension have not undergone the rigorous testing for efficacy and safety that is expected of modern drugs. None have undergone the gold standard of randomised placebo controlled trials. On top of that, there are reports that various herbal preparations (usually in capsule form) have been adulterated with modern drugs. For example, glibenclamide has been found in anti-diabetic preparations, and sildenafil has been found in compounds to increase male virility. Corticosteroids have also been added to traditional herbal medicine, with prolonged usage causing Cushing's Syndrome and hypertension. Hence, anecdotal reports on the efficacy of certain herbs cannot be relied on.

## SUMMARY

- There is no conclusive evidence that traditional medicine produces sustained reductions in BP with good clinical outcomes.

## RECOMMENDATIONS

- Traditional medicines are not recommended for the treatment of hypertension.

### 9.6.2 Relaxation Exercises for Hypertension

Since the 1970s there have been reports on the efficacy of yoga in the treatment of hypertension (SBP -17 mmHg and DBP -10 mmHg). These trials, albeit small, have been compared against a control group and are credible.[64,475,476] Qigong has also been demonstrated to lower the BP (SBP -17 mmHg and DBP -10 mmHg). But when compared against conventional exercise there was no significant difference.[477,478]

The American Heart Association,[479] in their Scientific Statement on Meditation and Cardiovascular Risk Reduction, noted that BP may be lowered but the results were variable and inconsistent.

The regimes are postulated to work by reducing excessive sympathetic outflow from the brain, and in the case of qigong, to improve blood flow to various organs in the body.

Relaxation regimes as part of a healthy living regime can be useful in the holistic management of hypertension. Yoga and qigong or any other form of relaxation exercises may usefully complement drug treatment.

## SUMMARY

- Relaxation therapy may complement non-pharmacological and pharmacological treatment of hypertension however it is not recommended as primary treatment for hypertension.

# 10 Resistant and Refractory Hypertension

## 10.1 Resistant Hypertension

Resistant hypertension is defined as uncontrolled hypertension (>140/90 mmHg) with good medication adherence while on three[26,480] or four anti-hypertensive agents (including a diuretic) in adequate doses. In a study of a primary care center involving 1,217 hypertensives in Malaysia, the prevalence of resistant hypertension (as defined above) was reported to be 8.8%.[481] Similar prevalence was observed in national surveys in the United States (National Health and Nutritional Examination Survey from 2003-2008), the estimated prevalence was 8.9%.[482] It is however worth noting that the prevalence may be an overestimate if white coat resistance is excluded. Ambulatory Blood Pressure Monitoring studies on treatment resistant patients have demonstrated that between 30-35% of patients have pseudo resistant or office resistant hypertension.[483] This is consistent with a study from a tertiary center in Malaysia.[484]

**Before labeling a patient as having resistant hypertension, it is important that the practitioner ascertain that:**

a. the patient adheres to medication (by definition at least 80%)
b. the blood pressure is measured appropriately
c. the patient does not have 'office resistant hypertension'
d. an appropriate combination and dosage of drugs is prescribed, namely 3 drugs including a RAS blocker, a CCB and a diuretic
e. the patient is not taking any substances which may antagonise the hypertensive effects of the drugs taken (e.g. NSAID, sympathomimetics, liquorice, oral contraceptives, corticosteroids)

It is therefore important that a thorough review of the patient's history, physical examination and investigations be done including estimation of renal function glomerular filtration rate (eGFR). A home or ambulatory blood pressure measurement should be done to exclude isolated office hypertension. (Refer to chapter 2 on Measurement of Blood Pressure).

Once a patient is confirmed to have true resistant hypertension, consider referral for exclusion of secondary causes (Refer to chapter 3 on Diagnosis and Initial Assessment).

## Excluding Secondary Hypertension

Although the prevalence of secondary hypertension is around 5%, its prevalence is higher in patients with resistant hypertension. Depending on series, prevalence of secondary hypertension among patients with resistant hypertension can be as high as 66%, with obstructive sleep apnoea, accounting for most of it.[485,486] In two large series, primary aldosteronism was diagnosed in 11% of patients with resistant hypertension.[487,488] Subsequent investigations arranged should be guided by symptoms present, examination findings elicited and results from preliminary investigations. It is prudent that any investigations to be ordered or arranged must be rational with cost effectiveness in mind.

## Treatment options in resistant primary hypertension

**a. Non-pharmacological Management**

Non-pharmacological approaches (healthy living) must be re-emphasised. (Refer to chapter 4 on Non-Pharmacological Management)

**b. Pharmacological Management**

A fourth drug should be added to the combination of RAS blocker, CCB and diuretic. Two recent metaanalyses of randomised and non-randomised controlled trials showed that spironolactone is superior to active controls (which includes alpha blockers, ß-blockers, candesartan, frusemide or alpha methyldopa) in reducing office, home and ambulatory blood pressures.[489,490 (Level 1)] These meta analyses of disparate studies was strengthened by a multicenter randomised controlled double blind trial which confirmed that spironolactone is the drug of choice as the fourth drug in resistant hypertension.[491 (Level 1)]

## 10.2 Refractory Hypertension

The definition has been proposed to be used on patients whose BP are not controlled after ≥5 antihypertensives.[492]

If blood pressures are still not controlled with four drugs, a fifth drug may be considered. Subsequent therapeutic options include a ß-blocker, an alpha blocker or a centrally acting drug. The prevalence of refractory hypertension among patients referred to a specialty clinic for resistant hypertension was reported to be 2.7%[489] in one series and 9.5% in another.[493]

Both resistant and refractory hypertensives are candidates for devise-based intervention.

### RECOMMENDATIONS

- Treat patients with at least 3 drugs (inclusive of a diuretic) before diagnosing resistant hypertension. (Grade C)
- Consider drug non-adherence and secondary hypertension before diagnosing resistant hypertension. (Grade C)
- Add spironolactone as a fourth drug in resistant hypertension. (Grade A)
- Consider referring for device based therapy in patients with true resistant and refractory hypertension. (Grade C)

# 11 Aspirin in Hypertension

Although the benefits of aspirin in secondary CV prevention is incontrovertible, that for primary prevention remains controversial.[494] A large meta analysis suggested that for primary prevention, the risk of significant bleeding outweigh the benefits of CV protection.[495] In patients with hypertension a large RCT showed that low dose aspirin (75 mg daily) reduced major CV events especially for MI but had no effect on the incidence of stroke. Non-fatal major bleeds were however twice as common with aspirin.[299] Subgroup analysis of this large trial showed that patients who benefited most are those with well treated hypertensive at higher baseline CV risk or higher baseline BP. [299] The benefits of low dose aspirin were also most convincing in patients with well controlled BP and moderate rise in serum creatinine (>114 umol/L).[496]

A recent large cohort study in Asia showed that aspirin given to uncomplicated hypertensive patients for primary prevention significantly reduced all cause and cardiovascular mortality.[497] However, since it is associated with an increased risk of major bleed, careful evaluation of risk/benefit analysis must be made by the doctor before initiating aspirin.

## RECOMMENDATIONS

- Consider using aspirin in patients with higher baseline BP. (Grade B)
- Treat patients BP to target first before initiating aspirin therapy. (Grade A)

# 12 Device and Procedure Based Therapy in Hypertension

One of the potential approaches in treating true resistant hypertension and severe newly diagnosed hypertension is device therapy. This includes renal denervation therapy (RDN) and carotid sinus stimulation. In these patients, blood pressure rise is initiated and sustained by sympathetic over activation[498] and BP reduction can result from its inhibition.[499,500]

Renal denervation therapy gained popularity following early blood pressure reduction result seen in patients with resistant hypertension on medical therapy in the SIMPLICITY HTN-1 and 2 trials. However, the 24-hour ambulatory blood pressure was not significantly reduced. SIMPLICITY HTN-3, which had a sham control arm showed a neutral result suggesting a lack of benefit with the single electrode radiofrequency catheter.[501(Level 1)]

Since 2014, several sham controlled randomised trials employing variations in improved techniques (multi-electrode catheter, ultrasound and alcohol based denervation) have been initiated. The recently published SPYRAL HTN-OFF MED examined the effect of RDN in 80 newly diagnosed hypertensive patients. They included patients with SBP of 150-180 mmHg without any anti-hypertensive medications and found a significant reduction (-5.5 mmHg for SBP) when compared to sham control at 3 months follow up.[502(Level II-1)] This may suggest a potential for this intervention in newly diagnosed hypertensives. Further confirmatory results from other trials are awaited to confirm the clinical indication for multi-electrode RDN for newly diagnosed hypertension.[503]

Baroreceptor activation therapy (BAT) is based on sympathetic inhibition by carotid sinus stimulation. The arterial stretch baroreceptors respond with a higher discharge rate, to lower blood pressure, in the setting of rising blood pressure. In chronic hypertension, this firing is blunted, rendering it less sensitive to respond to changes in blood pressure.[504] Carotid stimulation via surgical implantation of electrodes onto the carotid bulbs have resulted in lowering the blood pressure.[505] This invasive procedure is still limited by technical, safety issues and cost.

Clinical development in this area should be accompanied by investigations identifying predictors for good treatment response. Device based therapy should not be part of routine medical care until further evidence is available.[472,506]

# 13 Suggested Areas of Research

This latest CPG on hypertension has incorporated key references from research done in Malaysia. It is also heartening to know that several multicentre international trials cited in this CPG also had Malaysia as one of the centers involved. There are however a few unanswered question unique to Malaysia which needed to be addressed in future CPGs. It is suggested that Malaysian researchers should focus on these research areas and funding authorities should give due importance to these areas of research.

## Epidemiology

- Burden of disease in lower income group and association with BP
- Prevalence of hypertension in children and adolescents
- Cost effectiveness of hypertension treatment
- Health system research in hypertension

## Drugs

- Differences in antihypertensive drug response among different ethnic groups

## Monitoring

- Blood pressure goal for patients with hypertension with different co morbidities
- Intervention thresholds for people aged under 40 with hypertension
- Methods of assessing cardiovascular risk in people aged under 40 years with hypertension
- Barriers to good BP control in community
- Acceptability of ambulatory and home blood pressure monitoring
- Psychological impact of home blood pressure monitoring

## Treatment

- Precision medicine and hypertension
- Should white coat hypertension be treated?
- New drug for resistant hypertension
- What are the reasons for treatment inertia among doctors?
- Randomised Control Trial comparing reduced sodium intake with usual diet on efficacy of blood pressure lowering
- Patient empowerment in blood pressure management

## Complications

- Sleep apnea, obesity and hypertension
- Reasons for higher rate of haemorrhagic stroke in Asian compared to Caucasian

## Risk Factors

- Hypertension and Dementia – link and prevention
- Use of Information and Communication Technology and blood pressure
- Risk factors of hypertension in younger age group
- Effects of environmental pollution on blood pressure

## Pregnancy

- Screening and management of hypertension in early pregnancy
- Prevalence of preeclampsia and its outcome
- Risk of mortality in preeclampsia
- What level of proteinuria is considered significant in women with hypertension and its correlation with outcome?
- Is there a difference in maternal and fetal outcomes in using mercury sphygmomanometer vs automated device for BP measurement?
- Home Blood Pressure Monitoring in pregnancy

# Appendices

## APPENDIX 1 Estimated BP Values After 2 Weeks of Age in Infants from 26 to 44 Weeks Postconceptual Age

| Postconceptual age | 50th percentile | 95th percentile | 99th percentile |
|---|---|---|---|
| **44 Weeks** | | | |
| SBP | 88 | 105 | 110 |
| DBP | 50 | 68 | 73 |
| **MAP** | **63** | **80** | **85** |
| **42 Weeks** | | | |
| SBP | 85 | 98 | 102 |
| DBP | 50 | 65 | 70 |
| **MAP** | **62** | **76** | **81** |
| **40 Weeks** | | | |
| SBP | 80 | 95 | 100 |
| DBP | 50 | 65 | 70 |
| **MAP** | **60** | **75** | **80** |
| **38 Weeks** | | | |
| SBP | 77 | 92 | 97 |
| DBP | 50 | 65 | 70 |
| **MAP** | **59** | **74** | **79** |
| **36 weeks** | | | |
| SBP | 72 | 87 | 92 |
| DBP | 50 | 65 | 70 |
| **MAP** | **57** | **72** | **71** |
| **34 Weeks** | | | |
| SBP | 70 | 85 | 90 |
| DBP | 40 | 55 | 60 |
| **MAP** | **50** | **65** | **70** |
| **32 Weeks** | | | |
| SBP | 68 | 83 | 88 |
| DBP | 40 | 55 | 60 |
| **MAP** | **48** | **62** | **69** |
| **30 Weeks** | | | |
| SBP | 65 | 80 | 85 |
| DBP | 40 | 55 | 60 |
| **MAP** | **48** | **65** | **68** |
| **28 Weeks** | | | |
| SBP | 60 | 75 | 80 |
| DBP | 38 | 50 | 54 |
| **MAP** | **45** | **58** | **63** |
| **26 Weeks** | | | |
| SBP | 55 | 72 | 77 |
| DBP | 30 | 50 | 56 |
| **MAP** | **38** | **57** | **63** |

## APPENDIX 2 Blood Pressure Levels for Boys by Age and Height Percentile

| Age year | BP Percentile | Systolic BP (mmHg) | | | | | | | Diastolic BP (mmHg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile | | | | | | | Height Percentile | | | | | | |
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 85 | 85 | 86 | 86 | 87 | 88 | 88 | 40 | 40 | 40 | 41 | 41 | 42 | 42 |
| | 90th | 98 | 99 | 99 | 100 | 100 | 101 | 101 | 52 | 52 | 53 | 53 | 54 | 54 | 54 |
| | 95th | 102 | 102 | 103 | 103 | 104 | 105 | 105 | 54 | 54 | 55 | 55 | 56 | 57 | 57 |
| 2 | 50th | 87 | 87 | 88 | 89 | 89 | 90 | 91 | 43 | 43 | 44 | 44 | 45 | 46 | 46 |
| | 90th | 100 | 100 | 101 | 102 | 103 | 103 | 104 | 55 | 55 | 56 | 56 | 57 | 58 | 58 |
| | 95th | 104 | 105 | 105 | 106 | 107 | 107 | 108 | 57 | 58 | 58 | 59 | 60 | 61 | 61 |
| 3 | 50th | 88 | 89 | 89 | 90 | 91 | 92 | 92 | 45 | 46 | 46 | 47 | 48 | 49 | 49 |
| | 90th | 101 | 102 | 102 | 103 | 104 | 105 | 105 | 58 | 58 | 59 | 59 | 60 | 61 | 61 |
| | 95th | 106 | 106 | 107 | 107 | 108 | 109 | 109 | 60 | 61 | 61 | 62 | 63 | 64 | 64 |
| 4 | 50th | 90 | 90 | 91 | 92 | 93 | 94 | 94 | 48 | 49 | 49 | 50 | 51 | 52 | 52 |
| | 90th | 102 | 103 | 104 | 105 | 105 | 106 | 107 | 60 | 61 | 62 | 62 | 63 | 64 | 64 |
| | 95th | 107 | 107 | 108 | 108 | 109 | 110 | 110 | 63 | 64 | 65 | 66 | 67 | 67 | 68 |
| 5 | 50th | 91 | 92 | 93 | 94 | 95 | 96 | 96 | 51 | 51 | 52 | 53 | 54 | 55 | 55 |
| | 90th | 103 | 104 | 105 | 106 | 107 | 108 | 108 | 63 | 64 | 65 | 65 | 66 | 67 | 67 |
| | 95th | 107 | 108 | 109 | 109 | 110 | 111 | 112 | 66 | 67 | 68 | 69 | 70 | 70 | 71 |
| 6 | 50th | 93 | 93 | 94 | 95 | 96 | 97 | 98 | 54 | 54 | 55 | 56 | 57 | 57 | 58 |
| | 90th | 105 | 105 | 106 | 107 | 109 | 110 | 110 | 66 | 66 | 67 | 68 | 68 | 69 | 69 |
| | 95th | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| 7 | 50th | 94 | 94 | 95 | 97 | 98 | 98 | 99 | 56 | 56 | 57 | 58 | 58 | 59 | 59 |
| | 90th | 106 | 107 | 108 | 109 | 110 | 111 | 111 | 68 | 68 | 69 | 70 | 70 | 71 | 71 |
| | 95th | 110 | 110 | 111 | 112 | 114 | 115 | 116 | 71 | 71 | 72 | 73 | 73 | 74 | 74 |
| 8 | 50th | 95 | 96 | 97 | 98 | 99 | 99 | 100 | 57 | 57 | 58 | 59 | 59 | 60 | 60 |
| | 90th | 107 | 112 | 114 | 116 | 118 | 119 | 120 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th | 111 | 112 | 112 | 114 | 115 | 116 | 117 | 72 | 73 | 73 | 74 | 75 | 75 | 75 |
| 9 | 50th | 96 | 97 | 98 | 99 | 100 | 101 | 101 | 57 | 58 | 59 | 60 | 61 | 62 | 62 |
| | 90th | 107 | 108 | 109 | 110 | 112 | 113 | 114 | 70 | 71 | 72 | 73 | 74 | 74 | 74 |
| | 95th | 112 | 112 | 113 | 115 | 116 | 118 | 119 | 74 | 74 | 75 | 76 | 76 | 77 | 77 |
| 10 | 50th | 97 | 98 | 99 | 100 | 101 | 102 | 103 | 59 | 60 | 61 | 62 | 63 | 63 | 64 |
| | 90th | 108 | 109 | 111 | 112 | 113 | 115 | 116 | 72 | 73 | 74 | 74 | 75 | 75 | 76 |
| | 95th | 112 | 113 | 114 | 116 | 118 | 120 | 121 | 76 | 76 | 77 | 77 | 78 | 78 | 78 |
| 11 | 50th | 99 | 99 | 101 | 102 | 103 | 104 | 106 | 61 | 61 | 62 | 63 | 63 | 63 | 63 |
| | 90th | 110 | 111 | 112 | 114 | 116 | 117 | 118 | 74 | 74 | 75 | 75 | 75 | 76 | 76 |
| | 95th | 114 | 114 | 116 | 118 | 120 | 123 | 124 | 77 | 78 | 78 | 78 | 78 | 78 | 78 |
| 12 | 50th | 101 | 101 | 102 | 104 | 106 | 108 | 109 | 61 | 62 | 62 | 62 | 63 | 63 | 63 |
| | 90th | 113 | 114 | 115 | 117 | 119 | 121 | 122 | 75 | 75 | 75 | 75 | 75 | 76 | 76 |
| | 95th | 116 | 117 | 118 | 121 | 124 | 126 | 128 | 78 | 78 | 78 | 78 | 78 | 79 | 79 |

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## APPENDIX 3 Blood Pressure Levels for Girls by Age and Height Percentile

| Age year | BP Percentile | Systolic BP (mmHg) | | | | | | | Diastolic BP (mmHg) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Height Percentile | | | | | | | Height Percentile | | | | | | |
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 50th | 84 | 85 | 86 | 86 | 87 | 88 | 88 | 41 | 42 | 42 | 43 | 44 | 45 | 46 |
| | 90th | 98 | 99 | 99 | 100 | 101 | 102 | 102 | 54 | 55 | 56 | 56 | 57 | 58 | 58 |
| | 95th | 101 | 102 | 102 | 103 | 104 | 105 | 105 | 59 | 59 | 60 | 60 | 61 | 62 | 62 |
| 2 | 50th | 87 | 87 | 88 | 89 | 90 | 91 | 91 | 45 | 46 | 47 | 48 | 49 | 50 | 51 |
| | 90th | 101 | 101 | 102 | 103 | 104 | 105 | 106 | 58 | 58 | 59 | 60 | 61 | 62 | 62 |
| | 95th | 104 | 105 | 106 | 106 | 107 | 108 | 109 | 62 | 63 | 63 | 64 | 65 | 66 | 66 |
| 3 | 50th | 88 | 89 | 89 | 90 | 91 | 92 | 93 | 48 | 48 | 49 | 50 | 51 | 53 | 53 |
| | 90th | 102 | 103 | 104 | 104 | 105 | 106 | 107 | 60 | 61 | 61 | 62 | 63 | 64 | 65 |
| | 95th | 106 | 106 | 107 | 108 | 109 | 110 | 110 | 64 | 65 | 65 | 66 | 67 | 68 | 69 |
| 4 | 50th | 89 | 90 | 91 | 92 | 93 | 94 | 94 | 50 | 51 | 51 | 53 | 54 | 55 | 55 |
| | 90th | 103 | 104 | 105 | 106 | 107 | 108 | 108 | 62 | 63 | 64 | 65 | 66 | 67 | 67 |
| | 95th | 107 | 108 | 109 | 109 | 110 | 111 | 112 | 66 | 67 | 68 | 69 | 70 | 70 | 71 |
| 5 | 50th | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 52 | 52 | 53 | 55 | 56 | 57 | 57 |
| | 90th | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 64 | 65 | 66 | 67 | 68 | 69 | 70 |
| | 95th | 108 | 109 | 109 | 110 | 111 | 112 | 113 | 68 | 69 | 70 | 71 | 72 | 73 | 73 |
| 6 | 50th | 92 | 92 | 93 | 94 | 96 | 97 | 97 | 54 | 54 | 55 | 56 | 57 | 58 | 59 |
| | 90th | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 67 | 67 | 68 | 69 | 70 | 71 | 71 |
| | 95th | 109 | 109 | 110 | 111 | 112 | 113 | 114 | 70 | 71 | 72 | 72 | 73 | 74 | 74 |
| 7 | 50th | 92 | 93 | 94 | 95 | 97 | 98 | 99 | 55 | 56 | 56 | 57 | 58 | 59 | 60 |
| | 90th | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 68 | 68 | 69 | 70 | 71 | 72 | 72 |
| | 95th | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 72 | 72 | 73 | 73 | 74 | 74 | 75 |
| 8 | 50th | 93 | 94 | 95 | 97 | 98 | 99 | 100 | 56 | 56 | 57 | 59 | 60 | 61 | 61 |
| | 90th | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 69 | 70 | 71 | 72 | 72 | 73 | 73 |
| | 95th | 110 | 111 | 112 | 113 | 115 | 116 | 117 | 72 | 73 | 74 | 74 | 75 | 75 | 75 |
| 9 | 50th | 96 | 95 | 97 | 98 | 99 | 100 | 101 | 57 | 58 | 59 | 60 | 60 | 61 | 61 |
| | 90th | 108 | 108 | 109 | 111 | 112 | 113 | 114 | 71 | 71 | 72 | 73 | 73 | 73 | 73 |
| | 95th | 112 | 112 | 113 | 114 | 116 | 117 | 118 | 74 | 74 | 75 | 75 | 75 | 75 | 75 |
| 10 | 50th | 96 | 97 | 98 | 99 | 101 | 102 | 103 | 58 | 59 | 59 | 60 | 61 | 61 | 62 |
| | 90th | 109 | 110 | 111 | 112 | 113 | 115 | 116 | 72 | 73 | 73 | 73 | 73 | 73 | 73 |
| | 95th | 125 | 126 | 126 | 128 | 129 | 131 | 132 | 87 | 87 | 88 | 88 | 88 | 88 | 88 |
| 11 | 50th | 98 | 99 | 101 | 102 | 104 | 105 | 106 | 60 | 60 | 60 | 61 | 62 | 63 | 64 |
| | 90th | 111 | 112 | 113 | 113 | 116 | 118 | 120 | 74 | 74 | 74 | 74 | 74 | 75 | 75 |
| | 95th | 115 | 116 | 117 | 118 | 120 | 123 | 124 | 76 | 77 | 77 | 77 | 77 | 77 | 77 |
| 12 | 50th | 102 | 102 | 104 | 105 | 107 | 108 | 108 | 61 | 61 | 61 | 62 | 63 | 64 | 65 |
| | 90th | 114 | 115 | 116 | 118 | 120 | 122 | 122 | 75 | 75 | 75 | 75 | 76 | 76 | 76 |
| | 95th | 118 | 119 | 120 | 122 | 124 | 125 | 126 | 78 | 78 | 78 | 78 | 79 | 79 | 79 |

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## APPENDIX 4 Dosing Recommendation for the Initial Prescription of Antihypertensive Drugs for Outpatient Management of Chronic Hypertension in Children and Neonates [398,405]

| Drugs | Doses | Frequency |
|---|---|---|
| **Angiotensin-Converting Enzyme Inhibitors *** | | |
| **Captopril **** | 0.3 mg/kg/dose (Max 6 mg/kg/day *or* 50 mg/day) | BD or TDS |
| **Enalapril **** | **20-50 kg:** Initially 2.5 mg/day (Max 20 mg/day)<br>**≥50 kg:** Initially 5 mg/day (Max 40 mg/day) | Once daily or BD |
| **Angiotensin-Receptor Blockers *** | | |
| **Irbesartan #** | **6-12 years:** 75 – 150 mg/day<br>**>13 years:** 150 – 300 mg/day | Once daily |
| **Losartan **** | **≥6 years;**<br>**20-50 kg:** Initially 0.7 mg/kg/day (Max 50 mg/day)<br>**>50kg:** Initially 1.4 mg/kg/day (Max 100 mg/day) | Once daily |
| **Valsartan **** | **≥6 years;**<br>**<35kg:** Initially 40 mg/day (Max 80 mg/day)<br>**35-80kg:** Initially 80 mg/day (Max 160 mg/day) | Once daily |
| **Calcium Channel Blockers** | | |
| **Amlodipine **** | **6-17 years:** Initially 2.5 mg/day (Max 5 mg/day) | Once daily |
| **Nifedipine (Immediate release) ***** | **1 month - 11 years:** 0.2-0.3 mg/kg/day<br>(Max 3 mg/kg/day *or* 60 mg/day)<br>**12-17 years:** 5-20 mg TDS (Max 60 mg/day) | TDS or QID |
| **Felodipine #** | **≥6 years:** 2.5 -10 mg | Once daily |
| **Diuretics** | | |
| **Chlorothiazide **** | **6 months - 12 years:** 10-20 mg/kg/day<br>**<2 years:** Max 375 mg/day<br>**2-12 years:** Max 1,000 mg/day | Once daily or BD |
| **Hydrochlorothiazide **** | **6 months - 2 years:** 1-2 mg/kg/day (Max 37.5 mg/day)<br>**>2-12 years:** 1-2 mg/kg/day (Max 100 mg/day) | Once daily or BD |
| **Frusemide **** | 1-3 mg/kg/day (Max 80 mg/day) | Once daily or BD |
| **Spironolactone #** | 1-3 mg/kg/day (Max 100 mg/day) | Once daily or BD |
| **Beta Adrenergic Blockers** | | |
| **Metoprolol ***** | **1 month - 11 years:** Initially 1 mg/kg/dose<br>(Max 8 mg/kg/day *or* 200 mg/day)<br>**12-17 years:** Initially 50-100 mg/day (Max 200 mg/day) | BD |
| **Propranolol **** | Initially 1 mg/kg/day<br>Maintenance 2-4 mg/kg/day (Max 4 mg/kg/day) | BD or TDS |
| **Atenolol **** | **1 month - 11 years:** 0.5-2 mg/day (Max 50 mg/day)<br>**Child 12-17 years:** 25-50 mg/day (Max 50 mg/day) | Once daily or BD |

* ARB and ACEI are contraindicated in pregnant adolescent and neonates less than 44 weeks (Perindopril is not indicated in for the management of chronic hypertension in children and adolescents).
** Referenced from 153rd Edition, MIMS, 2018.
*** British National Formulary for Children (BNFC) 2018-2019.
# American Academy of Pediatrics (AAP) 2017.

## APPENDIX 5 Clinical Questions

1. What is the prevalence of hypertension in adults?
2. What are the causes of hypertension in adults?
3. What are the diagnostic criteria of hypertension in adults, pregnant women and neonates/children/adolescents?
4. What is the role of home blood pressure monitoring and how it should be measured?
5. What is the role of ambulatory blood pressure monitoring?
6. What are the secondary causes of hypertension in adults, pregnant women and neonates/children/adolescents?
7. How should patients with hypertension be assessed clinically?
8. Which investigation should be done in newly diagnosed hypertension?
9. How should patients be stratified according to global cardiovascular risk?
10. What non-pharmacological intervention is recommended and beneficial?
11. What and how should pharmacological management be started?
12. What target blood pressure should be aimed for in general hypertensive population and in specific sub-groups?
13. When should target blood pressure be achieved?
14. When should combination therapy be used?
15. How to recognise, evaluate and manage resistant hypertension?
16. How should severe hypertension be assessed and managed?
17. How should specific sub-groups with hypertension be managed?
    - Diabetes
    - Renal disease
    - Heart disease
    - Stroke
    - Older adults
    - Women
    - Neonates, children and adolescents
18. What are the current available pharmacological treatment for hypertension?
19. How cost effective is treating hypertensive?
20. How should resistant and refractory hypertension be diagnosed, assessed and managed?
21. Should aspirin be prescribed to patients with hypertension?
22. What is the role of device based therapy in hypertension?
23. What key research areas should be focused on to address unanswered clinical questions?

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ISBN 978-967-12406-1-8




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