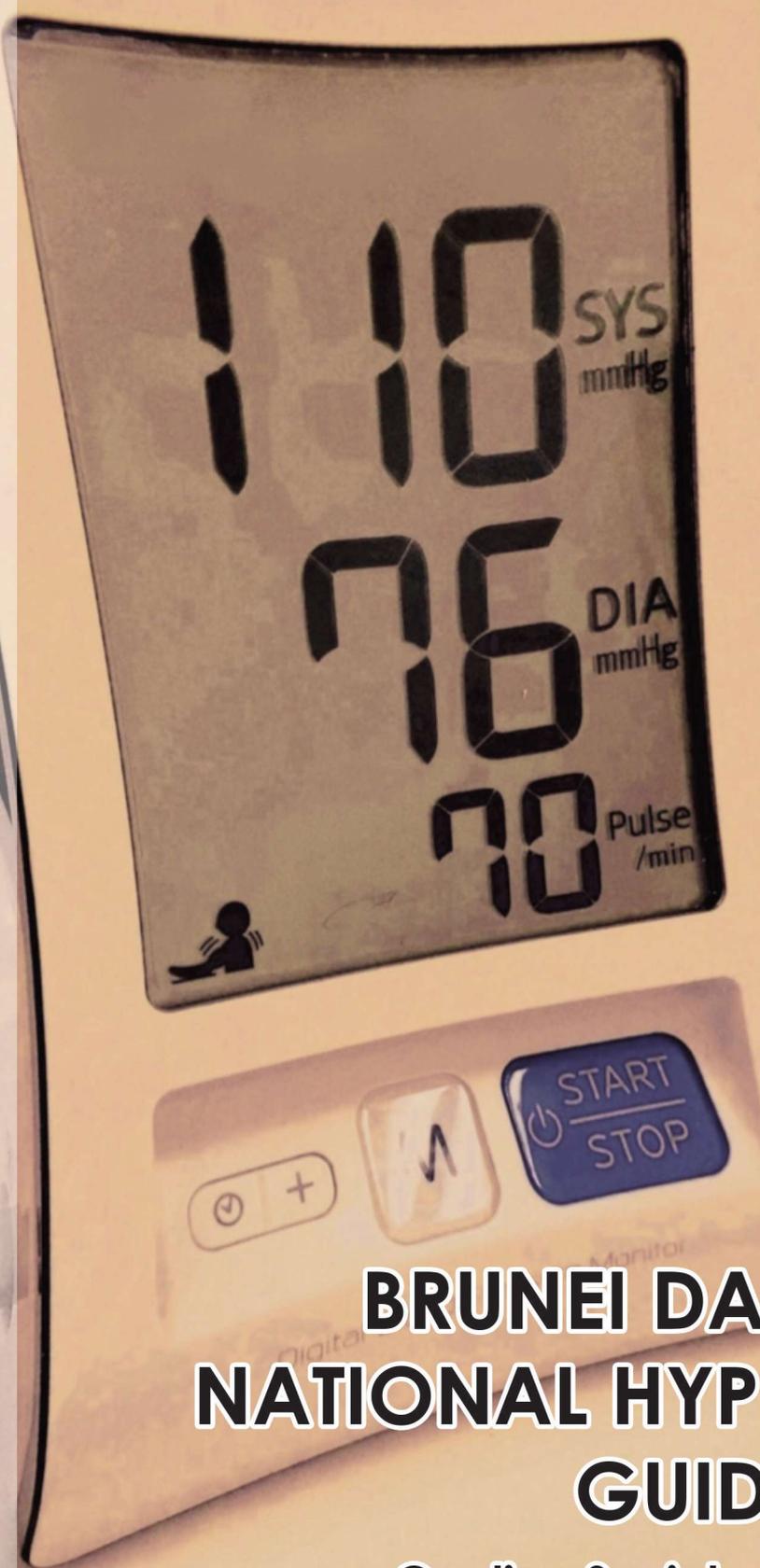


Ministry of Health  
Brunei Darussalam



# BRUNEI DARUSSALAM NATIONAL HYPERTENSION GUIDELINE 2019

Cardiac Society, Brunei Darussalam



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## **Message from Minister of Health**

Alhamdulillah, with the blessings of Allah Subhanahu Wata'ala, it is with great pleasure that I introduce the Brunei Darussalam National Hypertension Guideline 2019.

As a result of the combined efforts of many healthcare professionals, the Ministry of Health, in partnership with the Cardiac Society, Brunei Darussalam is launching the National Hypertension Guideline.

This is an important effort to provide a guideline for a very important health problem in Brunei Darussalam. Hypertension is a major risk factor for heart disease worldwide as well as in Brunei Darussalam. Indeed, according to the Health Information Booklet 2017 Heart Diseases and Hypertensive diseases are the 2<sup>nd</sup> and 5<sup>th</sup> most common causes of death in Brunei Darussalam. In addition, Cerebrovascular diseases, for which hypertension is also a risk factor, is the 4<sup>th</sup> leading cause of death.



This guideline covers all age ranges, from the neonatal period to older people, for men and women, including those of child-bearing age and during pregnancy to attempt to provide a comprehensive guideline for patients with hypertension in Brunei Darussalam. It aims to standardise the definitions and treatment algorithms for hypertension so that everybody is aware of what the standard of care should be in the management of hypertension.

It is my sincere hope that with the publication of this guideline the care of patients with hypertension can be improved. I would like to emphasise the early detection of hypertension through screening programmes and early treatment to reduce the considerable burden of morbidity and mortality of hypertension in Brunei Darussalam.

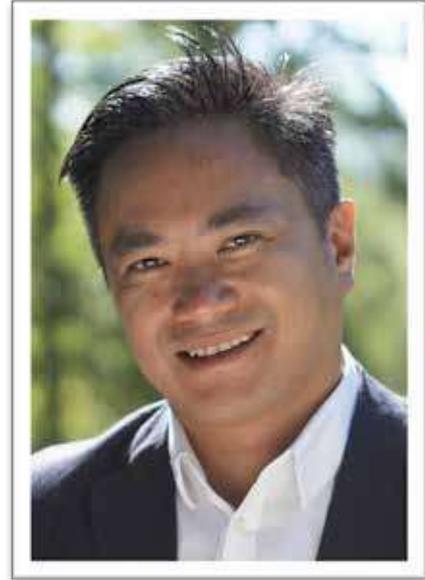
Lastly, I would like to congratulate all those who were involved in the writing of this guideline and hope that they will continue in their efforts to improve the management and care of patients with hypertension in Brunei Darussalam.

YB Dato Seri Setia Dr Haji Mohammad Isham bin Haji Jaafar

## **Foreword from President of Cardiac Society**

It gives me great pleasure to introduce the Brunei Darussalam National Hypertension Guideline 2019 which is a joint collaboration between the Cardiac Society Brunei Darussalam and the Ministry of Health.

This is actually the second edition of the National Hypertension Guideline – the first edition was published by the Ministry of Health in September 2002 and there has been a tremendous explosion in knowledge since then, making a new edition very timely. We see rapid changes every year in medicine and cardiology and it is hoped that future updates will occur regularly.



It has been an extremely rewarding and enlightening endeavour bringing together the many stakeholders with an interest in hypertension to write the guideline you see here today. The scope of the guideline includes the diagnosis and treatment of hypertension from birth to older persons, including women of childbearing age and during pregnancy and the post-partum period. It considers concomitant medical conditions such as heart disease, diabetes mellitus, cerebrovascular disease and chronic kidney disease. Screening for hypertension, treatment of hypertensive emergencies and secondary hypertension are also covered. Thus, it is hoped that this guideline will provide a comprehensive guide to the management of hypertension in Brunei Darussalam.

The key messages are listed in the Summary of Guidelines but I want to highlight 2 important points – the blood pressure target of  $\geq 140/90$  mmHg for the diagnosis and treatment of hypertension and the lower threshold of  $\geq 130/80$  mmHg where treatment can be considered for those at elevated cardiovascular risk. This has been an important change in the management of hypertension which has come from the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. This new target will be a difficult one to achieve but is important to reduce the morbidity associated with hypertension in those at greater risk.

Although the focus of the guideline is on hypertension, it is important not to forget that other conditions such as diabetes mellitus and hypercholesterolaemia contribute to overall cardiovascular risk and once a patient has been diagnosed with hypertension, then these conditions should be screened for and treated if appropriate.

In conclusion, I would like to thank everyone again who has been involved in the writing of this guideline and I hope that it will be useful to all practitioners caring for patients with hypertension.

Dr Sofian bin Dato Paduka Dr Haji Johar

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**Statement of Intent:** *This document acts as a guide for clinician on the management of condition based on the available evidence at the time of the development of the document. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every health care provider should consider the patient and management options available in the local setting and administer treatment with the best intent outcome possible guided by the CPG. Any deviations from the CPG should be documented if possible. In this guideline, no formal grading of levels of evidence or strength of recommendations is included. However, it represents an interpretation of the best available evidence as well as international guidelines.*

## List of abbreviations and acronyms used:

ABPM	Ambulatory Blood Pressure Monitoring
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes (Trial)
ACE-I	Angiotensin Converting Enzyme Inhibitor
ACR	Albumin to Creatinine Ratio
ADA	American Diabetes Association
AER	Albumin Excretion Rate
AFV	Amniotic Fluid Volume
AHA	American Heart Association
AIS	Acute Ischaemic Stroke
AKI	Acute Kidney Injury
ALLHAT	Antihypertensive Lipid-Lowering Treatment to Prevent Heart Attack Trial
ALT	Alanine Transaminase
AMI	Acute Myocardial Infarction
AOBP	Automated Office Blood Pressure
APO	Acute Pulmonary Oedema
ARB	Angiotensin II Receptor Blocker
ARNI	Angiotensin II Receptor blocker + Neprilysin Inhibitor
ARR	Aldosterone to Renin Ratio
ASEAN	Association of South East Asian Nations
AST	Aspartate Aminotransferase
ATACH-II	Antihypertensive Treatment of Acute Cerebral Haemorrhage 2 (trial)
AV	Atrioventricular
BB	Beta ( $\beta$ ) Blocker
BD	<i>Bis Die</i> (twice daily dosing)
BMI	Body Mass Index
BNF	British National Formulary

BNFc	British National Formulary for Children
BP	Blood Pressure
CAD	Coronary Artery Disease
CCB	Calcium Channel Blocker
CHD	Coronary Heart Disease
CK-MB	Creatinine Kinase Muscle and Brain isoenzyme
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPP	Cerebral Perfusion Pressure
CRP	C-Reactive Protein
CT	Computed Tomography
CTG	Cardiotocography
CV	Cardiovascular
CVD	Cardiovascular Disease
CXR	Chest radiograph
DASH	Dietary Approaches to Stop Hypertension (diet)
DBP	Diastolic Blood Pressure
DHP	Dihydropyridine
DIC	Disseminated Intravascular Coagulation
DM	Diabetes Mellitus
ECG	Electrocardiogram
ECHO	Echocardiogram
eGFR	Estimated Glomerular Filtration Rate
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
ESC	European Society of Cardiology
FBC	Full Blood Count
FN	False Negative
FP	False Positive
fullPIERS	Pre-eclampsia Integrated Estimate of Risk
GDMT	Guideline Directed Medical Therapy

GFR	Glomerular Filtration Rate
GP	General Practitioner
GTN	Glycerine Trinitrate
HbA1c	Haemoglobin A1c (Glycated haemoglobin)
HBPM	Home Blood Pressure Monitoring
HELLP	Haemolysis Elevated Liver Enzymes and Low Platelet count
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HIV	Human Immunodeficiency Virus
HMOD	Hypertension Mediated Organ Damage
ICP	Intra-cranial pressure
ICU	Intensive Care Unit
IDNT	Irbesartan Diabetic Nephropathy Trial
IGF-1	Insulin-like Growth Factor 1
INTERACT	Intensive blood pressure reaction in acute cerebral haemorrhage (trial)
IV	Intravenous
JNC 5	Joint National Committee 5
JNC 7	Joint National Committee 7
JVP	Jugular Venous Pressure
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LFT	Liver Function Tests
LMW	Low Molecular Weight
LV	Left Ventricular
LVEF	Left ventricular ejection fraction
LVH	Left Ventricular Hypertrophy
MAP	Mean Arterial Pressure
Mg	Magnesium
MH	Masked Hypertension

MI	Myocardial Infarction
MRA	Mineralocorticoid antagonist
MRI	Magnetic Resonance Imaging
MSG	Monosodium glutamate
NICE	National Institute of Clinical Excellence
NICU	Neonatal Intensive Care Unit
NSAIDS	Non-steroidal anti-inflammatory drugs
NT-proBNP	N-terminal pro B-type Natriuretic Peptide
NYHA	New York Heart Association
O&G	Obstetrics and Gynaecology
OBP	Office Blood Pressure
OD	Once daily
ONTARGET	Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial
OSA	Obstructive Sleep Apnoea
PAD	Peripheral arterial disease
PCC	Phaeochromocytoma Crisis
PCR	Protein to Creatinine Ratio
PD	Peritoneal Dialysis
PER	Protein Excretion Rate
PIGF	Placental Growth Factor
PP	Pulse Pressure
PREP-S	Prediction of complications in early-onset pre-eclampsia - survival
QRISK2	formal risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including the age of 84 years
RAAS	Renin Angiotensin Aldosterone System
RBC	Red Blood Cell
RCT	Randomised Control Trials
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (trial)
SBP	Systolic Blood Pressure

SCORE	Systematic Coronary Risk Evaluation score
SMO	Senior Medical Officer
SPRINT	Systolic Blood Pressure Intervention Trial
STEMI	ST elevation myocardial infarction
TDS	<i>Ter Die Sumendum</i> (three times daily in prescription)
TFT	Thyroid Function Tests
TIA	Transient Ischaemic Attack
UA	Umbilical Artery
UEC	Urea, electrolytes and creatinine
UKPDS	UK Prospective Diabetes Study
USPSTF	US Preventive Services Task Force
VA NEPHRON-D	Veterans Affairs Nephropathy in Diabetes (trial)
VEGF	Vascular endothelial growth factor
VMA	Vanillylmandelic acid
WCH	White Coat Hypertension
WHO	World Health Organisation
WHO-ISH WPR A	World Health Organisation – International Society of Hypertension Western Pacific Region A

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# **Summary of Guidelines**

Dr Moncy Jacob Oomen

This National Hypertension management guidelines provide recommendations for our doctors across Brunei Darussalam to diagnose hypertension and to reduce risk, with both lifestyle advice and medications. The development of the guidelines was made complete by our clinicians including the subspecialties of medicine.

The following are the eight key messages of the hypertension management guidelines in adults.

## **1. Definition of hypertension:**

Hypertension is defined as a persistent elevation in office systolic BP  $\geq 140$  mmHg and / or diastolic BP  $\geq 90$  mmHg which is equivalent to a 24h ambulatory BP monitoring (ABPM) average of  $\geq 130/80$  mmHg or a home BP monitoring (HBPM) average  $\geq 135/85$  mmHg.

## **2. Screening and diagnosis of hypertension:**

Screening programmes should be established to ensure that office BP is measured annually in all adults 40 years and above. In adults 18 to <40 years of age, annual screening is recommended when they are felt to be at increased risk of hypertension. The diagnosis is confirmed by elevated BP readings on at least 2 separate occasions. When hypertension is suspected but not confirmed, the diagnosis should be confirmed either by repeated office BP measurements, or by ABPM.

## **3. When to consider drug treatment of hypertension:**

Adults with Stage 1 hypertension (office BP  $>140$ - $159/90$ - $99$  mmHg) aged up to 70 years should receive drug treatment if their BP is not controlled after a period of lifestyle modification alone. For high-risk patients with Stage 1 hypertension or patients with higher stages of hypertension (e.g. Stage 2 hypertension  $\geq 160/100$  mmHg, drug treatment should be initiated alongside lifestyle interventions. For those adults with high normal / elevated BP ( $130$ - $139/80$ - $89$  mmHg) and elevated cardiovascular risk, drug therapy can be considered after a period of lifestyle modification.

## **4. How low should BP be lowered?**

Office BP should be lowered to  $<140/90$  mmHg in all treated patients, including independent older people who can tolerate treatment. In patients with elevated cardiovascular risk including patients with diabetes mellitus, chronic kidney disease, coronary artery disease and heart failure, the target BP should be  $<130/80$  mmHg. In patients who have side-effects from antihypertensive treatment, individualised BP targets may be appropriate.

**5. Treatment of hypertension - lifestyle interventions are important:**

Treatment of hypertension involves lifestyle interventions and drug therapy. Lifestyle interventions are important because they can delay the need for drug treatment or complement the BP lowering effect of drug treatment. Moreover, lifestyle interventions such as sodium restriction, alcohol moderation, healthy eating, regular exercise, weight control and smoking cessation, all have health benefits beyond their impact on BP.

**6. Start treatment in most patients with two drugs, not one.**

Monotherapy is usually inadequate therapy for most patients with hypertension to achieve the BP treatment targets. The only exception would be in a limited number of patients with a lower baseline BP close to their recommended target, who may achieve the target with a single drug.

**7. A simplified drug treatment algorithm:**

Combination of an ACE-I or ARB with a CCB or thiazide / thiazide like diuretic is the preferred initial therapy for most patients. For those requiring three drugs, a combination of an ACE-I or ARB with a CCB or thiazide / thiazide-like diuretic should be used.  $\beta$ -blockers should be used when there is a specific indication for their use, e.g. angina, post-myocardial infarction, heart failure with reduced ejection, or when heart rate control is required.

**8. Managing cardiovascular disease risk in hypertensive patients – going beyond BP**

Hypertensive patients frequently have concomitant cardiovascular risk factors such as diabetes mellitus and hypercholesterolaemia. These risk factors should be treated. Drug treatment may be considered in high normal / elevated BP (130-139/80-89 mmHg), when CV risk is elevated due to established CVD, especially CAD.

## 1. Introduction

Dr Moncy Jacob Oommen and Dr Sofian DP Dr Hj Johar.

It has long been known (at least since the 1920s) that the level of BP has been associated the risk of clinical complications and death <sup>(1)</sup>. Observational studies have demonstrated a relationship between SBP and DBP and increased CVD risk. In a large meta-analysis<sup>(2)</sup> the risk of CVD increased in a log-linear manner from SBP <115 mmHg to >180 mmHg and DBP <75 mmHg and >105 mmHg. In this analysis there was a two-fold increase in the risk of death from heart disease, stroke or other vascular disease with a 20 mmHg higher SBP and 10 mmHg higher DBP.

Hypertension is the most important known modifiable risk factor for CVD and is second only to smoking as a preventable cause of death<sup>(1)</sup>. It is estimated that >50% of deaths from coronary heart disease and stroke occurred among hypertensive individuals according to a follow-up study from the US NHANES study. In addition, from the ARIC study<sup>(1)</sup> 25% of the cardiovascular events (CHD, coronary revascularisation, stroke or heart failure) were attributed to hypertension. For end-stage renal disease (ESRD), i.e. those requiring dialysis and renal replacement therapy, hypertension was the 2<sup>nd</sup> leading cause of ESRD, second to diabetes mellitus in a US study.

The prevalence of hypertension in Brunei Darussalam is high in both women and men. A Brunei epidemiological cross-sectional stroke study which looked at patterns of hypertension and stroke risk to estimate the prevalence of hypertension aged above 18 years, showed 48.3% suffer from hypertension<sup>(3)</sup>. According to the 2014 2<sup>nd</sup> NHANSS study performed in Brunei Darussalam, 33.8% of 20-75 year olds were found to be hypertensive<sup>(127)</sup>. Other risk factors for heart disease were also found to be high, with 12.4% prevalence of diabetes and 73.8% prevalence of dyslipidaemia on the 20-75 age group. Thus, in Brunei Darussalam, treatment and control of BP is an enormous opportunity to reduce the burden of morbidity and mortality to the health care system.

The understanding of the pathophysiology of hypertension has never been as well-studied as it is now. The unravelling of the renin-angiotensin pathway, sympathetic cascade and neuro-hormonal potentiation has led to the discovery of several drugs such as ACE-I, ARBs and ARNI. These have led to much better management of hypertension and its sequelae. However, there is still much that is unknown, and many patients still have uncontrolled BP despite multiple combinations of medications. As stated earlier hypertension is the most important known modifiable risk factor for CVD and is a major preventable cause of death. Despite this, half of people with hypertension are on treatment but uncontrolled <sup>(4)</sup> and in the USA, nearly 20% of hypertensive patients are not aware that they have hypertension and are uncontrolled<sup>(5)</sup>.

We have seen the fundamental definition of hypertension itself differ from report to report. The new AHA/ACC guidelines from 2017 have redefined hypertension as  $\geq 130/80$  mmHg moving away from the conventional definition adopted by the ESC/ESH 2018 guidelines of  $\geq 140/90$  mmHg. This has increased the prevalence of adults with hypertension in the USA to 46% according to the new definition <sup>(6)</sup>. There is presently a robust debate taking place in the hypertension community regarding these new definitions. The Brunei Darussalam National Hypertension Guideline still keeps the traditional definition of  $\geq 140/90$  mmHg for the diagnosis of hypertension, but adopts the AHA/ACC treatment threshold of  $\geq 130/80$  mmHg for those at elevated cardiovascular risk.

The treatment strategies for hypertension have also changed over the years. Diuretics moved from being first line to third line between JNC 5 and JNC 7 reports.  $\beta$ -blockers too have had positional changes and generally are not first line anymore, unless the patient has co-existing medical conditions such as heart failure and angina, when these drugs may be considered earlier in the treatment algorithm.

This guideline is an effort to study and review the plethora of recent guidelines on hypertension and to try and synthesise this into one which can be applied to Brunei Darussalam. Geographical, genetic and lifestyle factors need to be interlaced with therapy to make hypertension manageable. All statements and recommendations formulated in this guideline by the contributors are based on standard references, guidelines and major clinical trials. There is no formal grading of evidence or strength of recommendations, however it represents a careful consideration of the evidence available from the major international guidelines and key randomised controlled trials and studies.

In conclusion, this guideline highlights both a burden and an opportunity. The burden is the high prevalence of hypertension in Brunei Darussalam which needs to be treated. The opportunity is that with good control of BP, the morbidity and mortality associated with hypertension in Brunei Darussalam can be reduced. It is our sincerest hope that with this guideline, the care of patients with hypertension can be improved and standardised and the burden of disease reduced.

## **2: Overview of existing international guidelines**

Dr Mohd Ezam Emran

<b>Regional guidelines</b>					
<b>Singapore (2017)<sup>(7)</sup></b>			<b>Malaysia (2018)<sup>(8)</sup></b>		
Classification	Systolic	Diastolic	Classification	Systolic	Diastolic
Normal	<130	<85	Optimal	<120	<80
High Normal	130 - 139	85 - 89	Normal	120 - 129	80 - 84
Grade 1 Hypertension	140 - 159	90 - 99	At Risk	130 - 139	85 - 89
Grade 2 Hypertension	160 - 179	100 - 109	Stage 1 (Mild)	140 - 159	90 - 99
Grade 3 Hypertension	≥180	≥110	Stage 2 (Moderate)	160 - 179	100 - 109
Isolated Systolic Hypertension	≥140	<90	Stage 3 (Severe)	≥180	≥110
			Isolated Systolic Hypertension	≥140	<90

**Table 1:** Comparing the classification of Hypertension in several regionally published guideline (BP in mmHg)

International guidelines									
NICE (2019) <sup>(9)</sup>			ESC (2018) <sup>(10)</sup>				AHA/ACC (2017) <sup>(11)</sup>		
Classification	Systolic	Diastolic	Classification	Systolic	Diastolic	Classification	Systolic	Diastolic	
			Optimal	<120	<80	Normal	<120	<80	
			Normal	120 - 129	80 - 84	Elevated	120 - 129	<80	
			High Normal	130 - 139	85 - 89	Stage 1 Hypertension	130 - 139	80 - 89	
Stage 1 Hypertension	140 - 159	90 - 99	Grade 1 Hypertension	140 - 159	90 - 99	Stage 2 Hypertension	≥140	≥90	
Stage 2 Hypertension	160 - 180	100 - 120	Grade 2 Hypertension	160 - 179	100 - 109				
Stage 3 (Severe) Hypertension	≥180	≥120	Grade 3 Hypertension	≥180	≥110				
			Isolated Systolic Hypertension	≥140	<90				

**Table 2:** Comparing the classification of Hypertension in several internationally published guideline (BP in mmHg)

Regional guidelines		
	<b>Singapore (2017)<sup>(7)</sup></b>	<b>Malaysia (2018)<sup>(8)</sup></b>
<b>Risk Stratification Tool</b>	Modified Framingham Risk Score	Framingham Risk Score
<b>Treatment Threshold (in general population)</b>	Initiate pharmacotherapy when BP >140/90 mmHg	<b>Stage 1 (low CV risk):</b> Non-pharmacological therapy + review in 3 - 6 months  <b>Stage 1 (medium/high CV risk):</b> initiate pharmacotherapy  <b>Stage 2:</b> initiate pharmacotherapy  <b>Stage 3 (Hypertensive Urgency with no Target Organ Damage):</b> Immediate pharmacotherapy + monitor (discharge if responding to therapy)  <b>Stage 3 (Hypertensive Emergency with evidence of Target Organ Damage):</b> Admit
<b>Initial monotherapy vs combination therapy</b>	Combination therapy preferable	<b>Stage 1 (low CV risk):</b> Monotherapy  <b>Stage 1 (moderate to high CV risk):</b> Combination therapy  <b>Stage 2:</b> Combination therapy
<b>Target BP for the Older Adults</b>	<80 years old: <140/90 mmHg >80 years old: <150/90 mmHg	<b>65 - 80 years old:</b> Systolic BP of <140 mmHg  <b>&gt;80 years old:</b> Systolic BP of <150 mmHg
<b>Target BP for patients with Diabetes</b>	<140/80 mmHg	High CV risk: <130/80 mmHg
<b>Target BP for patients with Chronic Kidney Disease</b>	<b>Non-proteinuric:</b> <140/90 mmHg <b>Moderate to severe albuminuria:</b> <130/80 mmHg	<b>Proteinuria (&lt;1g/24 hours):</b> <140/90 mmHg  <b>Proteinuria (&gt;1g/24 hours):</b> <130/80 mmHg

\*CV=Cardiovascular; HMOD=Hypertension mediated organ damage

**Table 3:** Comparing the treatment approach in Hypertension as published in several recent regional guideline

International guidelines			
	NICE (2019) <sup>(9)</sup>	ESC (2018) <sup>(10)</sup>	AHA/ACC (2017) <sup>(1)</sup>
<b>Risk Stratification Tool</b>	QRISK2 Assessment Tool	SCORE (Systematic Coronary Risk Evaluation) system	ASCVD (Atherosclerotic Cardiovascular Disease) Score
<b>Treatment Threshold (in general population)</b>	<b>Stage 1 + risk score <math>\geq 10\%</math>:</b> Pharmacotherapy can be considered	<b>High normal:</b> Consider pharmacotherapy in very high risk patients with CVD, particularly CAD  <b>Grade 1:</b> Initiate pharmacotherapy in high or very high risk patients with CVD, renal disease or HMOD	<b>Stage 1 &amp; ASCVD <math>\leq 10\%</math>:</b> Non-pharmacological therapy + review 3 – 6 months  <b>Stage 1 &amp; ASCVD <math>\geq 10\%</math>:</b> Initiate pharmacotherapy
<b>Initial monotherapy vs combination therapy</b>	Monotherapy recommended with subsequent up titration in a step-wise approach	<b>Grade 2 + 3:</b> Immediate pharmacotherapy in all patients	<b>Stage 1:</b> Monotherapy reasonable  <b>Stage 2:</b> Combination therapy recommended
<b>Target BP for the Older Adults</b>	<b>&lt;80 years old:</b> <140/90 mmHg <b>&gt;80 years old:</b> <150/90 mmHg	<b>65 - 80 years old:</b> Systolic BP of 130 - 139 mmHg <b>&gt;80 years old:</b> Systolic BP of 130 - 139 mmHg, if tolerated	Systolic BP <130 mmHg for most (unless frail + multiple co-morbidities)
<b>Target BP for patients with Diabetes</b>		<b>Systolic BP:</b> 120 - 130mmHg <b>Diastolic BP:</b> 70 - 80 mmHg <b>&gt;65 years old:</b> systolic BP of 130 - 139 mmHg	<130/80 mmHg
<b>Target BP for patients with Chronic Kidney Disease</b>		<b>Systolic BP:</b> 130 – 139 mmHg	<130/80 mmHg

**Table 4:** Comparing the treatment approach in Hypertension as published in several recent international guideline

## **3: Diagnosis of Hypertension and Investigations**

Dr Shuaib Ahmed Siddiqui and Dr Sofian DP Dr Hj Johar

### **Key messages:**

1. Office blood pressure should be measured with the patient sitting with the arm supported and ideally after resting for 5 minutes. The middle of an appropriately sized cuff should be at the midpoint of the sternum. At least 2 readings should be taken 1-2 minutes apart and averaged.
2. The diagnosis of hypertension is made when an office blood pressure  $\geq 140/90$  mmHg is measured on at least 2 occasions.
3. A blood pressure of  $\geq 130/80$  mmHg and  $< 140/90$  mmHg is considered high normal/elevated blood pressure and may need to be treated in patients at elevated global cardiovascular risk.
4. If the diagnosis is uncertain ABPM or HBPM can be used to help in making the diagnosis.
5. The newly diagnosed hypertensive patient should have an assessment of global cardiovascular risk.
6. Basic investigations include full blood count, liver and renal function tests, full lipid profile, fasting glucose, HbA1c, thyroid function tests, urinalysis and a 12-lead ECG.

### **3.1 Introduction**

#### **3.1.1 Office BP**

The diagnosis of hypertension rests critically on the correct method of measurement. Traditionally the diagnosis is made on measurement of blood pressure in the office/ outpatient clinic – the office blood pressure.

The following is the recommended method of measuring blood pressure in the office/ clinic

- When taking blood pressure in the office setting the patient should be allowed to rest in a comfortable chair for five minutes in a quiet environment.
- The patient should be sitting in the chair with his back and the head supported.
- Legs uncrossed and both feet should be on the floor
- The arm from which the blood pressure is being taken should be supported on a table approximately at the level of the heart, with the mid-point of the cuff at the level of the mid-point of the sternum
- The size of the cuff is important and the bladder inside the cuff should encircle 80% of the circumference of the arm. An inappropriately-sized cuff will give erroneous BP readings.
- After a resting period of five minutes, at least 2 blood pressure readings should be taken 1-2 minutes apart and averaged. If 3 readings are obtained then the first one is ignored and the average of the remaining 2 readings is taken as the office blood pressure of the patient at that particular time.

Category	Blood pressure	Intervention	
		High CV risk	Low to moderate CV risk
High normal / Elevated BP	130-139 / 80-89 mmHg	Promote optimal lifestyle habits and consider pharmacological treatment	Lifestyle advice
Stage 1 Hypertension	140-159 / 90-99 mmHg	Start pharmacological treatment immediately	Pharmacological treatment to start after 3 - 6 months of lifestyle intervention
Stage 2 Hypertension	160-179/100-109 mmHg	Start pharmacological treatment immediately	
Severe hypertension	≥180/110 mmHg	Start pharmacological treatment immediately	

**Table 5.** Classification of BP according to severity (based on Office BP) with suggested interventions (Adapted from ESC/ESH 2018 Guidelines) <sup>(10)</sup>.

The diagnosis of hypertension is made when an office BP  $\geq 140/90$  mmHg is measured on at least 2 occasions.

Those patients with an office BP  $\geq 130/80$  mmHg and  $< 140/90$  mmHg are considered to have a high normal BP / elevated BP and treatment may be required depending on an assessment of global cardiovascular risk.

All patients diagnosed with hypertension should have an assessment of global cardiovascular risk. Drug therapy together with life-style advice may be required early on for those at high global cardiovascular risk.

Blood pressure is categorised as follows:

- High normal / elevated BP  $\geq 130/80$  and  $< 140/90$  mmHg
- Stage 1 hypertension  $\geq 140/90$  and  $< 160/100$  mmHg
- Stage 2 hypertension  $\geq 160/100$  and  $< 180/110$  mmHg
- Severe hypertension  $\geq 180/110$  mmHg

Once hypertension is diagnosed, or if a high normal / elevated BP needs treatment due to elevated global cardiovascular risk, then lifestyle interventions should be advised and/or pharmacological treatment should be started (see **Chapter 5 & 6: Non-Pharmacological and Pharmacological Management of Hypertension**).

### 3.1.2 Orthostatic hypotension

In certain patients, especially the in older people or diabetic patients, management can be complicated by orthostatic hypotension. Therefore, a change in BP from a seated to a standing position after a period of 1 or 3 minutes should be measured in

these patients as this may complicate therapeutic decision-making. A decline of >20 mmHg in SBP or >10 mmHg in DBP is considered abnormal.

### **3.1.3 Automated Office Blood Pressure (AOBP)**

In most of the major hypertension studies office BP has been used for the measurement of BP due to its simplicity and cost. However, it is well known that office BP readings can be higher in the office or clinic compared to readings in the home – a phenomenon known as white coat hypertension.

One method to minimise this difference has been the use of AOBP, especially popularised by the SPRINT trial<sup>(11)</sup>. This is performed by using a dedicated BP measurement device which is designed to make unattended measurements of BP after a suitable rest period (usually 3 or 5 minutes). Several measurements are then made at 1-minute intervals and an average is taken. The first BP reading may be discarded.

It has been suggested that readings obtained in this manner correspond to average ambulatory awake BP and that this may minimise the white coat effect<sup>(12)</sup>. This method may be an option for the routine assessment of BP in the clinic.

### **3.1.4 Ambulatory blood pressure monitoring (ABPM)**

ABPM is performed with a BP monitor attached to the patient for 24 hours. The device checks the blood pressure at regular intervals throughout the day. Usually this happens every 15-30 minutes during the daytime and 30-60 minutes at night. BP continues to be measured during the night when the patient is asleep.

The normal parameters obtained include:

- Average 24h BP
- Awake ABPM
- Asleep ABPM
- Calculation of the nocturnal dip

ABPM is performed if there is doubt about the diagnosis of hypertension, to exclude the diagnosis of white coat hypertension, monitor the response to treatment and look for evidence of symptomatic hypotension.

From these parameters several observations can be made:

- a. White coat hypertension where office BP is significantly higher than awake ABPM. It has been associated with a slightly increased risk of CVD and all-cause mortality risk. It may convert to sustained hypertension.
- b. Masked hypertension where office BP is normal but out-of-office readings are elevated; this is a marker of elevated risk and should be treated. Masked hypertension is the reverse of white coat hypertension. The blood pressure that is recorded in the clinic is in the normal range or usually in the high normal range, Whereas the blood pressure at home as measured by the ABPM is in

the hypertensive range. The patients with masked hypertension usually have CKD, or OSA, or are obese with a BMI of  $\geq 30\text{kg/m}^2$ . These patients may have diabetes mellitus and usually have albuminuria and other evidence of HMOD such as LVH diagnosed by ECG or echocardiography. Patients with masked hypertension usually have a poorer prognosis, and in such patients, BP should be treated aggressively together with aggressive control of other atherosclerotic risk factors.

- c. The concept of dipper and non-dipper status. Normally BP drops when asleep and if the BP does not drop significantly then this is a marker of increased risk. Dipping of 10-20% is considered normal.
  - i. Normal dipper – 10-20% dip
  - ii. Non-dipper <10% dip
  - iii. Reverse dipper – rise in BP at night – nocturnal medication dosing may be considered
  - iv. Extreme dipper >20% dip

If the average 24-hour BP measurement shows that the blood pressure is greater than 130/80mmHg then a diagnosis of hypertension can be made (see **Table 6** for corresponding thresholds compared to office BP)

Office BP	HBPM	Awake ABPM	Asleep ABPM	24h ABPM
120/80	120/80	120/80	100/65	115/75
130/80	130/80	130/80	110/65	125/75
140/90	135/85	135/85	120/70	130/80
160/100	145/95	145/90	140/85	145/90

**Table 6.** BP thresholds (in mmHg) for HBPM and ABPM that correspond to Office BP levels

### 3.1.4 Home BP Monitoring (HBPM)

When borderline readings are obtained in the clinic the patient should be encouraged to check their BP at home.

The patient should first be trained in the method of measuring the blood pressure by the hospital staff.

The patient should be told that the BP should be measured when sitting down with the arm supported. After a five-minute rest period the BP is measured at least 2 times at 1-minute intervals.

For the initial diagnostic stage one set of readings should be taken in the early morning before medication is taken and another set before the evening meal. These can be taken for a period of a few weeks before the clinic appointment.

Patients should be instructed to bring the diary of these BP readings to the clinic for review. Modern BP devices store these readings in their memory and this can be brought to clinic instead.

If there is any significant discrepancy between the home and office BP readings the home BP machine should be brought to the clinic to check its calibration.

The BP thresholds are summarised in **Table 6** and a diagnosis of hypertension is made with consistent home BP readings of  $\geq 135/85$  mmHg. This corresponds to an office BP of  $\geq 140/90$  mmHg. At lower levels, office BP corresponds more closely with HBPM and awake ABPM and therefore the threshold for diagnosing high normal / elevated BP is  $\geq 130/80$  mmHg which is the same as the office BP threshold and the awake ABPM threshold.

Subsequently the HBPM can be used to monitor the effectiveness and to achieve the BP targets.

For older people, please refer to **Chapter 9: Hypertension in older people**.

### 3.2 Risk stratification

<b>LOW GLOBAL RISK</b>	With Stage 1 hypertension ( $\geq 140/90$ mmHg and $< 160/100$ mmHg), allow 3 to 6 months for lifestyle changes to show some effects before uptitrating to pharmacological therapy.
<b>HIGH GLOBAL RISK</b>	Pharmacological treatment should be considered even at $130/80$ mmHg. This must be associated with aggressive management of all the other risk factors.

**Table 7.** Hypertension in relation to the global cardiovascular risk of the patient

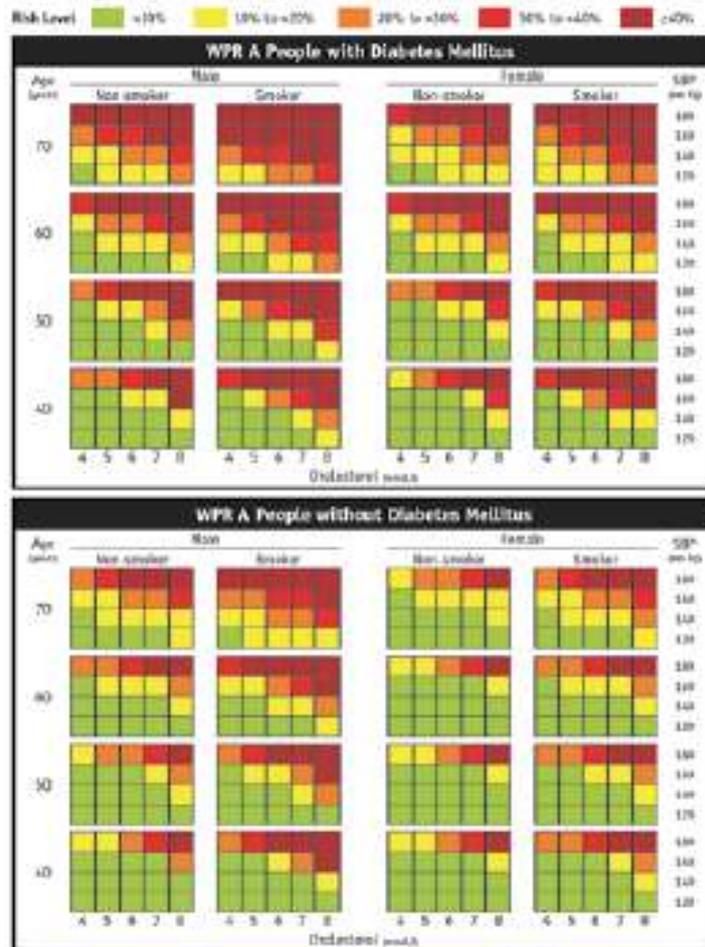
In all patients an assessment should be made of the global cardiovascular risk as those with an elevated risk may require treatment at the lower BP threshold of  $\geq 130/80$  mmHg.

The Ministry of Health is currently using the WHO-ISH WPR A chart for cardiovascular risk stratification (see **Figure 1**). However, there are many risk scoring systems available which could be used for this purpose. A comprehensive discussion on the available scoring systems is beyond the scope of these guidelines.

### 3.3 Investigations

All patients who have been given a diagnosis of hypertension should have basic laboratory investigations in order to facilitate assessment of global cardiovascular risk (see **Table 8**), establish a baseline for subsequent medication use and to screen for secondary causes of hypertension (see **Chapter 7: Secondary Hypertension** for a comprehensive discussion). In addition, tests can be performed to screen for end-organ damage.

Other tests include serum uric acid, hs-CRP, chest X-ray, echocardiography and a urine albumin/creatinine ratio or protein/creatinine ratio as necessary depending on clinical judgement and the results of the baseline investigations.



**Figure 1. WHO/ISH risk prediction chart for WPR A<sup>(13)</sup>.** 10-year risk of a fatal or non-fatal cardiovascular event by gender, age, systolic blood pressure, total blood cholesterol, smoking status and presence or absence of diabetes mellitus.

Full blood count
Liver and renal function tests
Full fasting lipid profile
Fasting glucose and HbA1c
Thyroid function tests
Urinalysis
12-lead ECG

**Table 8. Suggested baseline investigations<sup>(10)</sup>**

## **4: Screening for Hypertension**

Dr Chong Chean Lin and Dr Mohamad Ezam Emran

### **Key Messages:**

1. Annual screening for hypertension is recommended for all adults  $\geq 40$  years old.
2. For adults between 18 and less than 40 years old, annual screening should be undertaken if they are felt to be at increased risk of CVD.
3. For high normal / elevated BP (130-139/80-89 mmHg) annual BP measurements should be performed, and treatment considered if have elevated cardiovascular risk.
4. For individuals with BP  $< 130/80$  mmHg and aged 18 years to  $< 40$  years old, then BP may be checked every 3-5 years.

Hypertension is commonly referred to as ‘the silent killer’ as patients tend to be asymptomatic particularly in the early stages. It is an important risk factor for cardiovascular morbidity and mortality; predisposing to the development of coronary artery disease, heart failure, stroke, renal disease and peripheral arterial disease.

Worldwide, hypertension is estimated to cause 7.5 million deaths or approximately 12.8% of all deaths annually. The overall global prevalence of hypertension in adults aged 25 and over was around 40% in 2008 with an estimated 1.13 billion people being affected by the condition. There is a slight male predominance with 25% of male being affected compared to 20% of females<sup>(14)</sup>.

Within the ASEAN region, Malaysia in 2015 recorded an overall prevalence of 35.3% for hypertension amongst individuals aged 18 years and over<sup>(8)</sup>. These figures were lower in Singapore with the 2010 Singapore National Heart Survey showing a prevalence of 23.5% for hypertension in residents aged between 30 to 69 years old<sup>(7)</sup>.

Hypertension is also prevalent in Brunei Darussalam as evidenced by the high mortality rates from cardiovascular and cerebrovascular diseases. According to the 2017 Brunei Health Information Booklet<sup>(15)</sup>; when combined, these conditions contributed to 20.4% of deaths in 2016. Early diagnosis and treatment of hypertension is therefore vital, and it is hoped that this could be achieved through screening of asymptomatic individuals.

Screening for hypertension may be done in the office setting using methods described in the **Chapter 3: Diagnosis and Investigations of hypertension**. All individuals between 18 to 40 years old should be considered for periodic hypertension screening; either through structured population-based programmes or through opportunistic BP measurements. **Table 9** illustrates possible scenarios that could be encountered in clinical practice and its corresponding recommendations.

It should be highlighted that early pharmacological treatment needs to be considered in those with high normal BP (130-139/80-89 mmHg) **and** elevated cardiovascular risk. For individuals <40 years old with BP < 130/80 mmHg, their BP may be checked every 3-5 years.

<b>HYPERTENSION</b>		
<b>Target population</b>	<b>Asymptomatic adult population &gt;18 years old</b>	
<b>Definitions</b>	<b>NORMAL BP</b> is defined as SBP<130 mmHg & DBP <80 mmHg <b>HIGH NORMAL/ELEVATED BP</b> is defined as SBP130–139 mmHg & DBP 80-89 mmHg <b>HYPERTENSION</b> is defined as SBP>140mmHg & DBP >90 mmHg	
<b>Recommendation</b>	Periodic screening for hypertension is recommended for all adults >18 years old	
<b>Screening tools/test</b>	Office Blood pressure measurement in clinic	
<b>Screening interval</b>	Between 18 to 40 years old	If <b>NORMAL</b> , check at least once every 3-5 years
		If <b>HIGH NORMAL/ELEVATED BP</b> , check annually if increased risk of hypertension
		If <b>HIGH NORMAL/ELEVATED BP</b> with <b>ELEVATED CARDIOVASCULAR RISK</b> , to consider early treatment as per guidelines
		If <b>HYPERTENSIVE</b> , to confirm diagnosis & treat as per guidelines
	> 40 years old	If <b>NORMAL</b> , check annually
		If <b>HIGH NORMAL/ELEVATED BP</b> , check annually
		If <b>HIGH NORMAL/ELEVATED BP</b> with <b>ELEVATED CARDIOVASCULAR RISK</b> , to consider early treatment as per guidelines
		If <b>HYPERTENSIVE</b> , to confirm diagnosis & treat as per guidelines

**Table 9:** Summary of Hypertension Screening Recommendations

<b>HYPERTENSION</b>		
<b>Population</b>	<b>Asymptomatic adult general population &gt;18yrs</b>	
Strength of Evidence	ESC/ESH Hypertension guidelines 2018 <sup>(10)</sup> (Level of Evidence: B)	USPSTF, 2014 <sup>(16)</sup> (Level of Evidence: A)
Recommendation	Screening for high blood pressure is recommended	Screening for high blood pressure is recommended
<b>Risk Assessment</b>		
Screening tool/test:	Office Blood pressure measurement	Office Blood pressure measurement
Screening interval or timing	<p>Screening every 5 years if BP &lt;120/80 mmHg</p> <p>Screening every 3 years if BP 120-129/80-84 mmHg</p> <p>Annual screening if BP 130-139/85-89 mmHg</p> <p>In older patients (&gt;50 years), more frequent screening of office BP should be considered for each BP category in view of the steeper rise in SBP with ageing.</p>	<p>Screening every 2 years if BP &lt;120/80 mmHg</p> <p>Annual screening if BP 120-139/80-90 mmHg</p>

**Table 10:** International screening recommendations

## 5: Non-Pharmacological Management

Ms Chua Meah Lean

### Key Messages:

1. Maintain a healthy body weight and consume a healthy eating pattern that includes:
  - a. A variety of foods from different food groups namely carbohydrates, protein, fruit and vegetables.
  - b. Limit intake of sodium or salt, added sugars and fats especially saturated and trans fats
  - c. Base your meals preferably with more wholegrains
2. Encourage weight loss
3. Encourage physical activity
4. All newly diagnosed hypertension should be referred for dietary and lifestyle interventions.

### **NUTRITION**

Dietary modification represents a non-pharmacological approach in the management of hypertension. Several studies have been conducted from investigating individual nutrient component such as sodium, potassium, fats, fibre and food groups such as fruit and vegetables, dairy products to a variety of dietary pattern such as DASH Diet, Mediterranean Diet and Vegetarian Diet.

The dietary recommendation in the management of hypertension in Brunei emphasizes low sodium/ salt and fats especially saturated and trans fats and more fruit and vegetables, dietary fibre. **Table 11** shows a summary of the dietary recommendation for hypertension.

<b>Nutrients</b>	<b>Recommendation</b>
Sodium and Salt	Limit sodium intake to less than 2g (5g of salt) per day
Fruit and vegetables	Eat at least 2 serves of fruit and 3 serves of vegetables everyday
Dietary fibre	Include 55-65% of the energy intake from carbohydrates, with at least half of the carbohydrates from wholegrains
Fat	Limit intake of total fat to 20-35% of energy, of which total saturated and trans fats comprise no more than 10% and 1% respectively of energy intake
Alcohol	Limit alcohol intake to a maximum of 2 units daily for men and 1 unit daily for women

**Table 11:** Dietary recommendation for hypertension

#### **1. *Limit sodium intake to less than 2g (5g of salt) per day***

Sodium restriction has been shown to lower systolic and diastolic blood pressure, particularly in patients with hypertension. This is associated with better cardiovascular outcomes<sup>(17-19)</sup>. Evidence that includes results from animal studies, epidemiological studies, clinical trials and meta-analyses of trials have shown that

as dietary salt (sodium chloride) intake increases, blood pressure also increases<sup>(20)</sup>.

The WHO strongly recommends a reduction to <2 g/day sodium (5 g/day salt) to reduce blood pressure and risk of cardiovascular disease, stroke and coronary heart disease in adults<sup>(21)</sup>.

**Practical Recommendations:**

- Reduce salt intake to less than one teaspoon a day
- Cut down salt and other flavour enhancer such as MonoSodiumGlutamate (MSG), soy sauce and other sauces in cooking
- Use a pinch as a method to regulate the amount of salt added in cooking
- Avoid placing salt or other sauces at table
- Use spices, herbs and citrus to replace salt in cooking
- Choose food products with a 'Healthier Choice' logo or symbol
- Read food labels and choose food products with 'less salt', 'lower salt', 'reduced salt' or 'no added salt' content
- Order noodle soup with less salt or limit your intake of salty soup and gravy when eating out
- Request for MSG free and lower salt dishes when eating out
- Choose fresh and unprocessed foods
- Avoid salted, preserved or pickled foods
- Limit, or if possible, avoid salty snacks such as crisps and extruded snacks, and replace with fruits, nuts or healthier snacks.



**2. *Eat at least 2 servings of fruit and 3 servings of vegetables everyday***

Increase consumption of fruits and vegetables has been recommended as a key component of a healthy diet for the prevention of chronic diseases, through a variety of micronutrients, antioxidants, fibre and potassium. Research around the world have gathered strong evidence that a diet rich in fruits and vegetables can lower the risk of cardiovascular disease, coronary heart disease, hypertension and stroke<sup>(22)</sup>.

An increase in dietary potassium by increasing the amount of fruit and vegetables consumed everyday has been shown to lower blood pressure. A more recent trial among healthy volunteers recruited from a primary-care health centre, the Oxford Fruit and Vegetable Study, also found that after a 6-month intervention that encouraged increases in fruit and vegetable consumption to at least 5 servings/day, both systolic and diastolic blood pressure were substantially reduced compared with the control group that continued their usual diet without receiving specific advice<sup>(23)</sup>. This study also supports the recommendation by the WHO to consume at least 400g of fruit and vegetables every day to reduce the risk of high blood pressure.

### **Practical Recommendations:**

- Eat one serving of fruit in every main meal or as snack
- Bring fruit to your workplace or school
- Add fresh or dried fruits into cereals or oats
- Add fresh or dried fruit in plain (unflavoured) low-fat yoghurt
- Make fruit visible (e.g. put fruit in a fruit bowl in living room) to remind and encourage you to eat
- Prepare fruit in a creative way by cutting into different shapes and sizes
- Ensure that fruits are always available at home
- Always include vegetables during lunch and dinner
- Ensure half of your plate is filled with vegetables during lunch and dinner
- Add vegetables into your sandwiches, kebab, home-made pizza, pasta, noodles, soup
- Vegetables can also be eaten as soup (e.g. mushroom, mixed vegetables, *sawi*, *petola*, corn)
- Always include and request more vegetables when eating out
- Ensure that vegetables are always available at home
- Buy and enjoy a variety of fruits and vegetables, including fresh and frozen
- Make a rainbow of fruit salad of each colour

### 3. ***Dietary fibre: Include 55-65% of the energy intake from carbohydrates, with at least half of the carbohydrates from wholegrains***

A higher intake of dietary fibre is associated with a reduction in blood pressures<sup>(24)</sup>. This supports to the multiple meta-analyses that have shown benefits with dietary fibre intake on blood pressure<sup>(24-26)</sup>.

A pooled analyses from a recent Cochrane systematic review of randomized controlled trial showed a reduction in total cholesterol, low-density lipoprotein cholesterol and diastolic blood pressure with increased dietary fibre intake<sup>(27)</sup>.

### **Practical Recommendations:**

- Eat three main meals (breakfast, lunch and dinner) a day with optional one or two healthy snacks in between
- Start your day with high fibre carbohydrates such as wholemeal bread, oats, tubers, fruits and vegetables
- Include high fibre carbohydrates for every meal
- Choose healthy snacks such as fruits, nuts, wholemeal crackers and low fat milk.
- Mix half white rice with half brown (unrefined) rice
- Choose products that are labelled with 'whole grains', 'wholemeal', 'whole wheat', 'whole rye', or 'high fibre'
- Choose products with at least 50% of the total weight as whole grain ingredients

- Limit the intake of all products made with refined grains, especially those high in saturated fats, added sugars, and/or sodium such as biscuits, cakes, discretionary snacks.

#### **4. Limit intake of total fat to 20-35% of energy, of which saturated and trans fats comprise no more than 10% and 1% respectively of energy intake**

Total fats include saturated and unsaturated fats. There is no evidence that consumption of fat is directly associated with the development of hypertension, however, an intake of unhealthy fats such as saturated and trans fats is associated with the risk of cardiovascular diseases<sup>(28)</sup>.

It is currently recommended that the total fat intake account for 20-35% of energy and, saturated and trans fats should comprise to no more than 10% and 1% respectively of energy intake. This dietary goal can be met by limiting the intake of fat from dairy and meat sources, avoiding the use of hydrogenated oils and fats in cooking and manufacture of food products, using appropriate edible vegetable oils in moderation, and regular intake of fish (1–2 times per week). Practices of food preparation should preferentially employ non-frying methods.

##### **Practical Recommendations:**

- Avoid or limit intake of deep-fried and battered foods to no more than twice a week.
- Trim off any visible fat and/or skin on meat and poultry
- Avoid or limit intake of processed foods such as nuggets, corned beef and sausages.
- Avoid or limit intake of foods with high content of trans fat such as crisps, cakes and pastries, biscuits, margarine, ghee, butter-blend, and ice-cream.
- Replace foods high in saturated fats such as palm oil, butter, ghee, coconut oil with foods which contain predominantly polyunsaturated and monounsaturated fats such as canola oil, olive oil, sunflower oil, soybean oil and other cooking oil
- Avoid using used cooking oil repeatedly
- Replace deep frying with alternative low fat cooking methods such as steaming, baking, grilling and boiling
- Choose low fat dairy products such as skimmed/low fat milk to replace non-dairy creamer, evaporated milk and sweetened condensed milk
- Use reduced fat milk to replace coconut milk in dishes
- Consume at least two servings of fish per week, preferably oily fish such as *duai kuning*, *kembura*, *balanak*, *tamban*, *tenggiri* and salmon
- Choose 'trans-fat free' products.

## 5. Limit alcohol intake to a maximum of 2 units daily for men and 1 unit daily for women

Recent epidemiological and clinical studies have demonstrated that chronic alcohol consumption (more than three drinks per day, 30 g ethanol) is associated with an increased incidence of hypertension and an increased risk of cardiovascular diseases<sup>(29–32)</sup>.

1 unit of alcohol is equivalent to:

- 12 ounces beer
- 5 ounces wine
- 1.5 ounce distilled

## 6. Weight Control

Increased body weight is a strong risk factor for hypertension. In adults with a BMI greater than 35kg/m<sup>2</sup>, a weight reduction of 2kg can result in a clinically meaningful reduction in systolic blood pressure<sup>(33)</sup>. In two separate studies, a weight reduction of 1kg was associated with lowering systolic and diastolic blood pressure by an average of 1 mmHg<sup>(34)</sup> and a weight reduction of 5-10kg was associated with systolic and diastolic blood pressure reduction of 7/3 mmHg and 13/7 mmHg respectively<sup>(33,35)</sup>.

It is currently recommended for overweight or obese persons to lose weight and for non-overweight person to maintain a healthy body weight or BMI as part of non-pharmacological management of hypertension.

### **Practical Recommendations:**

- Eat according to estimated calorie needs based on age, sex and physical activity level
- Be more aware of foods & beverages high in sugar & fats
- Learn to use Nutritional Information Labels
- Compare similar products and choose one with lower calories
- Choose lower calorie snack options (such as fresh fruit, salads)
- Choose smaller portions.
- Encourage and advocate the use of calorie content labels (catering, workplace, etc.)
- Be habitually physically active

## 7. Physical activity <sup>(1)</sup>

- Physical activity is known to lower blood pressure, especially aerobic exercise (reduce BP by up to –5/8 mmHg in hypertensive patients). It also occurs during dynamic exercise and static exercise training to a lesser degree (reduce BP by –4 mmHg and –5 mmHg respectively in hypertensive patients)

- Current WHO recommendations and National physical activity guidelines <sup>(36)</sup> for moderate intensity exercise are that: adults aged 18-64 years should perform at least 150 minutes of aerobic moderate-intensity exercise per week, or 75 minutes of aerobic vigorous -intensity exercise per week, or a combination of the two.
  - For older patients, physical activity is encouraged and can be dictated by their ability to do so in line with existing comorbidities.

#### **POINT OF REFERRALS**

**Referrals for newly diagnosed hypertension patients will be seen by a dietitian within 10 working days at their respective health centres / hospitals**

## **6: Pharmacological Management**

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### **Key Messages**

1. Threshold BP for treatment is  $\geq 140/90$  mmHg for patients with a low cardiovascular risk and 130-139/80-89 mmHg for patients with an elevated cardiovascular risk
2. Threshold BP for treatment and treatment target is the same
3. Start treatment with an ACE-I/ARB or a dihydropyridine CCB in Stage 1 hypertension (140-159/90-99 mmHg)
4. If high normal / elevated BP is treated due to elevated cardiovascular risk follow Stage 1 treatment advice
5. Initial combination therapy with ACE-I/ARB and a dihydropyridine CCB is recommended for Stage 2 hypertension and above
6. Add diuretics /  $\beta$ -blockers /  $\alpha$ -blockers if BP is not controlled
7. Consider spironolactone for resistant hypertension

\*See relevant disease-specific chapters for situations where other drugs may be preferred

### **6.2.1 Target BP**

This guideline recommends a target BP according to their cardiovascular risk.

<b>Patients with low cardiovascular risk</b>	BP <140/90 mmHg
<b>Patients with elevated cardiovascular risk (e.g. DM, previous stroke, TIA, CKD with albuminuria)</b>	BP <130/80 mmHg
<i>Adapted from: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline <sup>(1)</sup></i>	

**Table 12:** Target BP

The target BP is an individualised decision and BP lowering should be monitored and as tolerated by the patient. Ideally, there should be a process of shared-decision making to decide on the appropriate target.

Please refer to individual chapters for more guidance.

Category	Systolic Blood pressure (mmHg)	Diastolic Blood pressure (mmHg)
High normal / Elevated BP	130-139	80-89
Stage 1 Hypertension	140-159	90-99
Stage 2 Hypertension	160-179	100-109
Severe hypertension	>180	>110

**Table 13:** Categories of BP level, adopted from ESC/ESH 2018 Guidelines <sup>(10)</sup>

### 6.2.2 Choice of Antihypertensive Medications

- The decision to start pharmacological treatment should involve overall CVD risk assessment.
- In general, a 10-year CVD risk of > 10% is considered elevated <sup>(13)</sup>.
- For most patients with a low 10-year CVD risk, pharmacological therapy should be started at and above BP of 140/90 mmHg <sup>(1)</sup>.
- For those at elevated CVD risk, pharmacological treatment can be started at and above 130/80 mmHg <sup>(1)</sup>.
- If drug therapy is started for a BP of  $\geq 140/90$  mmHg in patients with low cardiovascular risk, then the treatment target is <140/90 mmHg <sup>(10)</sup>.
- If drug therapy is started for a BP of 130-139/80-89 mmHg in patients with elevated cardiovascular risk, then the treatment target is <130/80 mmHg <sup>(1)</sup>.
- Where less aggressive therapy is chosen, such as in Stage 1 hypertension, the initial treatment can be started with a single drug which should be in most cases an ACE-I / ARB or CCB.
- In cases where the urgency of treatment is higher, such as patients with a higher risk profile or Stage 2 hypertension or above, it is recommended that the treatment is started with two anti-hypertensive medications (from different classes, started at low doses) <sup>(10)</sup>. This method not only achieves the target BP early but also reduces the likelihood of side-effects.
- The usual second line drug is a dihydropyridine CCB such as amlodipine. An ACE-I or ARB is 2<sup>nd</sup> line if it has not already been started.
- If BP remains uncontrolled a thiazide or thiazide-like diuretic is added. If the eGFR is <30ml/min/1.73m<sup>2</sup> then loop diuretics should be used instead. Furosemide if used in these situations, should generally not be used at a single daily dose but rather as a divided dose twice a day <sup>(10)</sup>.
- The next drug to be added is a  $\beta$ -blocker or  $\alpha$ -blocker depending on associated medical conditions. For example, if the patient has angina or systolic heart failure

with a reduced ejection fraction then a  $\beta$ -blocker may be used preferentially.  $\beta$  and  $\alpha$ -blockers may be used together.

- Lastly, mineralocorticoid receptors such as spironolactone can be considered (only if eGFR  $>45\text{ml}/\text{min}/1.73\text{m}^2$ ) <sup>(10)</sup>.
- If eGFR  $<30\text{ml}/\text{min}/1.73\text{m}^2$ , then patient should be referred to Renal services for further management.
- If an endocrine cause is suspected, then the patient should be referred to Endocrinology services. If other secondary causes are suspected referral to the appropriate specialties should be considered.
- Consider referring the patient to a hypertension clinic (under cardiology services) if the patient has uncontrolled hypertension despite being on 4 medications.
- Resistant hypertension is defined as uncontrolled office BP  $\geq 140/90$  mmHg on 3 or more drugs including a diuretic.

### **6.2.3 Summary of anti-hypertensive choices (in the absence of other compelling indications)**

Antihypertensive therapy should be titrated at monthly intervals until control is achieved <sup>(25)</sup>.

In general, treat Stage 1 hypertension with monotherapy; with Stage 2 or higher hypertension, consider initial combination therapy with two anti-hypertensives of different classes at low doses to minimise side-effects

Other options e.g. hydralazine, labetalol may be used in special situations. Other drugs may be used as first line treatment for hypertension in the presence of other compelling indications e.g. in heart failure.

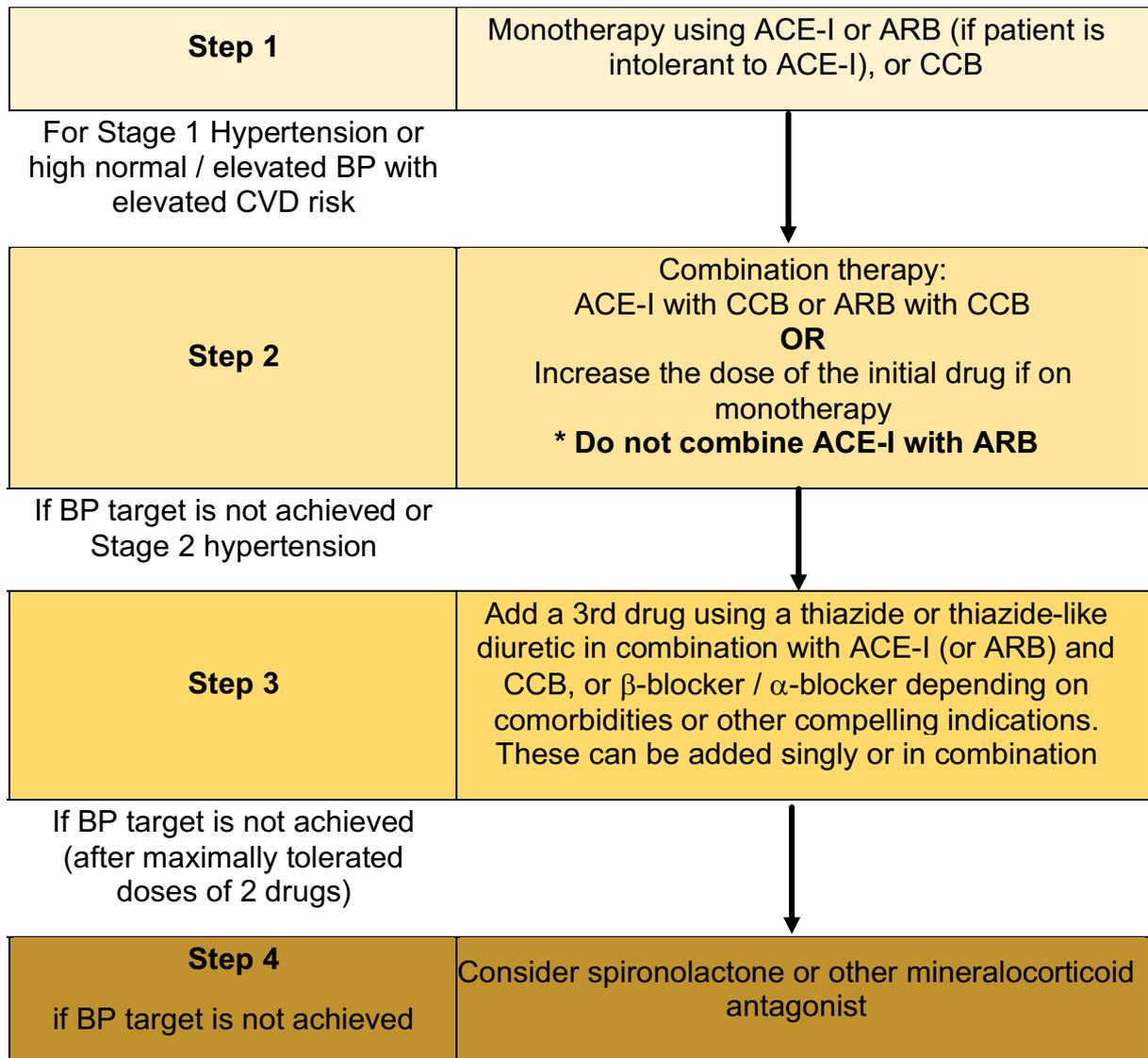
Consider referral of patients with uncontrolled hypertension where secondary causes are suspected to endocrinology or cardiology as appropriate.

#### **Combination Pills**

- Use of combination pills is to be encouraged if available.
- These should contain ACE-I or ARB and CCB as a base.

#### **Caution with ACE-I or ARB**

- Do not combine ACE-I with ARB
- To check UEC within 2 weeks of starting ACE-I or ARB.
  - If there is a rise in creatinine of 15%, repeat the test after a further 2 weeks and consider halving the dose.
  - If there is a rise in creatinine of  $> 30\%$ , stop the medication and discuss with nephrologist.
  - If there is a rise in serum potassium  $>5.5$  whilst on ACE-I, consider reducing the dose. Repeat serum potassium 2 – 3 days. If potassium remains  $> 5.5$ , stop medication.



**Figure 2:** Stepwise approach in antihypertensive therapy

For management of hypertension in pregnancy, please refer to **Chapter: 14 Hypertensive Disorders of Pregnancy.**

For women of child-bearing age, there are no specific recommendations regarding the choice of antihypertensive drugs. However, for women who are intending to become pregnant, pre-conception counselling may be required and drugs known to have detrimental effects on the foetus may need to be avoided.

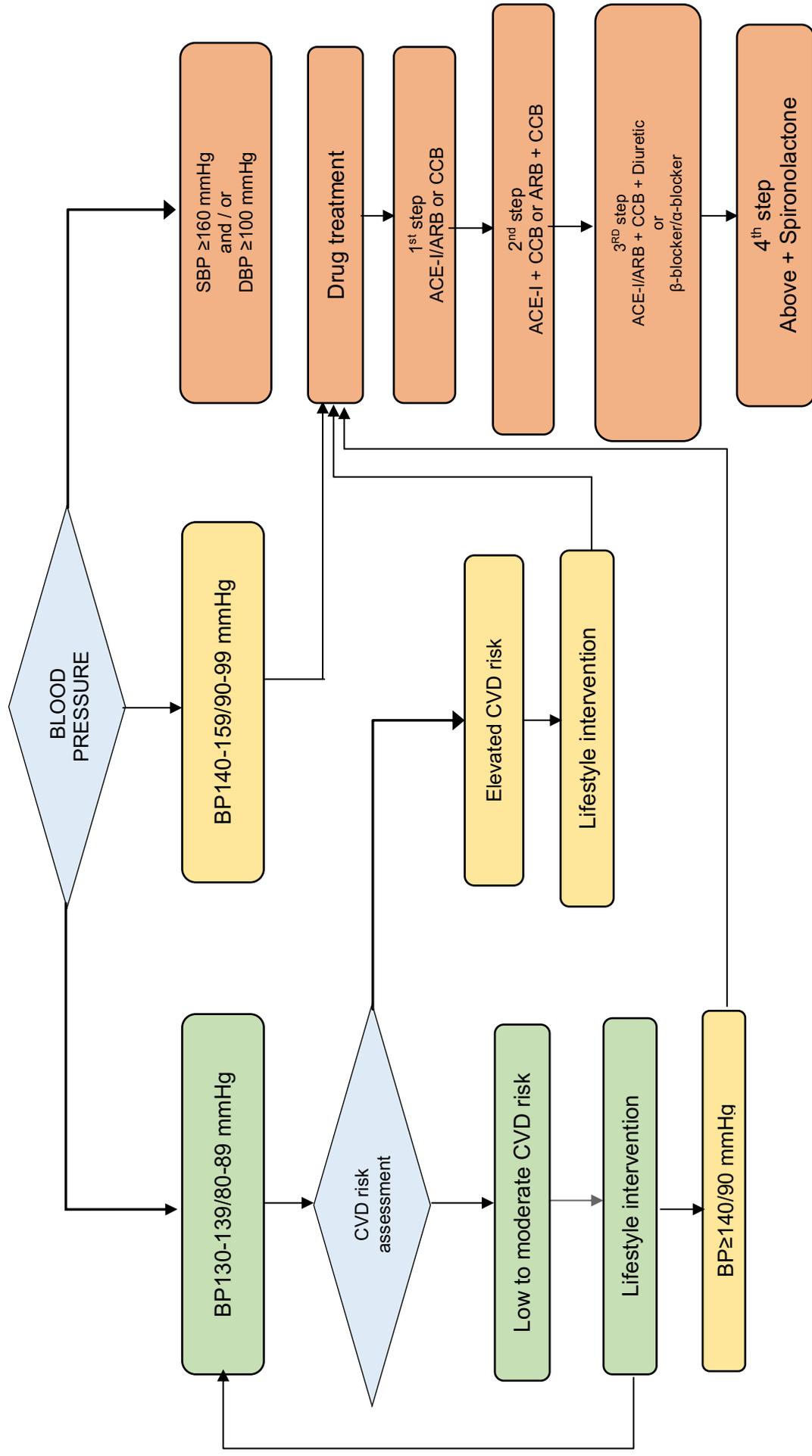


Figure 3: Summary of anti-hypertensive approach

## 7: Secondary Hypertension

Dr Lina Chong Pui Lin

### Key Messages:

1. Early detection of secondary causes of hypertension is important as interventions may be curative or may reduce the number of antihypertensive medications needed to achieve target BP control.
2. Screening for specific causes of hypertension is recommended when clinical indications and physical findings are present or in resistant hypertension.
3. Exclude pseudo-hypertension, pseudo-resistant hypertension and drug-induced hypertension in those with suspected secondary hypertension to avoid unnecessary investigations.
4. All patients in whom secondary hypertension is suspected should be referred to a specialist hypertension clinic following initial basic investigations so that further investigations can be undertaken.

### INTRODUCTION

Secondary hypertension is defined as hypertension due to an identifiable cause and occurs in 5-10% of people with hypertension<sup>(37)</sup>. Early recognition and diagnosis of secondary hypertension is essential as definitive treatment may be potentially curative. It is not uncommon for essential hypertension to co-exist in patients with secondary hypertension, particularly with increasing age<sup>(37)</sup>.

It is beyond the scope of this guideline to discuss *in detail* the clinical management of specific causes of secondary hypertension. This chapter will focus on commoner causes of secondary hypertension with recommendations on their clinical evaluation.

### SCREENING

- Take a thorough medical history including cardiovascular risk factors and a detailed drug history.
- Specific history of possible secondary hypertension is shown in **Table 14**<sup>(10)</sup>.
- Physical examination should include anthropometric measurements (body mass index and waist circumference), evaluation of hypertension-mediated organ damage (HMOD), and possible indications of secondary hypertension (**Table 15**)<sup>(10)</sup>.
- Based on local patient characteristics, metabolic syndrome occurs in younger adults and an age cut-off of <30 years is preferable as an indication to investigate secondary causes of hypertension<sup>(1)</sup>. However, individuals age 30-40 years with a high index of suspicion of secondary hypertension should be investigated.
- Pseudo-hypertension and pseudo-resistant hypertension should be excluded prior to biochemical or radiological evaluation of patients with suspected secondary hypertension<sup>(10,37)</sup>.

Young onset (age <30 years) of stage 2 hypertension or more (BP ≥160/100 mmHg) or onset of any stage of hypertension in childhood
Sudden development of hypertension or rapidly worsening BP in older adults
Severe hypertension (BP ≥180/110 mmHg) or hypertensive emergencies
History of renal or urinary tract disease
Recreational drugs, substance abuse or concurrent therapies (corticosteroids, nasal vasoconstrictor, chemotherapy, yohimbe, liquorice)
Repetitive episodes of sweating, headache, anxiety or palpitations suggestive of pheochromocytoma
History of spontaneous or diuretic-provoked hypokalaemia, episodes of muscle weakness, and tetany may be suggestive of hyperaldosteronism
Symptoms suggestive of thyroid disease or hyperparathyroidism
History of obstructive sleep apnoea
Resistant hypertension*
Presence of extensive hypertension-mediated organ damage**

**Table 14:** History suggestive of secondary hypertension

Ref: Adapted from ESC/ESH 2018 guidelines<sup>(10)</sup>

\*Resistant hypertension defined as hypertension (BP >140/90 mmHg) despite 3 antihypertensive medications including a diuretic at optimal doses

\*\*Hypertension-mediated organ damage (HMOD) to cardiac, brain, retina, kidneys and vasculature

Clinical features suggestive of obstructive sleep apnoea
Cutaneous features: café-au-lait patches of neurofibromatosis (pheochromocytoma)
Kidney palpation for signs of renal enlargement in polycystic kidney disease
Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation, or renovascular hypertension
Comparison of radial and femoral pulses to detect radio-femoral delay in aortic coarctation
Signs of Cushing's syndrome or acromegaly
Signs of thyroid disease

**Table 15:** Physical features suggestive of secondary hypertension

Ref: Adapted from ESC/ESH 2018 guidelines<sup>(10)</sup>

### **Pseudo-hypertension**<sup>(10,37)</sup>

- Defined as cuff diastolic BP at least 15 mmHg higher than simultaneously measured intra-arterial BP which occurs in the elderly with heavily calcified arteries.
- Patients with marked brachial artery calcification have falsely high BP readings and generally do not manifest significant HMOD.

### **Pseudo-resistant hypertension**

Several causes of pseudo-resistant hypertension are described below:

#### *1. Inadequate BP measurement techniques*

BP should be measured with patient sitting quietly for at least 5 minutes using an adequate cuff size (relative to arm circumference). Correct BP measurement techniques must be undertaken to spurious readings<sup>(10,37)</sup>.

#### *2. White coat hypertension*

- A phenomenon in which patients have elevated 'office' BP readings but normal/controlled BP readings at home or as demonstrated on ambulatory BP monitoring (ABPM).
- Frequent cause of pseudo-resistance with a prevalence of approximately 20-30%<sup>(38)</sup>.
- A 24-hour ABPM is a valuable tool to assess the likelihood of secondary hypertension in this group of patients.

#### *3. Non-adherence to antihypertensive medications*

- Poor adherence to antihypertensive medications is the most important cause of uncontrolled BP resulting in approximately 75% of patients not achieving optimum BP control.
- Adherence to pharmacotherapy for hypertension varies between 50% and 70%. Improving adherence has to be a shared responsibility between healthcare professionals and the patient<sup>(39)</sup>.

#### *4. Clinician inertia*

This refers to physicians' failure to titrate therapy to reach target BP control and may be a consequence of inadequate dosing or irrational combination of antihypertensive medications<sup>(10,37)</sup>.

## **CAUSES OF SECONDARY HYPERTENSION**

### **Drug-related hypertension**

A list of medications and substances which may increase BP is shown **Table 16**<sup>(10,40)</sup>. By stopping the offending medication, unnecessary investigations may be avoided.

Common causes of secondary hypertension are described below and summarised in **Table 17**. Rare monogenic causes are not discussed.

Oral contraceptive pill	Especially oestrogen containing; cause hypertension in 5% of women, usually mild but can be severe
Diet pills	For example, phenylpropanolamine and sibutramine
Nasal decongestants	For example, phenylephrine hydrochloride and naphazoline hydrochloride
Stimulant drugs	Amphetamine, cocaine, and ecstasy; these substances usually cause acute rather than chronic hypertension
Liquorice	Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism
Immunosuppressive medications	For example, cyclosporin A (tacrolimus has less effect on BP and rapamycin has almost no effect on BP) and steroids (e.g. corticosteroids and hydrocortisone)
Antiangiogenic cancer therapies	Antiangiogenic drugs such as VEGF inhibitors (e.g. bevacizumab), tyrosine kinase inhibitors (e.g. sunitinib), and sorafenib have been reported to increase BP
Other drugs and substances	Anabolic steroids, erythropoietin, non-steroidal anti-inflammatory drugs, and herbal remedies (e.g. ephedra)

**Table 16:** Drug-induced hypertension  
Ref: Adapted from ESC/ESH 2018 guideline<sup>(10)</sup>

### Renal causes

- *Renal parenchymal disease* is the most common cause of secondary hypertension in children and the second most common cause in adults<sup>(37)</sup>.
- *Renal artery stenosis*<sup>(37)</sup>
- *Fibromuscular dysplasia* of the renal artery is one of the commonest causes of secondary hypertension in children and young adults
- *Atherosclerotic renal artery stenosis* is the commonest form of renovascular disease in adults.
- Beware *Takayasu arteritis* which is a rare large vessel vasculitis associated with renal artery stenosis. It is most commonly seen in Japan and South East Asia.

### Endocrine causes

- *Primary hyperaldosteronism or Conn syndrome*<sup>(10,37)</sup>
- Accounts for about 11% of patients with hypertension<sup>(41)</sup> but higher in those with resistant hypertension.
- Characterised by arterial hypertension, suppressed plasma renin activity and increased adrenal aldosterone production.
- Most commonly caused by aldosterone producing adenoma.
- Hypokalaemia occurs in 40% of patients and other clinical features include muscle weakness, fatigue, constipation and resistant hypertension.
- If primary aldosteronism is suspected, the first screening test is a plasma aldosterone-renin ratio (ARR). Accuracy of ARR can be affected by several factors such as medications and hypokalaemia (**Table 18**)<sup>(42)</sup>

Cause	Prevalence in hypertensive patients	Suggestive symptoms and signs	Screening investigations
Renal parenchymal disease	2-10%	Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD	Plasma creatinine and electrolytes, eGFR; urine dipstick for blood and protein, urinary ACR; renal ultrasound
Atherosclerotic renal artery stenosis	1-10%	Older; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit	Duplex renal artery Doppler or CT angiography or MR angiography
Fibromuscular dysplasia		Younger; more common in women; abdominal bruit	
Primary hyperaldosteronism	5-15%	Mostly asymptomatic; muscle weakness (rare); hypokalaemia (found in about 40%)	Plasma aldosterone and renin, and ARR* (specialist test); UEC  <i>NB: hypokalaemia can depress aldosterone levels; ensure normal serum potassium before measuring aldosterone</i>
Phaeochromocytoma	<1%	Episodic symptoms (the 5 'Ps': paroxysmal hypertension, pounding headache, perspiration, palpitations, and pallor); labile BP; BP surges precipitated by drugs (e.g. $\beta$ -blockers, metoclopramide, sympathomimetics, opioids, and tricyclic antidepressants)	24h urinary VMA* analysis is done locally and can be considered as a screening test in non-specialist clinics (subject to availability)  24h urinary catecholamines or 24h urinary fractionated metanephrines, or plasma free metanephrines* (specialist test)
Cushing's syndrome	<1%	Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use	1mg overnight dexamethasone suppression test or 24h urinary free cortisol

Thyroid disease (hyper and hypothyroidism)	1-2%	Symptoms and signs of hyper or hypothyroidism	TFT
Primary hyperparathyroidism	<1%	Hypercalcaemia and hypophosphataemia	Serum calcium, phosphate and parathyroid hormone
Acromegaly	unknown	Acral and soft tissue overgrowth, headaches, hyperhidrosis, coarse facial features, prognathism, increased interdental spacing, degenerative arthritis; presence of associated conditions such as diabetes, sleep apnoea and carpal tunnel syndrome	IGF-1 (specialist test)
Obstructive sleep apnoea	5-10%	Snoring; obesity (can be present in non-obese); morning headache; daytime somnolence	Epworth score and ambulatory polygraphy
Coarctation of aorta	<1%	Usually detected in children or adolescence; different BP ( $\geq 20/10$ mmHg) between upper-lower extremities and/or between right-left arm and delayed radial-femoral femoral pulsation; low ABI; interscapular ejection murmur; rib notching on chest X-ray	Echocardiogram

Ref: Adapted from ESC/ESH 2018 guideline<sup>(10)</sup>

\*ARR: 24h urinary VMA requires and 24h urinary catecholamines/metanephrines measurements require special preparation of patient with particular attention to interfering medications and food substances

NB: 24h urinary VMA has high specificity (95%) but poor sensitivity (64%) compared with 24h urinary catecholamines (88% and 86%), and 24h urinary fractionated metanephrines (86% and 95% respectively)<sup>(43,44)</sup>

**Table 17:** Common causes of secondary hypertension and proposed screening investigations

a) *Phaeochromocytoma*

- Tumours arising from adreno-medullary chromaffin cells which commonly secrete one or more catecholamines: epinephrine, norepinephrine and dopamine<sup>(45)</sup>.
- Prevalence of phaeochromocytoma in unselected hypertensive patients is about 0.2%<sup>(37)</sup>.
- Screening should be performed in patients with one or more of the following<sup>(37,45)</sup>:
  - resistant hypertension and hyperadrenergic symptoms ('five Ps': paroxysmal hypertension, palpitations, perspiration, pallor and pounding headache)
  - family history of phaeochromocytoma
  - hereditary predisposition or syndromic features suggesting hereditary phaeochromocytoma (multiple endocrine neoplasia type 2, Von Hippel Lindau, neurofibromatosis type 1)
- adrenal incidentaloma with or without hypertension.

Factors	Effect on Aldosterone	Effects on Renin	Effect on ARR
β blockers	↓	↓↓	↑ (FP)
Central agonists (e.g. clonidine, α-methyldopa)	↓	↓↓	↑ (FP)
NSAIDS	↓	↓↓	↑ (FP)
K <sup>+</sup> wasting diuretics	→ ↑	↑↑	↓ (FN)
K <sup>+</sup> sparing diuretics	↑	↑↑	↓ (FN)
ACE-I	↓	↑↑	↓ (FN)
ARBs	↓	↑↑	↓ (FN)
Ca <sup>2+</sup> blockers (DHPs)	→ ↓	↑	↓ (FN)
Renin inhibitors	↓	↓ ↑	↑ (FP); ↓ (FN)

**Table 18:** Medications that may affect plasma aldosterone and renin levels<sup>(42)</sup>

b) *Cushing's syndrome*

- Rare disorder comprising of symptoms and signs that reflect prolonged and inappropriately high exposure of tissue to glucocorticoids.
- Hypertension occurs in about 80% of patients with Cushing's syndrome<sup>(37,46)</sup>.
- Typical features include obesity, moon face, facial plethora, easy bruising, reddish purple striae and proximal myopathy.
- Any screening test for Cushing's syndrome should only be undertaken after the exclusion of exogenous glucocorticoid exposure.

c) *Thyroid diseases*

- Both hyper- and hypothyroidism are associated with arterial hypertension.
- Hyperthyroidism increase systolic BP by decreasing systemic vascular resistance, increasing heart rate and raising cardiac output.
- Hypothyroidism is predominantly associated with elevated diastolic BP due to increased systemic vascular resistance.

d) *Primary hyperparathyroidism*

- Common endocrine disorder characterised by excessive secretion of parathyroid hormone from one or more of the 4 parathyroid glands leading to hypercalcaemia.
- Hypertension is associated with primary hyperparathyroidism although the exact mechanism is unknown.

e) *Acromegaly*<sup>(47)</sup>

- Rare disorder characterised by chronic growth hormone excess due to a growth hormone secreting pituitary adenoma.
- Hypertension occurs in 33-46% patients with acromegaly.
- Clinical features include acral and soft tissue overgrowth, headaches, hyperhidrosis, coarse facial features, prognathism, increased interdental spacing, degenerative arthritis and carpal tunnel syndrome.

## **Other causes of secondary hypertension**

### **Obstructive sleep apnoea (OSA)**<sup>(10,37)</sup>

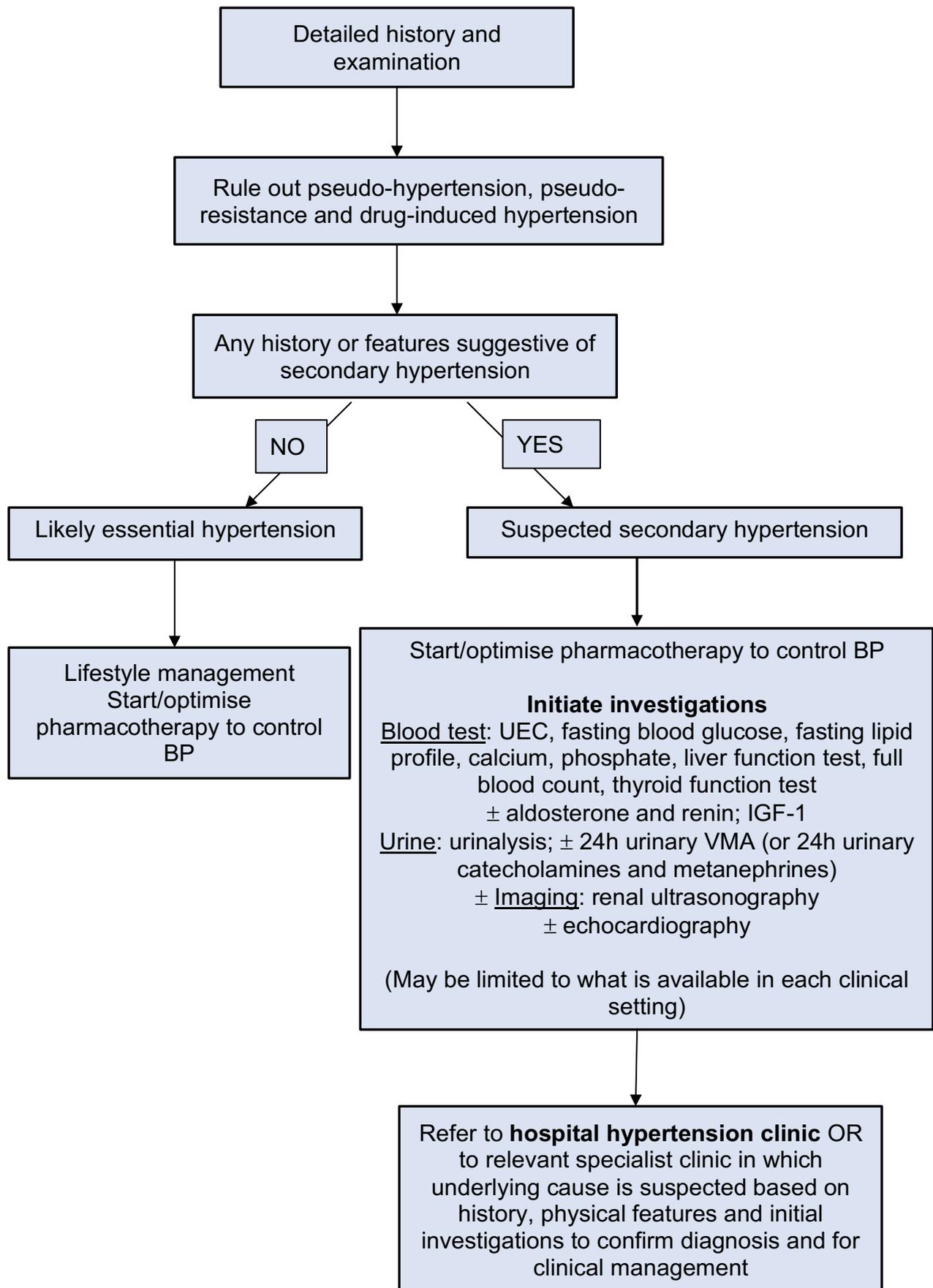
- One of the commonest causes of secondary hypertension occurring in 5-10% of hypertensive patients.
- Characterised by recurrent obstructive apnoeas and hypopnoeas caused by the collapse of the upper airways during sleep.
- Patients are typically obese with a large neck and macroglossia; and symptoms include snoring, exaggerated daytime somnolence, morning headache, irritability, and lack of concentration.

### **Coarctation of aorta**<sup>(10,37)</sup>

- Second most common cause of hypertension in children and young adults.
- Characterised by constriction of the lumen of the aorta usually near the ligamentum arteriosum.
- Symptoms and signs include headache, cold feet, pain in the legs during exercise, arterial hypertension, systolic murmurs in the front and/or back of the chest, and the presence of weak femoral pulses.

## **INVESTIGATIONS**

Secondary causes of hypertension are rare and undertaking investigations for every patient with hypertension is not cost-effective. Evaluation of patients with suspected secondary hypertension is proposed in **Figure 3**. Screening investigations on specific causes of secondary hypertension are summarised in **Table 17**. Additional confirmatory tests, not discussed in this guideline, may be considered following discussion or referral to relevant specialist clinic.



**Figure 4:** Evaluation of Patients with Suspected Secondary Hypertension

## 8: Hypertension Crisis - Urgency and Emergency

Dr Linawati Haji Jumat

### Key Messages:

1. Hypertensive urgency is defined as acutely elevated BP  $\geq 180/110$  mmHg without evidence of new or worsening organ dysfunction and can usually be treated with oral medication and does not require admission.
2. Hypertensive emergency is defined as acutely elevated BP  $\geq 180/110$  mmHg with evidence of complications or organ dysfunction and requires urgent treatment and inpatient admission.

### 1. Introduction

Patients with poorly-controlled hypertension may present to the Primary Health Centre or Emergency Department with markedly elevated blood pressure (BP) and is a source of anxiety, not only for the patients, but also for the doctors and nurses who care for them. Patients can present with highly heterogeneous profiles ranging from absence of symptoms to life-threatening target organ damage. Common presentations include:

- an incidental finding of newly-diagnosed severe hypertension in an asymptomatic patient;
- a finding of severe hypertension in an asymptomatic patient already on treatment with GP or outpatient clinic follow-up;
- a patient with non-specific symptoms like headache, dizziness, lethargy;
- a patient with symptoms and signs of acute target organ damage, such as acute heart failure, acute coronary syndromes, acute renal failure, dissecting aneurysm, subarachnoid haemorrhage, hypertensive encephalopathy and pre-eclampsia/eclampsia.

Severe acute arterial hypertension is usually defined as '**Hypertensive Crisis**', which is often used to include both hypertensive emergencies and urgencies:

- **Hypertensive Urgency** is an acute severe elevation in blood pressure ( $\geq 180/110$  mmHg) **without** clinical or laboratory evidence of new or worsening target organ dysfunction.
- **Hypertensive Emergency** is an acute severe elevation in blood pressure ( $\geq 180/110$  mmHg) **with** complications of impending or progressive target organ dysfunction involving neurological, cardiac or renal systems. Common clinical manifestations of target organ damage in hypertensive emergency are shown in **Table 19**.

Within the hypertensive crises, hypertensive emergencies account for only around one-fourth of presentations compared with hypertensive urgencies, which account for around three-fourths <sup>(48)</sup>.

## 2. Initial Clinical Evaluation and Diagnostic Workup for Hypertensive Crisis

The appropriate treatment strategies for patients with hypertensive crisis 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 and causes of secondary hypertension with diagnostic workup as shown in **Table 20**. Do not treat the patient based on a single blood pressure reading alone. Recheck the BP when patient is comfortable using an appropriately-sized cuff.

## 3. Recommendations for the Management of Hypertensive Crisis

The Joint National Committee<sup>(49,50)</sup> and the European Society of Hypertension<sup>(10)</sup> suggest different diagnostic and therapeutic approaches for hypertensive emergency and hypertensive urgency. There is a paucity of literature regarding the preferred rate of decline of blood pressure, while treating these patients, as well as the appropriate medications to be used. However, based on expert opinion and anecdotal data, it is recommended that the initial management should focus on promptly identifying impending or established end-organ damage and decreasing the blood pressure by about 25% in the first 2 hours, except in aortic dissection where rapid lowering of blood pressure is recommended.

Recommendations
Do not reduce BP rapidly (within minutes to hours) in hypertensive urgencies as it may precipitate ischaemic events.
For patients whose BP responded with adequate rest (after 2 hours), discharge them with Hypertensive Urgency Discharge Plan.
For patients whose BP do not respond to adequate rest, start with combination oral pharmacotherapy targeting a BP reduction of 25% within 24 hours.
Recommendations
Reduce BP by 10%-25% within minutes to hours but not lower than 160/100 mmHg. This is best achieved with parenteral drugs.
Reduce SBP to less than 140 mmHg during the first hour for patients with severe pre-eclampsia or eclampsia, and pheochromocytoma crisis. Reduce to less than 120 mmHg for patients with aortic dissection.
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.

## 4. Management of Hypertensive Urgency

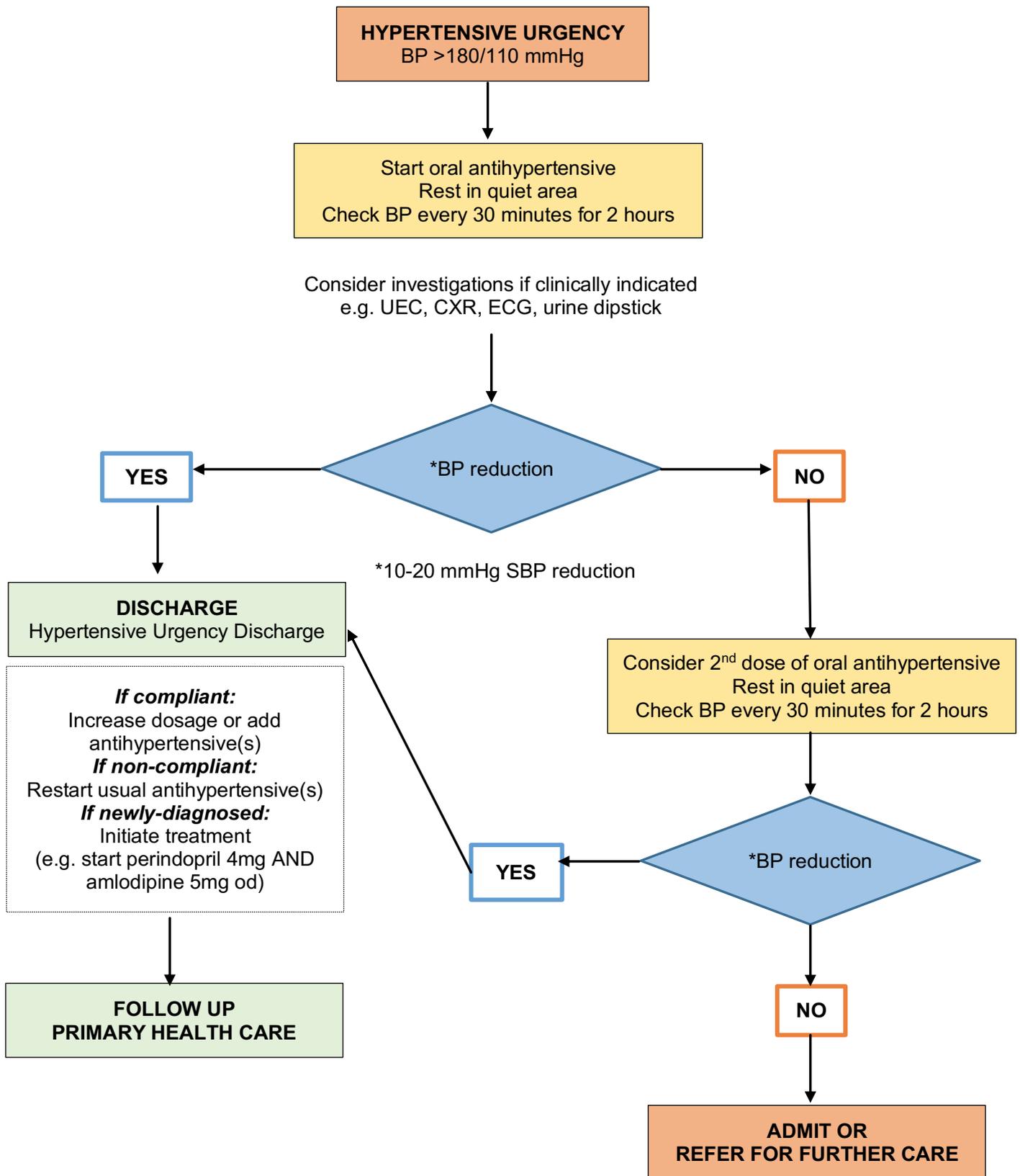
Many of these patients have been non-compliant with their anti-hypertensive therapy. They may have vascular injury presenting as grade III or IV retinal changes (also known as accelerated and malignant hypertension) but do not have clinical or laboratory evidence of acute target organ damage. Other possible precipitating factors for hypertensive urgency include less effective outpatient blood pressure control, acute pain, herbal supplement and emotional stress.

Hypertensive Emergency BP >180/120 mmHg with impending target organ dysfunction				
Neurological	Cardiac	Renal	Catecholamine Crisis	Pregnancy
<ul style="list-style-type: none"> <li>• Hypertensive Encephalopathy</li> <li>• Acute Ischaemic Stroke</li> <li>• Acute Haemorrhagic Stroke / Intracerebral Haemorrhage</li> </ul>	<ul style="list-style-type: none"> <li>• Acute Coronary Syndrome</li> <li>• Acute Decompensated Heart Failure / Acute Cardiogenic Pulmonary Oedema</li> <li>• Acute Aortic Dissection</li> </ul>	<ul style="list-style-type: none"> <li>• Acute Glomerulonephritis</li> <li>• Reno-vascular Hypertension</li> <li>• Renal Artery Stenosis</li> </ul>	<ul style="list-style-type: none"> <li>• Pheochromocytoma</li> <li>• Post-carotid Endarterectomy Status</li> <li>• Drugs: Cocaine, Methamphetamine, Monoamine Inhibitors</li> <li>• Drug Withdrawal e.g.: Clonidine, Tizanidine</li> </ul>	<ul style="list-style-type: none"> <li>• Eclampsia</li> <li>• Severe Pre-eclampsia</li> </ul>

**Table 19.** Common clinical scenarios associated with hypertensive emergency.

<b>Patient History</b>	<ul style="list-style-type: none"> <li>• <b>Signs and Symptoms related to any acute target organ involvement</b></li> <li>• <b>Hypertensive history</b></li> <li>• <b>Baseline blood pressure at home or in ambulatory setting</b></li> <li>• <b>Medication(s)</b></li> <li>• <b>Last dose of antihypertensive medication taken</b></li> <li>• <b>Medication compliance</b></li> <li>• <b>History of recreational drug use</b></li> </ul>
<b>Physical Examination</b>	<ul style="list-style-type: none"> <li>• <b>Is the Blood Pressure reading correct?</b> <ul style="list-style-type: none"> <li>- Check BP on both arms with an appropriately sized cuff</li> <li>- Use a manual sphygmomanometer, if possible</li> <li>- Serial BP rechecks are required, especially if patient is asymptomatic</li> </ul> </li> <li>• <b>Is there any target organ dysfunction suggesting Hypertensive Emergency?</b> <ul style="list-style-type: none"> <li>- Neurological examination for focal deficits and altered mental status</li> <li>- Fundoscopy examination for exudates, haemorrhages or papilloedema</li> <li>- Cardiovascular examination for left ventricular failure, new aortic regurgitation murmurs and evidence of dissection, for example: <ul style="list-style-type: none"> <li>• Crepitations in the lung fields</li> <li>• Pathologic gallops and murmurs</li> <li>• Elevated JVP</li> <li>• Pulsatile mass and/or tenderness in the abdomen</li> <li>• Unequal distal pulses</li> </ul> </li> </ul> </li> </ul>
<b>Bedside Investigations</b>	<ul style="list-style-type: none"> <li>• <b>12-Lead ECG</b> - To look for LVH, arrhythmias, acute ischemia or infarction.</li> <li>• <b>Urinalysis</b> - To look for haematuria and proteinuria.</li> <li>• <b>Urine Pregnancy Test</b> - In all women of child-bearing age if suspect severe pre-eclampsia or eclampsia.</li> </ul>
<b>Laboratory Workup</b>	<ul style="list-style-type: none"> <li>• <b>Urea, Electrolytes &amp; Creatinine (UEC)</b></li> <li>• <b>Cardiac Enzymes - Troponin, CK-MB and NT-proBNP</b></li> <li>• <b>Full blood count (FBC)</b></li> <li>• <b>Liver function test (LFT)</b> - if the patient is pregnant to identify <b>HELLP</b> (<b>H</b>aemolysis, <b>E</b>levated <b>L</b>iver Enzymes, and <b>L</b>ow <b>P</b>latelet count) syndrome</li> <li>• <b>Urine Drug Screen</b> if suspected substance abuse (methamphetamine, cocaine)</li> </ul>
<b>Radiographic Studies</b>	<ul style="list-style-type: none"> <li>• <b>Chest X-ray</b> to assess for fluid overload, cardiomegaly or widened mediastinum</li> <li>• <b>Echocardiography</b> (aortic dissection, heart failure, ischaemia)</li> <li>• <b>Renal Ultrasound</b> (for suspected renal artery stenosis)</li> <li>• <b>CT or MRI brain</b> (if suspected nervous system involvement or stroke)</li> <li>• <b>CT angiography of thorax or abdomen</b> (suspected acute aortic disease / aortic dissection)</li> </ul>

**Table 20.** Initial clinical evaluation and diagnostic workup for patients with Hypertensive Crisis.



**Figure 5:** Algorithm of the management of Hypertensive Urgency.

## HYPERTENSIVE URGENCY DISCHARGE PLAN

### 1) Blood pressure monitoring

- Home BP monitoring 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 unwell symptoms, seek medical help.

### 2) Medication

- Do take anti-hypertensive as prescribed.

### 3) Follow up care

- Do not miss any clinic follow-up appointment.

### 4) When to call 991

- When you experience symptoms such as chest pain, difficulty in breathing, weakness on one side of your arms or legs, facial drooping, slurred speech, drowsiness or confusion.

**Figure 5** is the algorithm of the management of hypertensive urgency in the Emergency Department and outpatient setting. Patients with hypertensive urgencies may benefit from treatment with an oral, short-acting agent (**Table 21** and **Table 22**). The initial treatment should aim for about 25% reduction in BP over 24 hours but not lower than 160/100 mmHg. Rapid lowering of BP (within minutes to hours) in asymptomatic patients is unnecessary and can be harmful as it can precipitate cerebral, myocardial or renal ischaemia. When treatment is initiated, attempt to lower BP **gradually**.

Patients can be discharged if response is prompt and the blood pressure is acceptable after 4 hours of monitoring. However, follow-up should be arranged. In patients with newly-diagnosed hypertension where the cause is uncertain, may be admitted for evaluation and exclusion of secondary causes of hypertension.

## 5. Management of Hypertensive Emergency

Hypertensive emergencies demand immediate reduction of BP with early initiation of appropriate antihypertensive treatment to prevent or limit further target organ damage. Examples of target organ damage include hypertensive encephalopathy, acute haemorrhagic stroke or intracranial haemorrhage, acute ischemic stroke, acute coronary syndrome, acute myocardial infarction (MI), acute left ventricular (LV) failure with pulmonary oedema, dissecting aortic aneurysm, acute renal failure, and severe pre-eclampsia / eclampsia. **Figure 6** is the algorithm of the management of hypertensive emergency. These patients should be managed in a closely monitored area (e.g. Priority 1 in the Emergency Department) as the clinical state may change rapidly. Patients should be admitted to an intensive care unit (ICU).

Drug	Starting Dose	Onset of Action	Contraindications
Amlodipine	2.5 - 5 mg	30 - 50 min	Hypersensitivity reactions
Captopril	12.5 - 25 mg	15 - 30 min	Renal artery stenosis, Hyperkalaemia, Angioedema, Pregnancy
Labetalol	100-200 mg	2 hrs	Asthma, COPD, Heart Failure, Heart Block, Sick Sinus Syndrome
GTN patch	5 - 10 mg	30 min - 1 hr	Recent use of phosphodiesterase-5 inhibitor
Irbesartan	150 mg	1 - 2 hrs	Renal artery stenosis, hyperkalaemia, angioedema, pregnancy
Hydralazine (consider in pregnant patients)	10 – 20 mg	5 - 20 min	Known hypersensitivity. Watch for reflex tachycardia.
Perindopril (erbumine)	2 – 4 mg	1 hr	Renal artery stenosis, hyperkalaemia, angioedema, pregnancy

**Table 21.** Oral Antihypertensive Medications for Hypertensive Urgencies

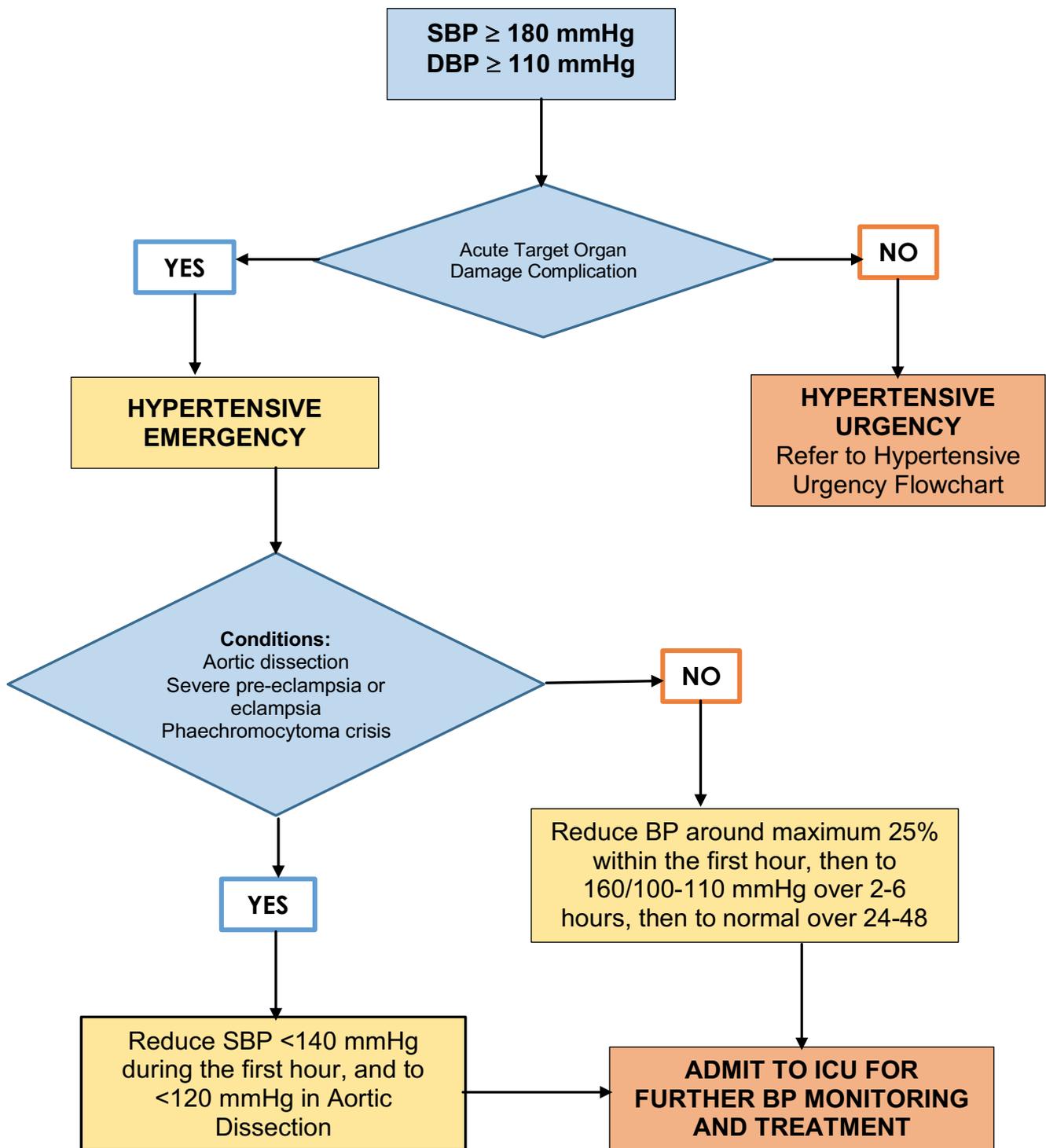
*\*For the specific management of pregnant patients with severe hypertension, please refer to **Chapter 14: Hypertensive Disorders of Pregnancy.***

Drug	Starting Dose	Contraindication
Perindopril	2 - 4 mg	Renal artery stenosis, hyperkalaemia, angioedema, pregnancy
Amlodipine	5 - 10 mg	Hypersensitivity reaction
Irbesartan (or other ARB e.g. losartan)	150 mg	Renal artery stenosis, hyperkalaemia, angioedema, pregnancy

**Table 22.** Oral Antihypertensive Medications at Discharge for Hypertensive Urgency

The BP should be reduced by no more than 25% within minutes to hours but not lower than 160/100 mmHg. Specific clinical scenarios requiring rapid lowering of SBP, usually to at least <140 mmHg, in the first hour of treatment include aortic dissection, severe pre-eclampsia or eclampsia, and phaeochromocytoma crisis. In general, use of oral therapy is discouraged for hypertensive emergencies and BP reduction is best achieved with parenteral drugs (see **Table 23**). 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 (see **Table 24**).

Management is challenging as despite the availability of several drugs, their universal use is somewhat limited by side effects, ease of administration or availability.



**Figure 6** Algorithm of the management of Hypertensive Emergency

*\*For the specific management of pregnant patients with severe hypertension, please refer to **Chapter 14: Hypertension Disorders of Pregnancy.***

Drug	Mechanism of Action	Dose	Onset of Action / Duration	Adverse or Side Effects	Contraindications
<b>LABELALOL</b>	<ul style="list-style-type: none"> <li>• Combined <math>\alpha</math> and <math>\beta</math>-adrenergic blocker</li> <li>• <math>\downarrow</math> heart rate &amp; cardiac contractility</li> </ul>	<p><b>BOLUS:</b></p> <ul style="list-style-type: none"> <li>• 5-10mg slow IV bolus over 2 mins</li> <li>• Repeat at 5-min intervals up to maximum dose of 20 mg</li> </ul> <p><b>INFUSION:</b></p> <ul style="list-style-type: none"> <li>• Dilute 250mg in 50ml normal saline</li> <li>• Start at 2 ml/hr</li> <li>• Increase rate by 1 ml/hr every 15 mins until maximum rate of 10 ml/hr</li> </ul>	5 – 10 min / 3 - 6 hr	<ul style="list-style-type: none"> <li>• Vomiting</li> <li>• Paraesthesia</li> <li>• Bronchoconstriction</li> <li>• Dizziness</li> <li>• Nausea</li> <li>• Heart block</li> <li>• Heart failure</li> <li>• Orthostatic hypotension</li> </ul>	<ul style="list-style-type: none"> <li>• Do not use in: <ul style="list-style-type: none"> <li>• Heart failure</li> <li>• Asthma / COPD</li> <li>• 2nd &amp; 3rd degree AV block</li> <li>• Phaeochromocytoma crisis</li> </ul> </li> </ul>
<b>GLYCERYL TRINITRATE (GTN)</b>	<ul style="list-style-type: none"> <li>• Venous vasodilator</li> </ul>	<p><b>INFUSION:</b></p> <ul style="list-style-type: none"> <li>• Dilute 50mg in 50ml normal saline</li> <li>• Start at 2ml/hr IV infusion</li> <li>• Increase rate by 1 ml/hr every 15mins until maximum rate of 10ml/hr</li> </ul>	1 - 5 min / 5 - 10 min	<ul style="list-style-type: none"> <li>• Reflex tachycardia</li> <li>• Flushing</li> <li>• Headache</li> <li>• Vomiting</li> <li>• Methaemoglobinemia</li> </ul>	<ul style="list-style-type: none"> <li>• Do not use in: <ul style="list-style-type: none"> <li>• Concomitant use of phosphodiesterase 5 inhibitors</li> <li>• Raised ICP</li> <li>• Inferior STEMI</li> </ul> </li> </ul>
<b>SODIUM NITROPRUSSIDE*</b>	<ul style="list-style-type: none"> <li>• Direct arterial and venous vasodilator</li> </ul>	<p><b>INFUSION:</b></p> <ul style="list-style-type: none"> <li>• Dilute 50mg in 250ml of 5% dextrose</li> <li>• 0.3-10<math>\mu</math>g/kg/min IV infusion</li> </ul>	Immediate / 1 - 2 min	<ul style="list-style-type: none"> <li>• Reflex tachycardia</li> <li>• Nausea &amp; vomiting</li> <li>• Flushing</li> <li>• Headache</li> <li>• Muscle spasm</li> </ul>	<ul style="list-style-type: none"> <li>• Do not use in: <ul style="list-style-type: none"> <li>• Pregnancy</li> </ul> </li> </ul>

		<ul style="list-style-type: none"> <li>• Start at 2ml/hr</li> <li>• Titrate up to desired BP but not to exceed 10µg/kg/min</li> </ul> <p><i>The diluted solution should be protected from light, using the supplied opaque sleeve, aluminium foil, or other opaque material. It is not necessary to cover the infusion tubing.</i></p>			<ul style="list-style-type: none"> <li>• Thiocyanate and cyanide intoxication at high doses and prolonged duration of use.</li> </ul>	Caution in renal / hepatic impairment
<b>HYDRALAZINE</b>	<ul style="list-style-type: none"> <li>• Direct arterial vasodilator</li> </ul>	<p><b>BOLUS:</b></p> <ul style="list-style-type: none"> <li>• 5mg slow IV bolus over 1-2 mins</li> <li>• Repeat every 20mins up to maximum dose of 20mg</li> </ul> <p><b>INFUSION:</b></p> <ul style="list-style-type: none"> <li>• Dilute 50mg in 50ml normal saline</li> <li>• Start at 2ml/hr</li> <li>• Increase rate by 1ml/hr every 15 mins until maximum rate of 10ml/hr</li> </ul>	10 - 20 min / 4 hr	<ul style="list-style-type: none"> <li>• Reflex tachycardia</li> </ul>	Caution in aortic dissection	
<b>NIFEDIPINE</b>	<ul style="list-style-type: none"> <li>• CCB</li> <li>• Vasodilator</li> </ul>	<p><b>INFUSION:</b></p> <ul style="list-style-type: none"> <li>• Dilute 5mg in 50ml normal saline</li> <li>• Start at 2ml/hr</li> <li>• Increase rate by 1ml/hr every 15 mins until maximum rate of 10ml/hr</li> </ul>	5 - 10 min / 1 - 4 hr	<ul style="list-style-type: none"> <li>• Reflex tachycardia</li> <li>• Flushing</li> <li>• Headache</li> <li>• Muscle spasm</li> <li>• Nausea</li> <li>• Oedema</li> </ul>	Do not use in: <ul style="list-style-type: none"> <li>• Heart failure</li> </ul>	

<b>CLONIDINE*</b>	<ul style="list-style-type: none"> <li>• Central <math>\alpha</math>-2-agonist</li> </ul>	<p>INFUSION:</p> <ul style="list-style-type: none"> <li>• Dilute 750<math>\mu</math>g in 50ml normal saline</li> <li>• Start at 2ml/hr</li> <li>• Increase rate by 1ml/hr every 15 mins until maximum rate of 10ml/hr</li> </ul>	30 - 60 min / 6 - 12 hr	<ul style="list-style-type: none"> <li>• Sedation</li> <li>• Dry Mouth</li> <li>• Bradycardia</li> <li>• QT prolongation</li> <li>• Intensify depression</li> <li>• Catecholamine excess (due to withdrawal)</li> </ul>	<p>Do not use in:</p> <ul style="list-style-type: none"> <li>• Known hypersensitivity to clonidine</li> <li>• Porphyria</li> </ul>
<b>URAPIDIL*</b>	<ul style="list-style-type: none"> <li>• <math>\alpha</math>-1-adrenoceptor antagonist &amp; 5-HT<sub>1A</sub> receptor agonist</li> <li>• <math>\downarrow</math> peripheral vascular resistance</li> </ul>	<p>INFUSION:</p> <ul style="list-style-type: none"> <li>• Dilute 150mg in 50ml normal saline</li> <li>• Start at 2ml/hr.</li> <li>• Increase rate by 1ml/hr</li> </ul>	Immediate, peaks in 2 - 5 mins / 4 hr	<ul style="list-style-type: none"> <li>• Tachycardia</li> <li>• Sweating</li> <li>• Dizziness</li> <li>• Headache</li> <li>• Nausea</li> <li>• Weakness</li> <li>• Orthostatic dysregulation</li> </ul>	<p>Do not use in:</p> <ul style="list-style-type: none"> <li>• Aortic isthmus stenosis</li> <li>• Aortic valve insufficiency</li> </ul>
<b>PHEHOTOLAMINE*</b>	<ul style="list-style-type: none"> <li>• <math>\alpha</math>-1 blocker</li> <li>• Vasodilation</li> </ul>	<p>BOLUS:</p> <ul style="list-style-type: none"> <li>• 5 to 15mg IV</li> <li>• Maximum dose 15mg</li> </ul> <p>INFUSION:</p> <ul style="list-style-type: none"> <li>• 300mg in 500mL dextrose 5% or normal saline</li> <li>• 0.1mg – 2mg/min</li> </ul>	1 – 2 min / 3 - 10 min	<ul style="list-style-type: none"> <li>• Reflex tachycardia</li> <li>• Flushing</li> <li>• Hypotension</li> <li>• Hypovolaemia</li> <li>• Increased gastric secretion</li> </ul>	

\* These medications may not be available in RIPAS Hospital

**Table 23** Parenteral Treatment Options for Hypertensive Emergencies

Specific Scenario	BP Reduction Recommendations	Treatment Considerations
<p><b>HYPERTENSIVE ENCEPHALOPATHY</b></p> <p><i>An organic brain syndrome associated with marked hypertension. Clinical features include headache, nausea and vomiting, visual disturbances, weakness, lethargy, seizures, confusion and papilloedema.</i></p>	<ul style="list-style-type: none"> <li>• Reduce BP 20%-25% within 1 hour to reduce intracranial pressure.</li> <li>• Then further towards 160/100 mmHg over 2-6 hours.</li> <li>• If the neurological status deteriorates during treatment, stop or lower the dose of medication.</li> <li>• If the patient remains stable and is tolerating the lowered blood pressure, a further gradual reduction towards normal blood pressure may be implemented in the next 8-24 hours.</li> </ul>	<ul style="list-style-type: none"> <li>• IV Labetalol generally effective.</li> </ul> <p>Sodium nitroprusside may lead to intracranial oedema but can be considered as last resort.</p>
<p><b>ACUTE ISCHAEMIC STROKE (AIS)</b></p> <p><i>AIS is frequently associated with hypertension due to compensatory mechanism to restore cerebral perfusion pressure (CPP) to the ischaemic brain. The decision to treat BP in acute setting is difficult due to risk of cerebral oedema and haemorrhagic transformation, while lowering BP may compromise the circulation to the ischaemic penumbra.</i></p>	<p><b>BEFORE IV THROMBOLYSIS:</b></p> <ul style="list-style-type: none"> <li>• Target BP <math>\leq 185/110</math> mmHg</li> </ul> <p><b>DURING/AFTER IV THROMBOLYSIS:</b></p> <ul style="list-style-type: none"> <li>• Target BP <math>\leq 180/105</math> mmHg</li> </ul> <p><b>RECEIVING MECHANICAL THROMBECTOMY:</b></p> <ul style="list-style-type: none"> <li>• Target BP <math>\leq 180/105</math> mmHg during and 24 hours after thrombectomy.</li> </ul> <p><b>NOT FOR IV THROMBOLYSIS / THROMBECTOMY:</b></p> <ul style="list-style-type: none"> <li>• If SBP <math>\leq 220</math> mmHg and DBP <math>\leq 120</math> mmHg (within 1<sup>st</sup> 2 weeks of onset) then defer BP lowering treatment</li> </ul>	<p><b>BEFORE IV THROMBOLYSIS:</b></p> <ul style="list-style-type: none"> <li>• Labetalol BOLUS, or</li> <li>• Hydralazine BOLUS, or</li> <li>• IV GTN INFUSION</li> </ul> <p><b>DURING/AFTER IV THROMBOLYSIS:</b></p> <ul style="list-style-type: none"> <li>• IV GTN INFUSION, or</li> <li>• IV Labetalol INFUSION, or</li> <li>• IV Nifedipine INFUSION, or</li> <li>• IV Clonidine INFUSION, or</li> <li>• IV Urapidil INFUSION, or</li> <li>• IV Hydralazine INFUSION</li> </ul>

<p><b>ACUTE HAEMORRHAGIC STROKE OR INTRACEREBRAL HAEMORRHAGE</b></p> <p><i>Cerebral autoregulation is lost in ICH and an elevated BP will directly result in excessive blood flow to the haemorrhaging area, leading to increased ICP. BP reduction goal is to limit haemorrhage and must be balanced with CPP reduction.</i></p>	<ul style="list-style-type: none"> <li>• If SBP &gt;220 mmHg or DBP &gt;120 mmHg, then target lowering of BP by 10-15% during 1<sup>st</sup> 24 hours after onset.</li> <li>• If co-morbid conditions present (IV thrombolysis, hypertensive encephalopathy, aortic dissection, acute renal failure, MI, acute pulmonary oedema, pre-eclampsia/eclampsia), then target BP &lt;180/110 mmHg.</li> </ul>	
<p><b>ACUTE AORTIC DISSECTION</b></p> <p><i>This must always be considered when patient presents with hypertension and acute chest pain or acute MI or a new aortic regurgitation murmur is detected. A classical history of tearing pain radiating to the back may not be present. Unequal arm blood pressure readings and/or a widened mediastinum on a CXR are clues to the diagnosis.</i></p>	<p><b>If SBP 150 – 220 mmHg:</b></p> <ul style="list-style-type: none"> <li>• Avoid aggressive SBP lowering to &lt;140 mmHg.</li> </ul> <p><b>If SBP &gt;220 mmHg:</b></p> <ul style="list-style-type: none"> <li>• Consider aggressive BP lowering within 6 hours with continuous intravenous infusion and close BP monitoring</li> <li>• Target: SBP lowering towards 140 mmHg</li> </ul>	<ul style="list-style-type: none"> <li>• IV Labetalol INFUSION, or</li> <li>• IV Nifedipine INFUSION, or</li> <li>• IV Clonidine INFUSION, or</li> <li>• IV Urapidil INFUSION, or</li> <li>• IV Hydralazine INFUSION</li> </ul> <p>Labetalol is a preferred agent as it is easily titrated and have minimal vasodilatory effects on cerebral blood flow. Avoid lowering BP abruptly with sublingual nifedipine in acute stroke as it can worsen ischaemia.</p>
	<ul style="list-style-type: none"> <li>• Rapidly reduce the SBP to &lt;120 mmHg within 10-20 minutes</li> </ul>	<ul style="list-style-type: none"> <li>• IV Labetalol is preferred.</li> <li>• It may be used concurrently with Sodium nitroprusside or <math>\alpha</math>-blocker if needed for BP control.</li> </ul> <p>Avoid drugs that increase reflex tachycardia (GTN. Sodium nitroprusside, CCB, Hydralazine, ACE-I) <b>unless paired</b> with a <math>\beta</math>-blocker. But avoid <math>\beta</math>-blockers if there is severe aortic regurgitation.</p> <p>Urgent Cardiothoracic consult is indicated</p>

<p><b>ACUTE LEFT VENTRICULAR FAILURE / ACUTE PULMONARY OEDEMA (APO)</b></p> <p><i>This occurs when severe hypertension results in acute LV failure from excessive afterload, causing decompensation. Clinically patients in APO is typically sitting up, in respiratory distress, with cold and clammy peripheries, diaphoresis and crepitation or rhonchi.</i></p>	<ul style="list-style-type: none"> <li>• Lower BP until there is symptom resolution and alleviation of signs of heart failure.</li> <li>• Reduce BP to &lt;25% within the first hour, then ≤160/100 mmHg over 2 to 6 hours.</li> </ul>	<ul style="list-style-type: none"> <li>• IV GTN is the drug of choice to reduce preload and afterload of the heart.</li> <li>• IV Furosemide should also be given.</li> </ul> <p>Caution in using β-blockers or CCB as it could cause exacerbation of symptoms.</p>
<p><b>Specific Scenario</b></p> <p><b>ACUTE CORONARY SYNDROME / ACUTE MYOCARDIAL INFARCTION (AMI)</b></p> <p><i>This occurs when the severe hypertension leads to increased ventricular wall tension and myocardial oxygen demands. BP of more than 180/110 mmHg is a contraindication for thrombolysis.</i></p>	<p><b>BP Reduction Recommendations</b></p> <ul style="list-style-type: none"> <li>• BP of &gt;180/110 mmHg is a contraindication to thrombolysis.</li> <li>• Reduce BP to reduce cardiac workload and improve coronary perfusion.</li> <li>• Reduce BP to &lt; 25% within the first hour, then ≤160/100 mmHg over 2 to 6 hours.</li> </ul>	<p><b>Treatment Considerations</b></p> <ul style="list-style-type: none"> <li>• Therapeutic options include GTN, β-blockers and ACE-I.</li> </ul> <p>Avoid selective β-blockers if concurrent cocaine abuse suspected. Sodium Nitroprusside can increase reflex tachycardia and therefore increase myocardial demand so best avoid.</p>
<p><b>ACUTE RENAL FAILURE</b></p> <p><i>This is both a cause and consequence of severe hypertension.</i></p>	<ul style="list-style-type: none"> <li>• The goal is to reduce BP while maintaining renal blood flow.</li> <li>• Reduce BP to around 25% within 3 to 24 hours.</li> </ul>	<ul style="list-style-type: none"> <li>• Therapeutic options include CCB, β-blockers, hydralazine and Sodium nitroprusside.</li> </ul> <p>Avoid ACE-I.</p>
<p><b>PRE-ECLAMPSIA AND ECLAMPSIA</b></p>	<ul style="list-style-type: none"> <li>• Reduce SBP to &lt;140 mmHg within the first hour for patients with severe pre-eclampsia or eclampsia</li> </ul>	<ul style="list-style-type: none"> <li>• Definitive treatment for severe pre-eclampsia and eclampsia is the delivery of the foetus.</li> </ul>

<p><i>This must be considered in all hypertensive (BP &gt;140/90 mmHg) pregnant women after 20 weeks of amenorrhea. Without a clear history, it may be hard to distinguish from pre-existing hypertension. The HELLP (Haemolysis, Elevated Liver Enzymes and Low Platelet count) syndrome is a severe manifestation of pre-eclampsia. Eclampsia occurs when a patient with pre-eclampsia develops a seizure.</i></p>	<p>The therapeutic goal is to maintain BP &lt;160/110 mmHg but not to lower DBP &lt;90 mmHg, as placental perfusion is reduced.</p> <ul style="list-style-type: none"> <li>• The American College of Obstetricians and Gynaecologists recommend keeping the blood pressure between 140-160 mm hg and diastolic blood pressure between 90-105 mmHg</li> </ul>	<ul style="list-style-type: none"> <li>• IV Magnesium Sulphate is currently the drug of choice for the prevention of eclampsia and to abort an eclamptic fit.</li> <li>• Drugs that can be considered: Methyldopa, Nifedipine, Hydralazine, Labetalol.</li> </ul> <p>ACE-I, ARBs, renin inhibitors, and Sodium nitroprusside are contraindicated.</p> <p>Urgent O&amp;G consult is indicated.</p>
<p><b>PHAECHROMOCYTOMA OR CATECHOLAMINE CRISIS</b></p> <p><i>Catecholamine excess can be due to endogenous (phaeochromocytoma) or exogenous sources (drugs of abuse such as cocaine or amphetamines), monoamine oxidase inhibitor crisis, rebound phenomena due to clonidine withdrawal and may occur in autonomic dysfunction such as Guillain-Barre syndrome. Clinical features include severe hypertension, tachycardia, diaphoresis and pyrexia. Pheochromocytoma crisis (PCC) is an endocrine emergency associated with significant mortality as it causes haemodynamic instability and end-organ damage or dysfunction. PCC should be considered in any patient with unexplained shock or left ventricular failure, multi-organ</i></p>	<ul style="list-style-type: none"> <li>• Reduce SBP to less than 140 mmHg during the first hour for patients with pheochromocytoma crisis.</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment is IV fluid resuscitation, followed by or in concurrent with <math>\alpha</math>-blockade, CCB and/or magnesium.</li> <li>• <math>\alpha</math>-blockers commonly used: <ul style="list-style-type: none"> <li>- Phenoxybenzamine IV 0.5mg/kg over 5 hours</li> <li>- Phentolamine IV 0.1mg – 2 mg/min</li> </ul> </li> <li>• In some cases, specific additional treatment for hypertension will be needed.</li> <li>• Other agents recommended: <ul style="list-style-type: none"> <li>- Sodium nitroprusside, or</li> <li>- Hydralazine, or</li> <li>- GTN</li> </ul> </li> </ul> <p>Avoid Labetalol as it can exacerbate a crisis. <math>\beta</math>-blockers should not be used prior to <math>\alpha</math>-blockade. The rationale for this is that in the presence of catecholamine excess, the stimulation of <math>\beta</math> 2 receptors promotes vasodilation, which attenuates the hypertensive and vasoconstrictive elements of a crisis. This will also remove this</p>

*failure, hypertensive crisis or unexplained lactic acidosis especially if also febrile.*

moderating effect and allow unopposed  $\alpha$ -adrenergic activity to exacerbate a hypertensive crisis. Furthermore, giving  $\beta$  blockade early after initiation of some  $\alpha$  blockade can cause hypotension, because it will prevent protective tachycardia induced by relative intravascular depletion.

**Table 24** Specific Scenario of Hypertensive Emergencies with Recommended Treatment (Please refer to individual chapters for more details on the specific condition)

## **9: Hypertension in older people**

Dr Teo Shyh Poh and Dr Muhammad Hanif Ahmad

### **Key Messages:**

1. The treatment of hypertension in older people requires an individualised approach.
2. In older people with uncomplicated hypertension, BP should be treated to <140/90 mmHg. For those with elevated CVD risk, BP should be <130/80 mmHg.
3. Monitor for adverse effects of antihypertensive treatment including orthostatic hypotension and acute kidney injury.
4. First line treatment for hypertension are ACE-I or ARB and / or CCB and / or thiazide diuretics.
5. For older people with hypertension, multiple comorbidities and limited life expectancy; clinical judgement, patient preference, and a team-based approach is required to assess risk / benefit of the intensity of BP lowering and choice of antihypertensive drugs.

The following recommendations are for treatment of isolated systolic hypertension in older people. For guidance in patients with specific medical conditions, such as diabetes, renal impairment or stroke, please refer to the relevant chapter. For the purposes of this guideline, older people will be defined as people  $\geq 70$  years old.

Isolated systolic hypertension (SBP  $\geq 160$  mmHg) is common in older people and is a major contributor of premature disability, morbidity and mortality. For every 20 mmHg increase in systolic blood pressure and 10mmHg increase in diastolic blood pressure, there is an associated doubling of the risk of death from stroke and coronary artery disease<sup>(2)</sup>.

### **Individualised approach to hypertension treatment in older people:**

In the majority of older people, the 10-year CVD risk is  $\geq 10\%$  (elevated) and would be recommended antihypertensive drug therapy for BP  $\geq 130/80$  mmHg. However, due to the heterogeneity of older people (in terms of comorbidities, polypharmacy, frailty, cognitive impairment and variable life expectancy), clinicians should have an individualised approach towards hypertension management.

It is important to note that older people with frequent falls, orthostatic hypotension, advanced cognitive impairment, multiple comorbidities and dependent older people, typically requiring residential care are excluded from RCTs. These patients have a high risk of adverse outcomes with intensive BP lowering, especially with multiple medications<sup>(1)</sup>.

## Target Blood Pressure for Older People:

Treatment of isolated systolic hypertension for independent older people was associated with reduced risk of fatal and non-fatal stroke, cardiovascular events and death <sup>(51)</sup>. In general, BP targets should be similar to younger patients, i.e. <140/90 mmHg for patients with low CVD risk and <130/80 mmHg in those with elevated CVD risk. In older people with high levels of comorbidities, limited life expectancy, clinical judgement and a team-based approach should be used in determining BP targets <sup>(1)</sup>. Clinicians should monitor for adverse effects, complications or intolerance associated with blood pressure lowering agents, including orthostatic hypotension and acute kidney injury <sup>(10)</sup>.

## Treatment of hypertension in older people:

### *Non-pharmacological Therapy:*

Older patients should be advised to reduced sodium intake and weight loss (if obese).

### *Pharmacological Therapy:*

For older patients, the 'start low, go slow' prescribing approach is recommended. It is appropriate to initiate treatment with monotherapy at the lowest available dose. First line treatment for isolated systolic hypertension are CCB, ACE-I or ARB and thiazide diuretics. Unless required for concomitant diseases, loop diuretics and  $\alpha$ -blockers should be avoided because of association with injurious falls <sup>(10,51)</sup>.

**Caution with Orthostatic Hypotension.** (Please refer to **Chapter 3** on measurement of orthostatic hypertension)

Patients in the following categories should be screened for orthostatic hypotension:<sup>(52)</sup>

1. Suspected or diagnosed neurodegenerative disorder associated with autonomic dysfunction e.g. Parkinson's Disease, Dementia with Lewy Bodies, Multiple System Atrophy
2. Unexplained falls or had an episode of syncope
3. Peripheral neuropathy associated with autonomic dysfunction (e.g. diabetes, amyloidosis, HIV)
4. Older people ( $\geq 70$  years of age) and frail or on multiple medications
5. Postural dizziness or non-specific symptoms that only occur when standing

## **10: Hypertension and Diabetes Mellitus**

Dr Alice Yong Moi Ling

### **Key Messages:**

1. Antihypertensive treatment should be initiated at a BP of  $\geq 130/80$  mmHg or higher in all adults with diabetes and hypertension, with a treatment goal of  $\leq 130/80$  mmHg in majority of patients.
2. First line treatment for adults with diabetes and hypertension should be an ACE-I or ARB, especially in the presence of albuminuria.
3. Add on therapy:
  - Second antihypertensive drug with a combination of ACE-I or ARB and a CCB.
  - Third antihypertensive drug by using a thiazide-like diuretic in combination with ACE-I or ARB and CCB if BP target is not achieved after maximum tolerated doses of two drugs.
  - Fourth antihypertensive drug i.e.  $\alpha$ -blocker,  $\beta$ -blocker and other diuretics or spironolactone.

### **Background:**

- Hypertension is common in patients with diabetes mellitus. Early treatment of hypertension is particularly important in diabetic patients both to prevent cardiovascular disease and to minimize progression of renal disease and diabetic retinopathy<sup>(53)</sup>.

### **Rationale for BP target:**

- All diabetic patients with blood pressures persistently above 140/90 mmHg should be started on antihypertensive drug therapy<sup>(49,54–56)</sup>.
- The 2017 American Heart Association hypertension guidelines recommend that the goal blood pressure in patients with diabetes mellitus is  $\leq 130/80$  mmHg<sup>(1)</sup>.
- The 2017 ADA consensus report, while endorsing the highest level of evidence for  $< 140/90$  mmHg, specifically states that attaining lower blood pressure levels (between 125 to 130 mmHg) should be attempted if tolerated, to prevent cardiovascular events<sup>(57)</sup>.
- In addition, these guidelines suggest maintaining a diastolic blood pressure  $\geq 60$  mmHg in older adults.
- ACCORD study showed that in patients with type 2 diabetes who are at high risk for cardiovascular events, targeting a SBP of  $< 120$  mmHg (intensive), as compared with  $< 140$  mmHg (standard therapy), did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events<sup>(58)</sup>. Hence guidelines published after ACCORD raised the blood pressure target in diabetic patients to  $< 140/90$  mmHg<sup>(49,55)</sup>.
- However, there was positive outcomes where intensively lowering systolic BP to  $< 120$  mmHg was associated with significant reductions in the annual rates of total stroke and nonfatal stroke.

## Management:

- ACE-I are the drugs of choice given the proven cardiovascular benefits and renoprotective effects in patients with diabetic kidney disease<sup>(59)</sup>. They have also been reported to prevent the onset of nephropathy in normo-albuminuric diabetic patients with or without hypertension<sup>(60-62)</sup>. They have no adverse effects on lipid metabolism.
- If an ACE-I is not tolerated, an ARB should be considered. Two major trials, the Irbesartan Diabetic Nephropathy Trial (IDNT) and the RENAAL trial, demonstrated a clear benefit in terms of renoprotection with ARBs in patients with nephropathy due to type 2 disease<sup>(63,64)</sup>. For type 1 diabetes with nephropathy, ACE-Is are the recommended agent<sup>(65)</sup>. For type 2 diabetes, both the ACE-Is & ARBs may be used. The combination therapy of an ACE-I and ARB is not recommended due to the increased in renal adverse events.
- CCBs do not have adverse effects on lipid or carbohydrate metabolism. They can be effectively used in addition to ACE-Is or ARBs to lower blood pressure in hypertensive diabetics.
- In the UKPDS study of patients with type 2 diabetes, atenolol was as effective as captopril in terms of both blood pressure lowering and protection against microvascular disease<sup>(66)</sup>. It may lead to dyslipidaemia or deterioration of glucose tolerance, and ability to lose weight. In addition, they have been concerns about masking of hypoglycaemic symptoms and possible exacerbation of peripheral artery disease. Carvedilol is a combined nonselective  $\beta$ - and  $\alpha$ -1 adrenergic antagonist that improves survival in patients with heart failure and may have certain advantages compared to other  $\beta$  blockers in patients with diabetes<sup>(67,68)</sup>.
- Low-dose thiazide diuretics are effective in hypertensive diabetic patients. However, they have the ability to increase insulin resistance, dyslipidaemia and hyperuricaemia. These adverse metabolic side effects and a possible increase in cardiovascular risk have been a major concern with high doses of diuretics in diabetic patients<sup>(69)</sup>.
- $\alpha$ -blockers such as doxazosin are as effective in lowering blood pressure as ACE-I and CCB and have a more favourable metabolic profile<sup>(70)</sup>. However it should not be used as primary treatment given the side effects such as postural hypotension and increased rate of new onset heart failure as shown in the ALLHAT trial<sup>(71,72)</sup>.

# **11: Hypertension and Cerebrovascular Disease**

Dr Chan Guan Choon and Dk Dr Hjh Siti Nur'Ashikin Pg DP Hj Tengah

## **Key Messages**

### **1. Acute Ischemic Stroke NOT eligible for intravenous thrombolysis or mechanical thrombectomy with no comorbid conditions\***

- SBP < 220 mmHg or DBP < 120 mmHg - Defer introduction or reintroduction of BP lowering medications within the first 72 hours after onset of acute stroke
- SBP  $\geq$ 220 mmHg or DBP  $\geq$  120 mmHg - Target lowering of BP by 10 - 15% during the first 24 hours after onset of acute ischaemic stroke

### **2. Acute Ischemic Stroke eligible for intravenous thrombolysis or mechanical thrombectomy**

- target BP of < 185/110 mmHg pre-thrombolysis
- maintain BP < 180/105 mmHg during and for at least the first 24 hours after treatment

### **3. Acute Ischemic Stroke with comorbid conditions\***

- Target BP < 180/110 mmHg

### **4. Acute Haemorrhagic Stroke**

- SBP between 140 – 220 mmHg - Patient with no contraindication to acute BP treatment, acute lowering of SBP to 140mmHg is safe and can be effective for improving functional outcome. However, 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 (arterial BP monitoring)

### **5. Secondary prevention of stroke, TIA or after acute phase of ischemic stroke**

- Severe cerebrovascular stenosis **outruled-** Target BP  $\leq$ 130/80 mmHg
- Patients with severe cerebrovascular stenosis- Target BP >130/80 mmHg (individualized)

\* Comorbid conditions: hypertensive encephalopathy, aortic dissection, acute renal failure, acute myocardial infarction, acute pulmonary oedema, symptomatic intracerebral haemorrhage, pre-eclampsia or eclampsia

Hypertension is the most important potentially reversible risk factor for ischaemic and haemorrhagic stroke<sup>(73,74)</sup>. It is also associated with increased risk of recurrent stroke in patients who have already had an ischemic or hemorrhagic event<sup>(2)</sup>. It results in hyalin degeneration of smaller cerebral vessels and arteriosclerosis in larger cerebral vessels. Blood pressure management during the acute phase of hemorrhagic and ischemic stroke remains an area of uncertainty. Blood pressure can and is often elevated at presentation with acute stroke but often reduces without intervention<sup>(75)</sup>.

## Treatment of Hypertension in Acute Ischaemic Stroke (AIS)

The beneficial effects of BP reduction are not very clear-cut in acute ischemic stroke. Stress can be related to high BP and can be present in up to 80% of patients with acute ischaemic stroke<sup>(76)</sup>. In a majority of patients, blood pressure will reduce without any specific medical treatment within days or weeks<sup>(75,77)</sup>. However, a slightly higher systemic blood pressure is preferred to maintain the cerebral perfusion. A key consideration of BP treatment will depend if the patient is receiving recanalization therapy.

### a) AIS patient not eligible for recanalization therapy (not for IV thrombolysis or mechanical thrombectomy)

The benefit of acute BP lowering in patients with AIS who do not receive recanalization therapy is uncertain. Meta-analysis suggested that BP lowering early after acute ischemic stroke had a neutral effect on the prevention of death or dependency<sup>(78,79)</sup>. Moreover during the first 10 days of hospital stay, BP of AIS patients decreases spontaneously by 20/10 mmHg<sup>(80)</sup>. In patient with markedly elevated SBP  $\geq 220$  mmHg or DBP  $> 120$  mmHg (or both), clinical judgement should define whether to intervene with drug therapy, in which case a reasonable goal may be to lower BP by 10 - 15% with close monitoring during the first 24 hours after the onset of acute ischaemic stroke<sup>(78,81)</sup>.

Those patients with BP  $\geq 220/120$  mmHg might need to have BP lowered more rapidly to below 180/110 mmHg in AIS patient who has received IV thrombolysis, hypertensive encephalopathy, aortic dissection, acute renal failure, acute myocardial infarction, acute pulmonary oedema, symptomatic intracerebral haemorrhage, pre-eclampsia or eclampsia<sup>(82)</sup>.

Patients with acute ischaemic stroke and a BP  $< 220/120$  mmHg in the first 72 hours after the onset of acute stroke does not seem to benefit from the introduction or reintroduction of BP lowering medications<sup>(78,83)</sup>. For stable patients who remain hypertensive after 72 hours, initiation or reintroduction of antihypertensive should be considered<sup>(84)</sup>.

Acute Phase of Ischaemic Stroke	
SBP $\leq 220$ mmHg or DBP $\leq 120$ mmHg	Defer introduction or reintroduction of BP lowering medications within the first 72 hours after onset of acute stroke
SBP $> 220$ mmHg or DBP $> 120$ mmHg	Target: Lowering of BP by 10 - 15% during the first 24 hours after onset of acute ischaemic stroke
Patient with comorbid conditions: IV thrombolysis, hypertensive encephalopathy, aortic dissection, acute renal failure, acute myocardial infarction, acute pulmonary oedema, symptomatic intracerebral haemorrhage, pre-eclampsia or eclampsia.	Target BP $< 180/110$ mmHg

**Table 25:** Management of BP in acute phase of ischaemic stroke

Patient eligible for acute intravenous thrombolysis therapy that SBP >185 mmHg OR DBP >110 mmHg	
<p>Pre-IV Thrombolysis</p> <p>Measure BP every 15 minutes</p> <p>(Target BP <math>\leq</math>185/110 mmHg)</p>	<ol style="list-style-type: none"> <li>1. Labetalol 5-10mg slow IV bolus over 2 minutes. Repeat at 5minute intervals up to maximum dose of 20mg (contraindicated in 2nd &amp; 3rd degree AV block, asthma)</li> <li>2. Urapidil 5mg IV bolus. Repeat every 5 minutes to a maximum dose of 25mg</li> <li>3. Hydralazine 5mg IV bolus over 1-2mins. Repeat every 20 mins to a maximum dose of 20mg</li> <li>4. IV GTN - 50mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> </ol>
<p>During / After IV Thrombolysis</p> <p>Monitor BP every 15mins for 2 h from start of IV thrombolysis then every 30mins for 6 h and then every hour for 16 h</p> <p>(Target BP <math>\leq</math> 180/105mmHg)</p>	<ol style="list-style-type: none"> <li>1. IV GTN - 50mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> <li>2. Labetalol 250mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> <li>3. Nifedipine 5mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> </ol> <p>OR</p> <ol style="list-style-type: none"> <li>Nicardipine 5mg/hr, uptitrate 2.5mg/hr every 5-15min, maximum 15mg/hr</li> <li>4. Clonidine 750<math>\mu</math>g in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> <li>5. Urapidil 150mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> <li>6. Hydralazine 50mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> </ol>

**Table 26:** Management of BP in patients receiving IV thrombolysis

**b) AIS patient receiving intravenous thrombolysis**

Observational studies have reported an increased risk of intracerebral haemorrhage in patients with a markedly elevated BP who received intravenous thrombolysis<sup>(85,86)</sup>. In patients receiving intravenous thrombolysis, BP should be carefully lowered so that

SBP <185 mmHg and DBP <110 mmHg before IV thrombolysis is given. In the subsequent 24 hours BP should be kept  $\leq$ 180/105 mmHg

c) AIS patient receiving mechanical thrombectomy

Mechanical thrombectomy has been shown to be an effective revascularization therapy for patients who present with an acute ischemic stroke within 6 hours of symptom onset<sup>(87-90)</sup>, and up to 24 hours in appropriately selected patients<sup>(91,92)</sup>. However, optimal postoperative management of these patients remains uncertain, especially with regard to blood pressure control. Currently there are no randomised control trial data to support optimal blood pressure control. The vast majority of patients selected for <6hours mechanical thrombectomy trial also received IV thrombolysis thus protocols stipulate blood pressure  $\leq$ 180/105 mmHg during and 24hrs after mechanical thrombectomy. While the DAWN protocol recommends maintaining SBP<140 mmHg in subjects who are reperfused after mechanical thrombectomy. Thus, at this moment in time without any randomised control trial data it is reasonable to recommend that patients who undergo mechanical thrombectomy that it is reasonable to maintain the BP  $\leq$ 180/105 mmHg during and 24 hours after the procedure

AIS Patient receiving mechanical thrombectomy	
Maintain BP $\leq$ 180/105mmHg during and 24 hours after mechanical thrombectomy	

**Table 27:** Management of BP in patients receiving mechanical thrombectomy

d) Secondary prevention of stroke, TIA patient or after acute phase of ischaemic stroke (after 72 hours of acute ischaemic stroke)

For stable patients who remain hypertensive ( $\geq$ 140/90 mmHg) after 72 hours of an ischaemic stroke or patient who is diagnosed with transient ischaemic attack, initiation or reintroduction of BP lowering medication should be considered<sup>(84)</sup>. All 5 major pharmacological classes of antihypertensive drugs are appropriate i.e. renin-angiotensin-system blocker, calcium channel blocker, thiazide diuretic,  $\beta$ -blocker and  $\alpha$ -blocker. The absolute target BP level is uncertain. Recent Secondary Prevention of Small Subcortical Strokes 3 study in patients with a recent lacunar stroke suggested an SBP target of <130 mmHg<sup>(93)</sup>. With this we would recommend that in hypertensive patients with ischemic stroke due to small vessel disease should have an SBP target range of 120-130 mmHg. However, patient with ischaemic stroke secondary to severe cerebrovascular stenosis a higher blood pressure might be beneficial and a target of 120-130 mmHg might cause harms instead<sup>(94,95)</sup>.

TIA patient or after acute phase of ischaemic stroke	
Severe cerebrovascular stenosis <b>outruled</b>	Patients with severe cerebrovascular stenosis
Target SBP range 120 -130 mmHg	Target SBP range higher than 130 mmHg

**Table 28:** Target BPs for TIA patients or after acute phase of ischaemic stroke

## Treatment of Hypertension in Acute Haemorrhagic Stroke

In acute haemorrhagic stroke, an increased in BP is associated with a greater risk of haematoma expansion, increased risk of death and a worse prognosis for neurological recovery. Result from the INTERACT 2 and subsequent meta-analysis trial suggested that immediate BP lowering within 3-6 hours of intracerebral haemorrhage to <140/90 mmHg did not show benefit on the primary outcome of disability or death at 3 months, but might reduce haematoma expansion and improve functional recovery and was generally safe.

Acute phase of haemorrhagic stroke	
SBP 150 – 220 mmHg	<p>Patient with no contraindication to acute BP treatment, acute lowering of SBP to 140 mmHg is safe and can be effective for improving functional outcome.</p> <p>However, avoid aggressive SBP lowering to &lt;140 mmHg</p>
SBP > 22 mmHg	<p>Consider aggressive BP lowering within 6 hours with continuous intravenous infusion and close BP monitoring (arterial BP monitoring)</p> <p>Target: SBP lowering towards 140 mmHg</p>
Intravenous antihypertensive infusion for acute haemorrhagic stroke	
<ol style="list-style-type: none"> <li>1. Labetalol 250mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> <li>2. Nicardipine 5mg/hr, uptitrate 2.5mg/hr every 5-15min, maximum 15mg/hr</li> <li>3. Nifedipine 5mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> </ol> <p>OR</p> <p>Nicardipine 5mg/hr, uptitrate 2.5mg/hr every 5-15min, maximum 15mg/hr</p> <ol style="list-style-type: none"> <li>4. Clonidine 750µg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> <li>5. Urapidil 150mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> <li>5. Hydralazine 50mg in 50ml normal saline. Start at 2ml/hr. Increase rate by 1ml/hr every 15min until maximum rate of 10ml/hr</li> </ol> <p><i>Avoid lowering BP abruptly with sublingual nifedipine in acute stroke</i></p>	

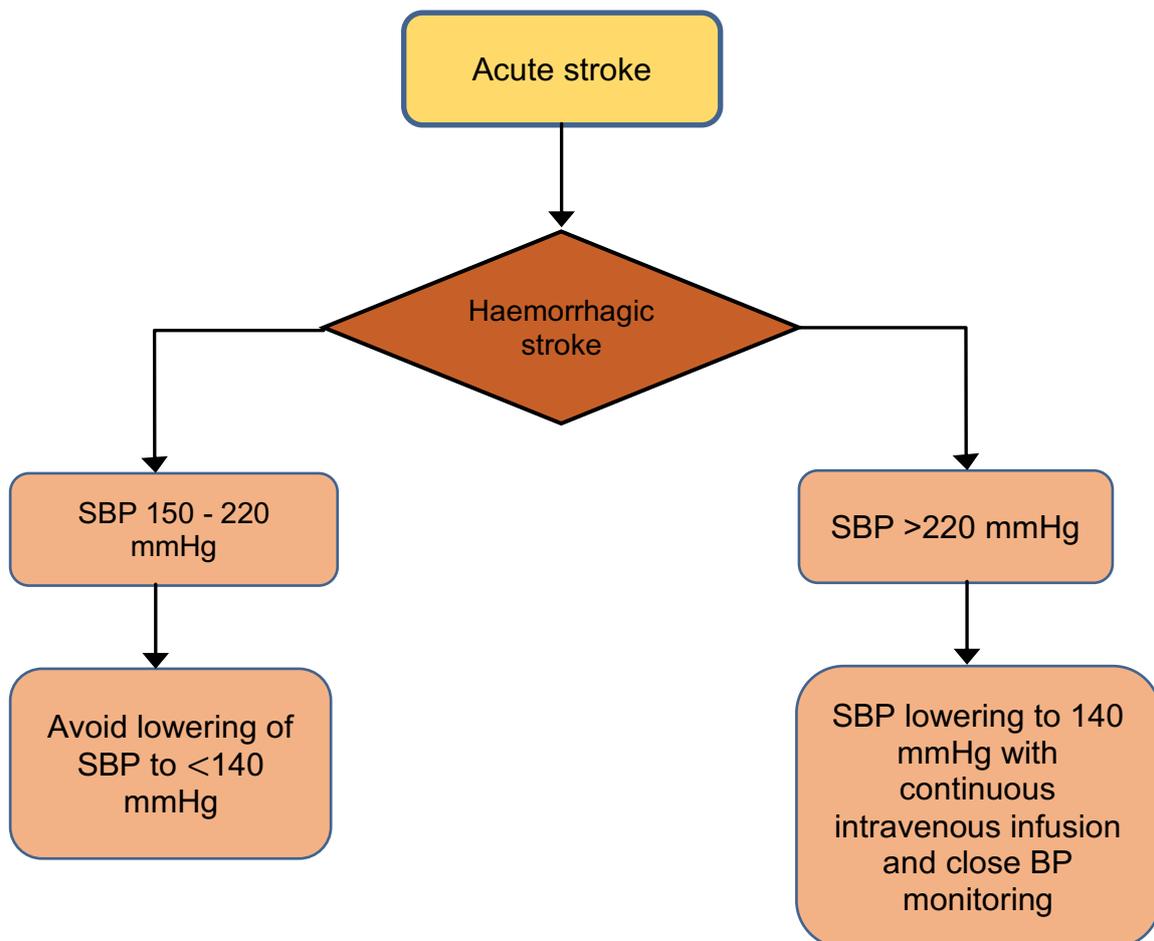
**Table 29:** Management of BP in acute haemorrhagic stroke

The more recent ATACH-II trial enrolled patients within 4.5 hours of intracerebral haemorrhage onset. Patients were randomly assigned to blood pressure reduction with intravenous nicardipine to achieve systolic blood pressure in the range of 140 to 179 mmHg (standard care) or 110 to 139 mmHg (intensive blood pressure 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.

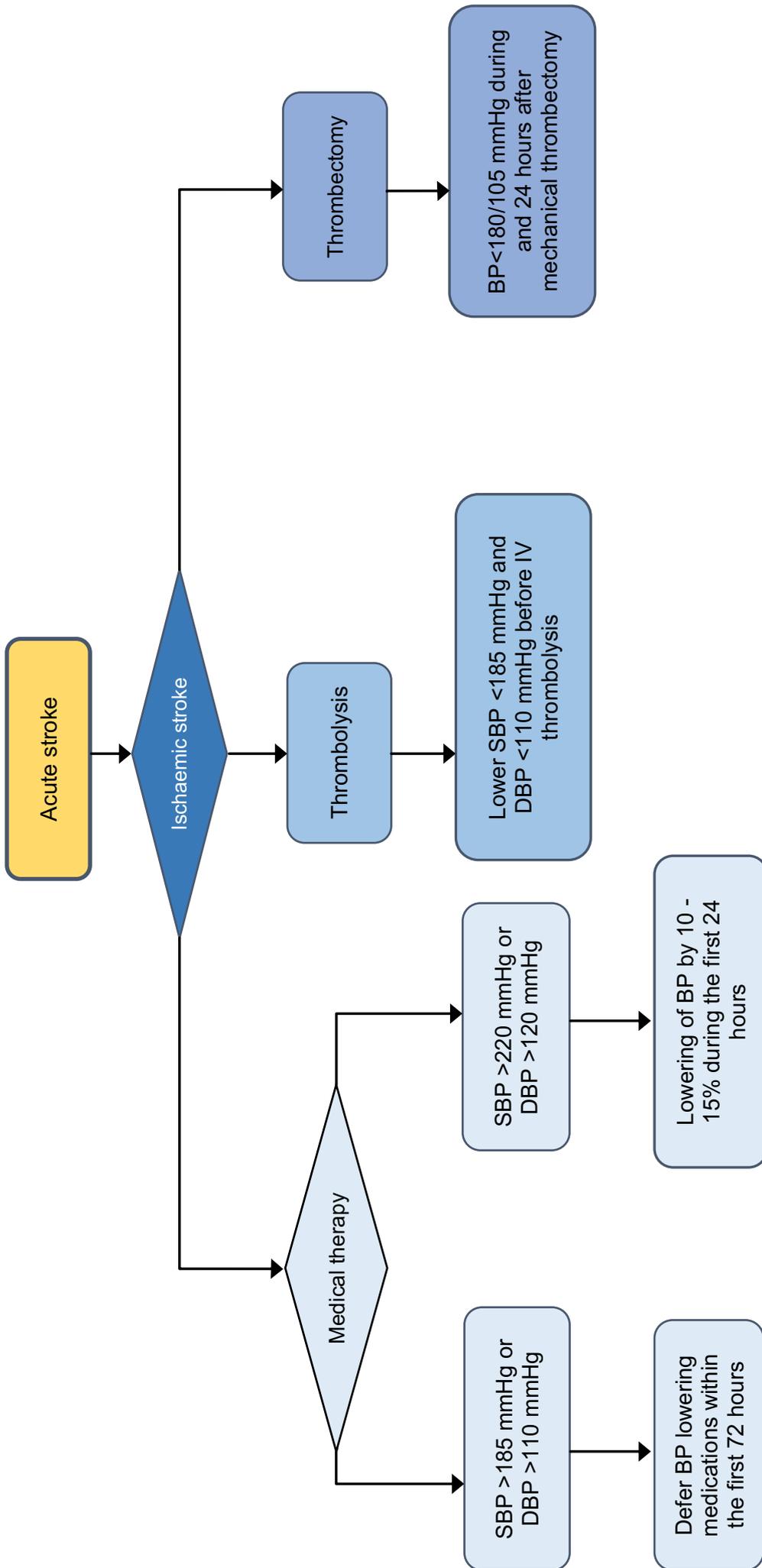
Parenteral agents such as labetalol or nicardipine that are easily titrated and have minimal vasodilatory effects on cerebral blood flow are preferred. The use of sublingual nifedipine should be avoided because of the risk of abrupt BP reduction and possible worsening ischaemia.

### Secondary prevention of stroke, TIA or after acute phase of ischemic stroke

- Severe cerebrovascular stenosis ruled out - Target BP  $\leq 130/80$  mmHg
- Patients with severe cerebrovascular stenosis- Target BP  $>130/80$  mmHg (individualised)



**Figure 7:** Target BP for patients with acute haemorrhagic stroke



**Figure 8:** Target BP for patients with acute ischaemic stroke

## 12: Hypertension in Chronic Kidney Disease

Dr Mohammad Abdul Mabood Khalil

### Key Messages:

- 1. Blood Pressure (BP) management in CKD non-dialysis patients:**
  - Target BP <140/90 mmHg in non-albuminuric and <130/80 mmHg in albuminuric CKD
- 2. BP management in haemodialysis:**
  - Pre-dialysis BP should be <140/90 mmHg and post-dialysis BP <130/80 mmHg. Avoid SBP <110 mmHg.
- 3. BP management in Peritoneal Dialysis (PD):**
  - It is recommended to treat BP if  $\geq 140/90$  mmHg with volume management and antihypertensive medications
- 4. Kidney transplantation:**
  - It is recommended to target BP to <130/80 mmHg
- 5. Drug therapy and selection of medications in CKD, haemodialysis and peritoneal dialysis:**
  - ACE-I or ARB should be used as first line of agent in patients with CKD having albuminuria.
  - Thiazide diuretic should be used in patients with eGFR of  $\geq 30$  ml/min/1.73m<sup>2</sup>. Loop diuretics (furosemide) should be used in patients with GFR <30 ml/min/1.73m<sup>2</sup>.

### **1. Definition of CKD, hypertension and albuminuria estimation:**

- CKD is defined as the presence of reduced kidney function (an estimated glomerular filtration rate [eGFR] <60ml/min/1.73m<sup>2</sup> or kidney damage (often indicated by the presence of albuminuria) for  $\geq 3$  months duration<sup>(96)</sup>).
- It is important to estimate albuminuria in CKD patients as it is associated with CKD progression and incident cardiovascular disease (CVD).
- Twenty-four-hour urine collection remains the gold standard method for quantification of proteinuria but sampling errors are common
- Several studies have demonstrated equivalency or superiority of ACR or PCR over 24h albumin or protein excretion in predicting CKD progression<sup>(97)</sup>.
- A spot urine ACR or PCR can be used to estimate albuminuria and proteinuria respectively. Albuminuria can be graded as normal to mild, moderate and severe. **Figure 8** shows various stages of CKD and albuminuria.
- Target BP will depend on the presence of albuminuria.
- All patients with hypertension having severely increased (see **Figure 8**) or eGFR <30ml/min/1.73m<sup>2</sup> or microscopic haematuria or having concurrent AKI should be referred to the nephrologist.

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

**Figure 9:** CKD stages and grades of albuminuria

## 2. BP management in CKD non-dialysis patients:

- Intensity of blood pressure reduction and reducing progression of CKD is dependent on albuminuria.
- Various studies have shown that intensive blood pressure control is beneficial in slowing the progression of CKD if base line proteinuria was more than 1 gram.
- Keeping in view these studies, most guidelines recommended intensive blood pressure reductions only in patients with significant proteinuria<sup>(98,99)</sup>.
- Recently SPRINT (Systolic Blood Pressure Intervention Trial) compared a systolic BP target of <140 mmHg with a more intensive systolic goal of <120 mmHg.
- In SPRINT trial, the intensive treatment group demonstrated a statistically significant reduction in the primary outcome, a composite of MI, acute coronary syndrome, stroke, heart failure or death from CVD. A reduction in the secondary outcome of death from any cause was also significant. The trial excluded all the diabetics and non-diabetic with GFR <20 ml/min/1.73m<sup>2</sup> and therefore missed good chunk of CKD patients<sup>(11)</sup>.
- Unfortunately, no benefit was shown in slowing down CKD progression. The risk of AKI and development of CKD was more in intensive blood pressure control arm in SPRINT trial.

- We, therefore recommend KDIGO guidelines which suggest BP <140/90 mmHg in non-albuminuric and <130/80 mmHg in albuminuric CKD<sup>(100)</sup>.

*Recommendations:*

- In hypertensive patients with CKD due to diabetes or other causes and urine albumin excretion <30mg per 24 hours (or equivalent) whose office BP is consistently >140 mmHg systolic or >90 mmHg diastolic, they should be treated with anti-hypertensives to maintain a BP that is consistently ≤140 mmHg systolic and ≤90 mmHg diastolic.
- In hypertensive patients with CKD due to diabetes or non-diabetic causes and urine albumin excretion >30mg and whose office BP is consistently >130 mmHg systolic or >80 mmHg diastolic, they should be treated with anti-hypertensives to maintain a BP that is consistently ≤ 130 mmHg systolic and ≤ 80mmHg diastolic.
- ARB or ACE-I should be used in CKD patients with urine albumin excretion > 30mg per 24 hours (or equivalent) in whom treatment with anti-hypertensives is indicated.

### 3. BP management in haemodialysis:

- Target blood pressure control in haemodialysis patient is quite complex.
- There is a U shape curve for cardiac related cardiovascular mortality with high mortality with SBP >180 mmHg or SBP <110 mmHg in haemodialysis patients<sup>(101)</sup>.
- An ideal BP in a haemodialysis patient would be associated with: hemodynamic stability during dialysis, orthostatic tolerance after dialysis, the best cardiovascular survival, and optimal health related quality of life.
- We agree with the National Kidney Foundation KDOQI guidelines suggest that pre-dialysis and post dialysis BPs should be <140/90 mmHg and 130/80 mmHg respectively<sup>(102)</sup>.
- European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and European Society of Hypertension along with KDOQI, suggested non-pharmacological measures initially to reduce sodium and volume overload in haemodialysis patients through achieving accurate dry weight, decreasing dialysate sodium towards pre-dialysis sodium in selected individuals<sup>(103)</sup>.

*Recommendations:*

- Pre-dialysis BP should be <140/90 mmHg and post-dialysis BP <130/80 mmHg. Please avoid systolic blood pressure <110 mmHg.
- In addition to blood pressure medication, non-pharmacological measures should also be tried. This includes achievement of dry weight, restriction of sodium intake, decreasing dialysate sodium towards pre-dialysis sodium and avoidance of short dialysis session of <4 hours.

**4. BP management in Peritoneal Dialysis (PD):**

- The prevalence of hypertension in PD is around 80% <sup>(104)</sup>.
- A relationship between high systolic blood pressure and an increased risk of mortality has been reported in PD.
- SBP of 110 mmHg or less was associated with an increased mortality, and a protective effect has been found with a systolic blood pressure above 120 mmHg.
- We agree, with recommendation of International Society of Peritoneal Dialysis which recommend to treat BP if >140/90 mmHg with volume management and antihypertensive medications<sup>(104)</sup>.

*Recommendations:*

- Blood pressure should be evaluated by home blood pressure measurement at least once a week and at each visit to the clinic.
- Peritoneal dialysis patients whose blood pressure is consistently >140/90 mmHg needs to be treated to maintain BP <140 mmHg systolic and <90 mmHg diastolic.
- Peritoneal dialysis patients with hypertension should have their volume status optimized before starting or increasing anti-hypertensive medications.

**5. Management of hypertension in kidney transplant patients:**

- More than 90% of the kidney transplant patients using calcineurin inhibitors have hypertension.
- Like haemodialysis no RCT was done in transplant population to identify ideal antihypertensive medications and target blood pressure.
- We agreed with KDIGO guideline which recommends a target BP of <130/80 mmHg<sup>(105)</sup>.
- Choice of antihypertensive agent will depend on several factors, including time from transplantation, concomitant prescriptions including immunosuppression, and co-morbidities.

- Calcium channel blocker such as dihydropyridine (amlodipine and nifedipine) may be effective in reversing calcineurin inhibitors induced vasoconstriction.
- Verapamil and diltiazem have interactions with calcineurin inhibitors (cyclosporin, tacrolimus) and should not be used.

*Recommendations:*

- Adult kidney transplant recipients whose office BP is consistently  $\geq 130$  mmHg systolic or  $\geq 80$  mmHg diastolic be treated to maintain a BP that is consistently  $\leq 130$  mmHg systolic and  $\leq 80$  mmHg diastolic, irrespective of the level of urine albumin excretion.
- In adult kidney transplant recipients, choose an anti-hypertensive after considering the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co-morbid conditions.

## 6. Drug therapy and selection of medications in CKD:

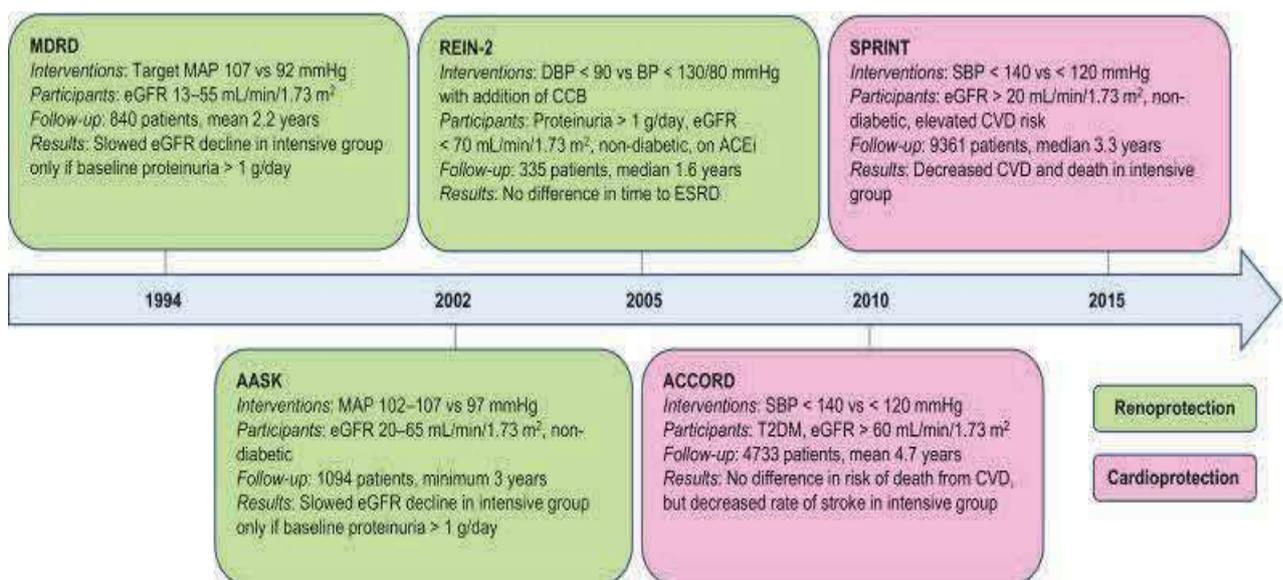
- ACE-I and ARBs has antiproteinuric effects and are drug of choice in CKD<sup>(99)</sup>.
- Uncertainty exists regarding the use of RAAS blockade in those with advanced CKD (eGFR $<30$ ml/min/1.73m<sup>2</sup>) as this population has been largely excluded from major randomized trials.
- The combination of ACE-I or ARB in ONTARGET and VA NEPHRON-D trial was associated with more adverse events with no significant reduction in primary outcome<sup>(106,107)</sup> and therefore, should be avoided
- CCB can be used as first-line therapy in non-albuminuric CKD, either alone or in combination. Addition of a dihydropyridine CCB to albuminuric patients with established RAAS blockade improves BP control without worsening proteinuria<sup>(108)</sup>. **Figure 9** shows landmark trials done which has patients with CKD.
- In non-albuminuric CKD, monotherapy with a thiazide or a thiazide-like diuretic may have a role and should be considered as a potential for first-line therapy<sup>(109)</sup> when eGFR is  $\geq 30$  ml/min/1.73m<sup>2</sup>.
- Loop diuretics (such as furosemide) should be considered in patients with eGFR  $< 30$  ml/min/1.73m<sup>2</sup>.
- $\alpha$ -blocker can be considered as an add on to get target blood pressure. **Figure 10** shows a flow diagram for selection of BP medications.

**Recommendations:**

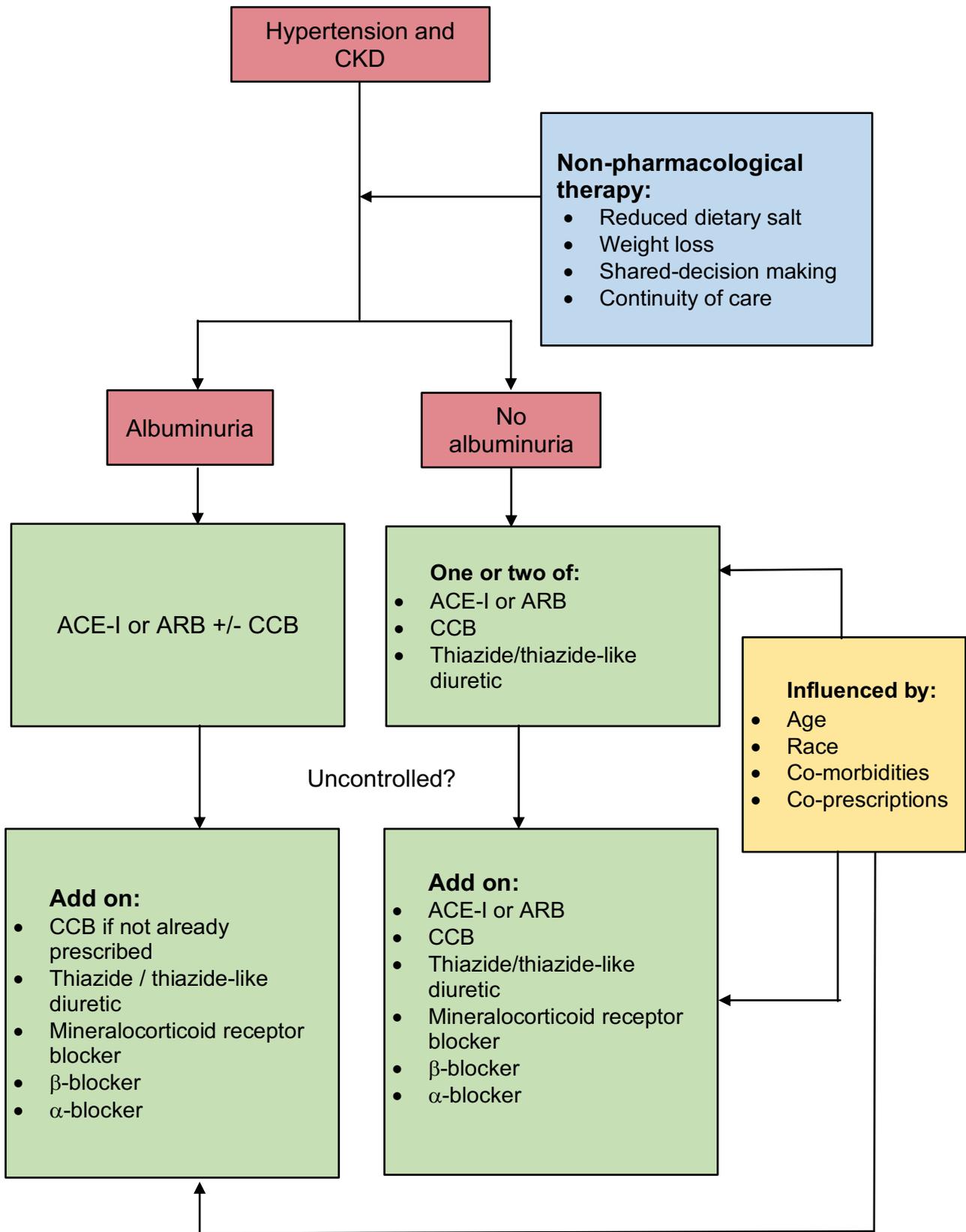
- ACE-I or ARB should be used as first line of agent in patients with CKD having albuminuria.
- Please consider age, race, co-morbidities and co-prescription while prescribing anti-hypertensives.
- In non-albuminuric CKD patients, please use one or two of ACE-I or ARB, CCB or thiazide diuretic.
- Do not combine ACEI and ARB.
- Please check potassium and creatinine within a week and then a month of initiation of ACE-I or ARB. If creatinine increases 30% from the base line or there is evidence of hyperkalaemia, then these medications should be held.
- Thiazide diuretic should be used in patients with eGFR of  $\geq 30$  ml/min/1.73m<sup>2</sup>. Loop diuretics (furosemide) should be used in patients with GFR < 30ml/min/1.73m<sup>2</sup>.

**Referral criteria to nephrologist:**

- All new hypertensive at point of diagnosis should have urine routine examination, serum creatinine for eGFR estimation and evaluation of albuminuria with ACR or PCR and then at least once a year.
- Referral criteria to nephrology services:
  - Hypertension with AKI or abrupt sustained fall in GFR
  - GFR  $\leq 30$  ml/min/1.73 m<sup>2</sup>
  - A consistent finding of significant albuminuria (ACR  $\geq 30$ mg/mmol) or AER  $\geq 300$  mg/24 hours, approximately equivalent to PCR  $\geq 500$ mg/g [ $\geq 50$ mg/mmol] or PER  $\geq 500$ mg/24 hours)
  - Presence of urinary red cell casts, RBC  $\geq 20$  per high power field that is sustained and not readily explained



**Figure 10: Lanmark trials in hypertension**



**Figure 11:** Management of BP in CKD patients

## **13: Hypertension and heart disease**

Dr Francis Lim Tiong Khim

### **Key Messages:**

1. Target BP is generally <130/80 mmHg as these patients have elevated cardiovascular risk
2. For patients with coronary artery disease  $\beta$  blockers may be considered earlier for relief of angina in stable disease or prognostic benefit following an acute coronary syndrome
3. In heart failure with reduced ejection fraction (LVEF<40%), preference should be given to  $\beta$ -blockers known to improve mortality (bisoprolol, carvedilol and metoprolol XL) in addition to ACE-I/ARB and spironolactone

Hypertension is a known major risk factor for developing cardiovascular disease. Patients who are known to have cardiovascular disease are at high risk for future events and thus good control of blood pressure is of paramount importance. Studies have shown that while lowering blood pressure itself is beneficial rather than due to any specific class of anti-hypertensive agents, there are certain classes of anti-hypertensive agents that are of benefit in certain cardiac conditions <sup>(8)</sup>.

### **Coronary artery disease**

#### **Acute coronary syndromes (ST and non-ST elevation myocardial infarction)**

Patients who have had an acute coronary event benefit from secondary prevention treatment – this includes ACE-I/ARB and beta blockers <sup>(8,10)</sup>. Patients who are hypertensive and not on these agents should be started on them, unless contraindicated) If BP remains elevated on these treatments, the recommendation is to follow the standard treatment pathway using anti-hypertensive medications that patients are not on.

#### **Stable angina/coronary artery disease**

In patients who have not had an acute coronary event, but has symptomatic angina, beta blockers and calcium channel antagonists are preferred agents as these would treat both hypertension and angina symptoms. ACE-I/ARB are beneficial in patients with hypertension and coronary artery disease and would be the preferred agent of choice in patients with known CAD without angina <sup>(1,8)</sup>.

If BP remains elevated on these treatments, the recommendation is to follow the standard treatment pathway using anti-hypertensive medications that patients are not on.

**Target BP for patients with known CAD: <130/80 mmHg <sup>(1,8)</sup> but not <120/70 mmHg <sup>(10)</sup>**

## **Heart failure**

### **Heart failure with reduced ejection fraction (HFrEF), LVEF $\leq$ 40%**

Hypertension is a significant cause of heart failure and uncontrolled hypertension leads to heart failure with reduced ejection fraction. Hypertension should therefore be well controlled to reduce the risk of developing heart failure, especially more so in those with other cardiovascular risk factors.

Patients with known HFrEF should be on anti-heart failure medications that have been shown to be beneficial with reduction in mortality and heart failure hospitalisations – these agents are ACE-I/ARB, beta blockers (bisoprolol, carvedilol and metoprolol XL) and mineralcorticoid receptor antagonist <sup>(1,8,10)</sup>.

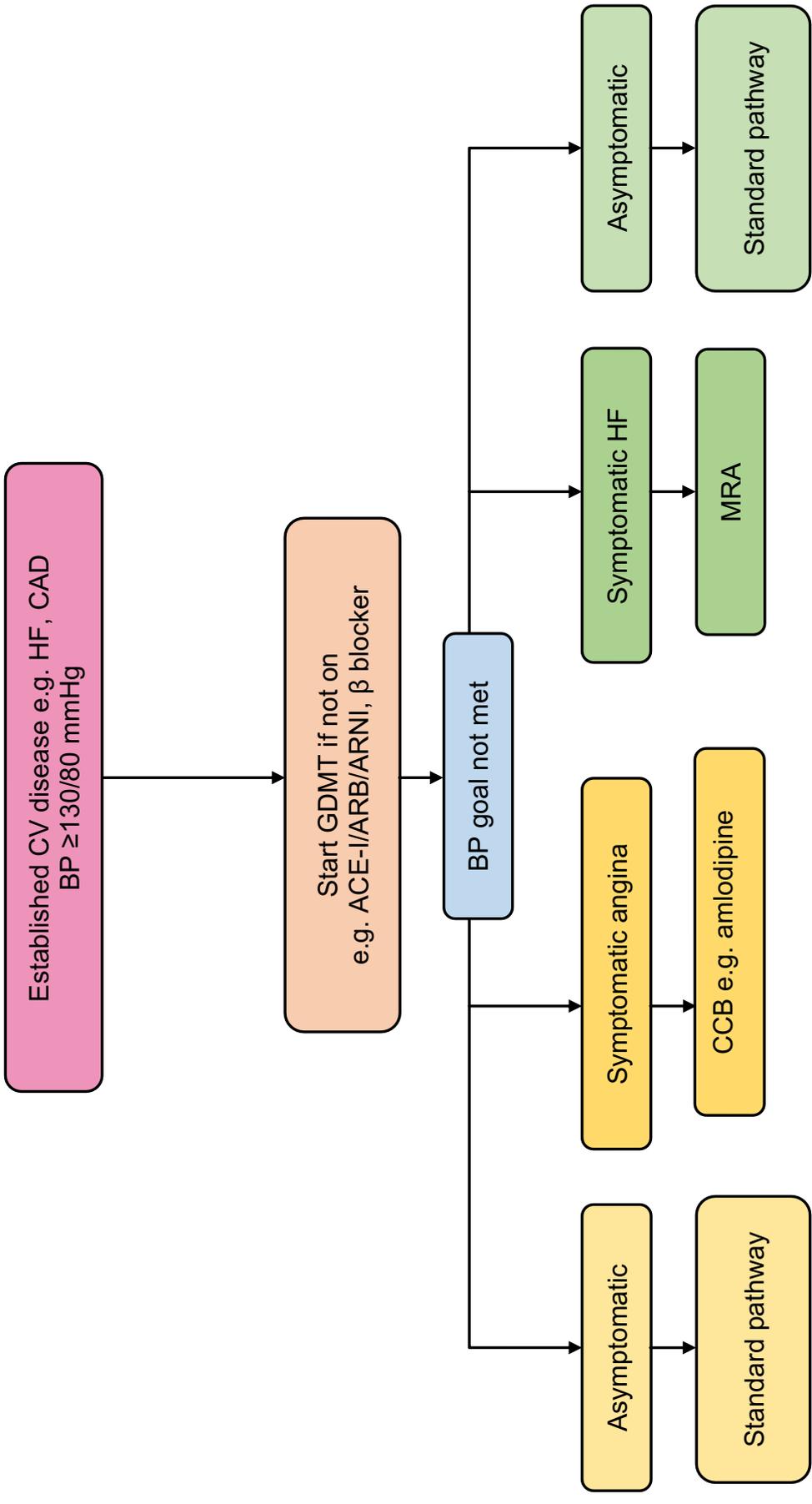
A new class of drug consisting of an angiotensin II receptor blocker and neprilysin inhibitor, which inhibits the breakdown of natriuretic peptides (ARNI) has recently been developed for the treatment of HFrEF<sup>(110)</sup>. The only drug currently available in this class is sacubutril/valsartan, a combination of a neprilysin inhibitor (sacubutril) and an angiotensin II receptor blocker (ARB; valsartan)<sup>(111)</sup>.

If blood pressure remains elevated on these treatments, the recommendation is to follow the standard treatment pathway using anti-hypertensive medications that patients are not on. Patients are usually on loop diuretics to control fluid status, if so to avoid thiazide diuretics. Non-dihydropyridine CCB,  $\alpha$ -blockers and centrally acting agents such as moxonidine should not be avoided <sup>(1,112)</sup>.

### **Heart failure with preserved ejection fraction (HFpEF), LVEF $\geq$ 50%**

Approximately 50% of HF patients seen in clinics have HFpEF <sup>(113)</sup>. The optimal treatment strategy for hypertensive patients with HFpEF is not known at this time, the recommended strategy is as for HFrEF patients<sup>(10)</sup>.

***Target BP for patients with heart failure:  $<130/80$  mmHg <sup>(1,10)</sup>***



**Figure 12:** Management of BP in patients with heart disease

## 14: Hypertension disorders of pregnancy

Dr Shaheen Basheer and Dr Mary Paul Chemmannoor

### Key messages:

1. There are various hypertensive disorders of pregnancy and they can be associated with adverse and foetal outcomes.
2. Educate all pregnant women about the symptoms of pre-eclampsia and when to seek medical attention.
3. Identify women at high risk of pre-eclampsia and advise them to take a low dose of aspirin from 12 weeks until delivery
4. The goals of antenatal care in hypertension disorders of pregnancy include control of BP, recognize pre-eclampsia early, prevent eclampsia, optimize birth for both women and baby.

- Hypertension disorders of pregnancy affects 8-10% of pregnancies <sup>(114)</sup>; they can be associated with adverse maternal and foetal outcomes.
- Hypertension disorders of pregnancy includes:
  1. **Gestational hypertension:** new onset BP  $\geq 140$  mmHg systolic or 90mmHg diastolic on at least two occasions, at least 6h apart, after 20 weeks gestation, in the absence of proteinuria.
  2. **Pre-eclampsia:** pregnancy-specific disorder that occurs after 20 weeks gestation. New onset hypertension with one or more conditions (proteinuria/ maternal organ dysfunction/ uteroplacental dysfunction). Pre-eclampsia can also occur superimposed upon chronic hypertension.
  3. **Eclampsia:** convulsive form of preeclampsia and affects 0.1% of all pregnancies <sup>(114)</sup>.
  4. **Chronic hypertension:** BP  $\geq 140/90$  mmHg before pregnancy or  $<20$ th week of gestation or use of antihypertensive medication before pregnancy
- Initial evaluation for early detection and to prevent maternal and foetal complications are:
  - Blood pressure monitoring
  - Weight
  - Urine dipstick
  - Lab analysis.
- Advise women that they will benefit from smoking cessation, maintaining healthy weight, regular exercise and eating a healthy diet

## **Reducing the risk of hypertensive disorders in pregnancy**

### **Symptoms of pre-eclampsia**

Advise pregnant women to see a healthcare professional immediately if they experience symptoms of pre-eclampsia. Symptoms include:

- Severe headache
- Rapid weight gain
- Visual disturbances e.g. blurring or flashing before the eyes
- Severe pain below the ribs (Epigastric pain)
- Nausea and vomiting
- Sudden swelling of face, hands and feet

### **Antiplatelet agents**

Advise pregnant women at high risk of pre-eclampsia to take 75–150mg of aspirin daily from 12 weeks until the birth of the baby. If they have 1 High risk factors or > 1 moderate risk factors at booking visit (ideally 9-11 weeks).

High Risk factors	Moderate Risk factors
<ul style="list-style-type: none"><li>• hypertensive disease during a previous pregnancy</li><li>• chronic kidney disease</li><li>• autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome</li><li>• type 1 or type 2 diabetes</li><li>• chronic hypertension</li></ul>	<ul style="list-style-type: none"><li>• first pregnancy</li><li>• age 40 years or older</li><li>• pregnancy interval of more than 10 years</li><li>• body mass index (BMI) of 35kg/m<sup>2</sup> or more at first visit</li><li>• family history of pre-eclampsia</li><li>• multi-foetal pregnancy</li></ul>

**Table 30:** Risk factors for developing pre-eclampsia

Pharmacological agents (Nitric oxide donor, Progesterone, diuretics and LMW heparin) and Nutritional Supplements (Mg, folic acid, Antioxidants, Fish oil and garlic) are not recommended for prevention or treatment of hypertensive disorders of pregnancy.

### **Assessment of proteinuria in Hypertensive Disorders of Pregnancy**

- Interpret proteinuria measurements for pregnant women in the context of a full clinical review of symptoms, signs and other investigations for pre-eclampsia.
- Use an automated reagent-strip reading device for dipstick screening for proteinuria in pregnant women in secondary care settings (if available; otherwise to use standard urine dipstick testing).
- If dipstick screening is positive for protein (1+ or more), use PCR to quantify proteinuria. (use 30mg/mmol as a threshold for significant proteinuria)

- Do not use first morning urine void or 24-hour urine collection to quantify proteinuria in pregnant women.
- The latest NICE guideline (June 2019)<sup>(114)</sup> on hypertension disorders of pregnancy suggested that ACR ( $\geq 8\text{mg}/\text{mmol}$ ) as a diagnostic threshold can be used to quantify proteinuria in pregnant women.

### **Management of chronic hypertension in pregnancy**

#### **Pre-pregnancy advice**

- Refer women with chronic hypertension to a specialist in hypertensive disorders of pregnancy to discuss the risks and benefits of treatment.
- Advise women who take ACE-I or, thiazide or thiazide-like diuretics that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy
- Stop antihypertensive treatment in women taking ACE-I or ARBs if they become pregnant (preferably within 2 working days of notification of pregnancy) and start antihypertensives safe in pregnancy i.e. labetalol (1<sup>st</sup> line), Nifedipine LA (2<sup>nd</sup> line) and Methyldopa (3<sup>rd</sup> line).
- Advise women who take antihypertensive treatments other than ACE-I, ARBs, thiazide or thiazide-like diuretics that the limited evidence available has not shown an increased risk of congenital malformation with such treatments.

#### **Treatment of chronic hypertension**

- Offer pregnant women with chronic hypertension advice on:
  - weight management
  - exercise
  - healthy eating
  - lowering the amount of salt in their diet.
- Continue with existing antihypertensive treatment if safe in pregnancy, or switch to an alternative treatment, unless BP is  $< 110/70$  mmHg or the woman has symptomatic hypotension.
- Offer antihypertensive treatment to pregnant women who have chronic hypertension and who are not already on treatment if they have blood pressure of  $140/90$  mmHg or higher (aim for a target blood pressure of  $135/85$  mmHg).
- Offer pregnant women with chronic hypertension aspirin 75–150mg once daily from 12 weeks gestation.

### Antenatal appointments

In women with chronic hypertension, schedule additional antenatal appointments based on the individual needs of the woman and her baby. This may include weekly appointments if hypertension is poorly controlled and appointments every 2 to 4 weeks if hypertension is well-controlled.

### **Management of gestational hypertension**

#### Assessment and treatment of gestational hypertension

- In women with gestational hypertension, a full assessment should be carried out in a secondary care setting by a healthcare professional who is trained in the management of hypertensive disorders of pregnancy.
- In women with gestational hypertension, take account of the following risk factors that require additional assessment and follow-up:
  - nulliparity
  - age 40 years or older
  - pregnancy interval of more than 10 years
  - family history of pre-eclampsia
  - multi-foetal pregnancy
  - BMI of 35 kg/m<sup>2</sup> or more at first visit
  - gestational age at presentation
  - previous history of pre-eclampsia or gestational hypertension
  - pre-existing vascular disease
  - pre-existing kidney disease.

*Management of pregnancy with gestational hypertension*

	Degree of Hypertension	
	Hypertension: blood pressure of 140/90 – 159/109mmHg	Severe Hypertension: blood pressure of $\geq$ 160/110
<b>Admission to hospital</b>	Do not routinely admit to hospital	Admit until BP is under 160/110mmHg
<b>Antihypertensive pharmacological treatment</b>	Offer pharmacological treatment if BP remains above 140/90mmHg	Offer pharmacological treatment to all women
<b>Target blood pressure once on antihypertensive treatment</b>	Aim for BP $\leq$ 135/85mmHg	Aim for BP of $\leq$ 135/85mmHg or less
<b>Blood pressure measurement</b>	Once or twice a week (depending on BP) until BP is $\leq$ 135/85 mmHg	Every 15-30 minutes until BP is $\leq$ 160/110 mmHg
<b>Dipstick proteinuria testing</b>	Once or twice a week (with BP measurement)	Daily while admitted
<b>Blood tests</b>	Measure full blood count, liver function, urea and electrolytes at presentation and then weekly	Measure full blood count, liver function, urea and electrolytes at presentation and then weekly
<b>Foetal assessment</b>	Carry out an ultrasound for foetal growth and Doppler at diagnosis. Repeat if clinically indicated. Only carry out CTG if foetal activity is abnormal.	Carry out ultrasound for foetal growth, Doppler and CTG at diagnosis and if normal repeat every 2 weeks. If foetal monitoring is normal then do not repeat CTG more than weekly unless clinically indicated.
<b>Weekly checks</b>	When checking the woman's BP, carry out foetal heart auscultation once a week.	When checking the woman's BP, carry out foetal heart auscultation once a week.

**Table 31:** Management of pregnancy with gestational hypertension

Offer placental growth factor (PIGF)-based testing to help rule out preeclampsia in women presenting with suspected pre-eclampsia (for e.g. with gestational hypertension) between 20 weeks and up to 35 weeks of pregnancy.<sup>(114)</sup>

## Management of pre-eclampsia

### Assessing pre-eclampsia

Assessment of women with pre-eclampsia should be performed by a healthcare professional trained in the management of hypertensive disorders of pregnancy.

Full clinical assessment at each antenatal appointment for women with pre-eclampsia and offer admission to hospital for surveillance and any interventions needed if there are concerns for the wellbeing of the woman or baby.

Concerns include any of the following:

- sustained systolic blood pressure of 160 mmHg or higher
- any maternal biochemical or haematological investigations that cause concern, for example, a new and persistent:
  - rise in creatinine (90µmol/L or more, 1mg/100ml or more) or
  - rise in alanine transaminase (over 70 IU/L, or twice upper limit of normal range) or
  - fall in platelet count (under 150,000/µL)
  - signs of impending eclampsia
  - signs of impending pulmonary oedema
  - other signs of severe pre-eclampsia
  - suspected foetal compromise
  - any other clinical signs that cause concern.

Consider using either the fullPIERS or PREP-S validated risk prediction models to help guide decisions about the most appropriate place of care (such as the need for in utero transfer) and thresholds for intervention.

When using a risk prediction model, please consider the following:

- fullPIERS\* is intended for use at any time during pregnancy
- PREP-S\*\* is intended for use only up to 34 weeks of pregnancy
- fullPIERS and PREP-S models do not predict outcomes for babies

\*fullPIERS – developed and validated with aim of identification risks and life-threatening complications in women with pre-eclampsia within 48hrs of hospital admission. Predictors of adverse maternal outcome include gestational age, chest pain or dyspnoea, oxygen saturation, platelet count and creatinine, AST. Score of > 30% is considered High risk and < 30% is low risk

\*\*PREP – S – Predicts risk of complication in early onset Pre-eclampsia at various time points following diagnosis until 34 weeks of pregnancy. Predictors include maternal age, gestational age, exaggerated tendon reflexes, pre-existing medical condition, PCR, serum urea, platelet, systolic BP, treatment with antihypertensive or magnesium sulfate, pulse oximetry, ALT and creatinine.

If Score is < 50% → women can be managed as outpatient and avoid transfer to hospital.

Management of Pregnancy with Pre-eclampsia

	Degree of Hypertension	
	Hypertension: BP of 140/90 – 159/109 mmHg	Severe hypertension: BP of 160/110 mmHg or more
<b>Admission to hospital</b>	Admit if any clinical concerns for the wellbeing of the woman or baby or if high risk of adverse events suggested by the fullPIERS or PREP-S risk prediction models	Admit, but if BP falls below 160/110 mmHg then manage as for hypertension.
<b>Antihypertensive pharmacological treatment</b>	Offer pharmacological treatment if BP remains above 140/90 mmHg	Offer pharmacological treatment to all women
<b>Target blood pressure once on antihypertensive treatment</b>	Aim for BP of 135/85 mmHg or less	Aim for BP of 135/85 mmHg or less
<b>Blood pressure measurement</b>	At least every 48 hours, and more frequently if the woman is admitted to hospital	Every 15-30 minutes until BP is less than 160/110 mmHg, then at least 4 times daily while the woman is an inpatient, depending on clinical circumstances
<b>Dipstick proteinuria testing</b>	Only repeat if clinically indicated, for example, if new symptoms and signs develop or if there is uncertainty over diagnosis	Only repeat if clinically indicated, for example, if new symptoms and signs develop or if there is uncertainty over diagnosis
<b>Blood tests</b>	Measure full blood count, liver function and renal function twice a week	Measure full blood count, liver function and renal function 3 times a week
<b>Foetal assessment</b>	Offer foetal heart auscultation at every antenatal appointment. Carry out ultrasound assessment of the foetus at diagnosis and, if normal, repeat every 2 weeks.	Offer foetal heart auscultation at every antenatal appointment. Carry out ultrasound assessment of the foetus at diagnosis and, if normal, repeat every 2 weeks.

	Carry out a CTG at diagnosis and then only if clinically indicated.	Carry out a CTG at diagnosis and then only if clinically indicated.
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**Table 32:** Management of pregnancy with pre-eclampsia

**Foetal monitoring**

Hypertensive Disorder of Pregnancy	USS (Foetal growth, AFV, UA Doppler)	Cardiotocopgraphy (CTG)
Chronic hypertension	28, 32, 36 weeks	If clinically indicated
Gestational hypertension	At diagnosis, if normal every 2 -4 weeks if clinically indicated	If clinically indicated
Pre-eclampsia / severe gestational hypertension	At diagnosis, repeat every 2weeks.  Write a care plan that includes all of the following: <ul style="list-style-type: none"> <li>the timing and nature of future foetal monitoring</li> <li>foetal indications for birth and if and when antenatal corticosteroids should be given</li> <li>plans for discussion with neonatal paediatricians and obstetric anaesthetists</li> </ul>	At diagnosis, repeat CTG if any of the following occur: <ul style="list-style-type: none"> <li>the woman reports a change in foetal movement</li> <li>vaginal bleeding</li> <li>abdominal pain</li> <li>deterioration in maternal condition</li> </ul>

**Table 33:** Foetal monitoring in patients with hypertensive disorders of pregnancy

**Additional foetal monitoring:**

Carry out an ultrasound for foetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry starting at between 28 and 30 weeks (or at least 2 weeks before previous gestational age of onset if earlier than 28 weeks) and repeating 4 weeks later in women with previous:

- severe pre-eclampsia
- pre-eclampsia that resulted in birth before 34 weeks
- pre-eclampsia with a baby whose birth weight was less than the 10th centile
- intrauterine death
- placental abruption

## **Timing of Birth**

### Chronic hypertension and gestational hypertension

- Do not offer planned early birth before 37 weeks to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment, unless there are other medical indications.
- For women whose blood pressure is <160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, maternal and foetal indications for birth should be agreed between the woman and the senior obstetrician.
- If planned early birth is necessary, offer a course of antenatal corticosteroids and magnesium sulfate.

### Pre-eclampsia

- Before 34 weeks: continue surveillance unless there are indications for planned early birth. Offer IV magnesium sulfate and a course of antenatal corticosteroids on pre-term labour and birth.
- From 34 to 36<sup>+6</sup> weeks: continue surveillance unless there are indications for planned early birth.
- When considering the option of planned early birth, please consider the woman's and baby's condition, risk factors (such as maternal comorbidities, multi-foetal pregnancy) and availability of neonatal unit beds. Consider a course of antenatal corticosteroids guideline on pre-term labour and birth.
- 37 weeks onwards: offer planned birth within 24-48 hours.

## **Intra-partum Care**

- BP monitoring
  - Hourly, in women with hypertension
  - Every 15-30 minutes until BP is <160/110 mmHg in women with severe hypertension
- Antihypertensives to continue
- Epidural analgesia
  - Do not pre-load women who have severe pre-eclampsia with IV fluids before establishing low-dose epidural analgesia or combined spinal epidural analgesia
- Second stage of labour
  - Do not routinely limit the duration of the second stage of labour in women with controlled hypertension
  - Consider operative or assisted birth in the second stage of labour for women with severe hypertension whose hypertension has not responded to initial treatment.

## **For pre-eclampsia**

- Record maternal and foetal thresholds for planned early birth before 37 weeks in women with pre-eclampsia.
- Thresholds for considering planned early birth could include (but are not limited to) any of the following known features of severe pre-eclampsia:
  - inability to control maternal blood pressure despite using 3 or more classes of
  - antihypertensives in appropriate doses
  - maternal pulse oximetry less than 90%
  - progressive deterioration in liver function, renal function, haemolysis, or platelet count
  - ongoing neurological features, such as severe intractable headache, repeated visual scotomata, or eclampsia
  - placental abruption
  - reversed end-diastolic flow in the umbilical artery doppler velocimetry, a non-reassuring cardiotocograph, or stillbirth.
  - Involve a senior obstetrician (SMO or consultant) in any decisions on timing of birth for women with pre-eclampsia

## **Postnatal care**

### Chronic hypertension

- Daily for the first 2 days after birth
- At least once between day 3 and day 5 after birth
- Aim to keep BP <140/90 mmHg
- Continue antihypertensive treatment, if required
- Review long-term antihypertensive treatment 2 weeks after the birth
- Methyldopa to stop within 2 days after birth
- Offer medical review 6-8 weeks after birth with GP or specialist.

### Gestational hypertension

- Daily for the first 2 days after birth
- At least once between day 3 and day 5 after birth
- Continue antihypertensive treatment, if required
- Reduce antihypertensive treatment if their BP falls <130/80 mmHg and if the woman was not taking treatment then start antihypertensive if BP  $\geq$ 150/100 mmHg
- Methyldopa to stop within 2 days after birth
- Transfer to community care with the care plan
- Medical review with GP or specialist at 2 weeks and 6-8 weeks after birth

### Pre-eclampsia

- At least 4 times a day while the woman is an inpatient
- At least once between day 3 and day 5 after birth
- Ask about signs and symptoms of severe pre-eclampsia
- Continue antihypertensive treatment

- Consider reducing antihypertensive treatment if their BP falls <140/90 mmHg
- Reduce antihypertensive treatment if their BP falls <130/80 mmHg
- If the woman was not taking treatment, then to start antihypertensive if BP  $\geq$ 150/100 mmHg
- Methyldopa to stop within 2 days after birth
- Transfer to community care with the care plan
- Medical review with GP or specialist at 2 weeks and 6-8 weeks after birth
- Measure platelet count, transaminases and serum creatinine measurements if results are normal at 48-72 hours
- In women with pre-eclampsia who have given birth, carry out a urinary reagent strip test 6-8 weeks after the birth
- Offer women who had pre-eclampsia and still have proteinuria (1+ or more) at 6-8 weeks after the birth, a further review at 3 months after the birth to assess kidney function.

#### Postnatal BP monitoring in pre-eclampsia patients

- In women with pre-eclampsia who did not take antihypertensive treatment and have given birth, measure blood pressure:
  - at least 4 times a day while the woman is an inpatient
  - at least once between day 3 and day 5 after birth on alternate days until normal, if blood pressure was abnormal on days 3–5.
- In women with pre-eclampsia who took antihypertensive treatment and have given birth, measure blood pressure:
  - at least 4 times a day while the woman is an inpatient every 1–2 days for up to 2 weeks after transfer to community care until the woman is off treatment and has no hypertension.

#### Medical management of severe hypertension, severe pre-eclampsia or eclampsia in a critical care setting

##### Anticonvulsants

- If a woman in a critical care setting who has severe hypertension or severe preeclampsia has or previously had an eclamptic fit, give intravenous magnesium sulfate.
- Consider giving intravenous magnesium sulfate to women with severe preeclampsia who are in a critical care setting if birth is planned within 24 hours.
- Consider the need for magnesium sulfate treatment, if 1 or more of the following features of severe pre-eclampsia is present:
  - ongoing or recurring severe headaches
  - visual scotomata
  - nausea or vomiting
  - epigastric pain

- oliguria and severe hypertension
- progressive deterioration in laboratory blood tests (such as rising creatinine or liver transaminases, or falling platelet count).
- Use the Collaborative Eclampsia Trial regimen for administration of magnesium sulfate:
  - A loading dose of 4g should be given intravenously over 5 to 15 minutes, followed by an infusion of 1g/h maintained for 24 hours. If the woman has had an eclamptic fit, the infusion should be continued for 24 hours after the last fit.
  - Recurrent fits should be treated with a further dose of 2-4g given intravenously over 5 to 15 minutes.
  - Do not use diazepam, phenytoin or other anticonvulsants as an alternative to magnesium sulfate in women with eclampsia

### Antihypertensives

Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with 1 of the following:

- labetalol (oral or intravenous)
- oral nifedipine
- intravenous hydralazine (Consider using up to 500ml crystalloid fluid before or at the same time as the first dose of intravenous hydralazine in the antenatal period)

**Likelihood of recurrence of hypertensive disorders of pregnancy  
(overall 1 in 5)**

Type of hypertension in previous or current pregnancy			
Prevalance of hypertensive disorder in a future pregnancy	Any hypertension in pregnancy	Pre-eclampsia	Gestational hypertesion
<b>Any hypertension</b>	Approximately 21% (1 in 5 women)	Approximately 20% (1 n 5 women)	Approximately 22% (1 in 5 women)
<b>Pre-eclampsia</b>	Approximately 14% (1 in 7 women)	Up to approximately 16% (1 in 6 women)  If birth was at 28-34 weeks, approximately 33% (1 in 3 women)  If birth was at 34-37 weeks, approximately 23% (1 in 4 women)	Approximately 7% (1 in 14 women)
<b>Gestational hypertension</b>	Approximately 9% (1 in 11 women)	Between approximately 6 and 12% (up to 1 in 8 women)	Between approximately 11 and 15% (up to 1 in 7 women)
<b>Chronic hypertension</b>	Not applicable	Approximately 2% (up to 1 in 50 women)	Approximately 3% (up to 1 in 34 women)

**Table 34:** Likelihood of recurrence of different hypertensive disorders of pregnancy

## **Cardiovascular risks**

<b>Risk of future cardiovascular disease</b>	<b>Any hypertension in pregnancy</b>	<b>Pre-eclampsia</b>	<b>Gestational hypertension</b>	<b>Chronic hypertension</b>
Major adverse cardiovascular event	Risk increased (up to approximately 2 times)	Risk increased (approximately 1.5 – 3 times)	Risk increased (approximately 1.5 – 3 times)	Risk increased (approximately 1.7 times)
Cardiovascular mortality	Risk increased (up to approximately 2 times)	Risk increased (approximately 2 times)	No data	No data
Stroke	Risk increased (up to approximately 1.5 times)	Risk increased (approximately 2-3 times)	Risk may be increased	Risk increased (approximately 1.8 times)
Hypertension	Risk increased (approximately 2-4 times)	Risk increased (approximately 2-5 times)	Risk increased (approximately 2-4 times)	Not applicable

**Table 35:** Cardiovascular risks in hypertensive disorders of pregnancy

### **Reducing Cardiovascular risks**

- Avoid smoking
- Healthy life style
- Healthy weight (BMI 18.5 – 24.9kg/m<sup>2</sup>)

### **Antihypertensive treatment safe during breastfeeding**

- Nifedipine
- Amlodipine if the woman has previously used this to successfully control her blood pressure
- Enalapril
- Atenolol
- labetalol
- Captopril
- Where possible, avoid using diuretics or angiotensin receptor blockers to treat hypertension in women in the postnatal period who are breastfeeding.

Treat women with hypertension in the postnatal period who are not breastfeeding and who are not planning to breastfeed in line with the NICE guideline on hypertension in adults<sup>(9)</sup>.

## **15. Paediatric Hypertension**

Dr Hjh Rohayati Hj Md Taib

### **Key messages:**

1. There is a high rate of false-positive high BP reading in a single clinic visit, hence, multiple visits are required to confirm the diagnosis of hypertension in children
2. Attention must be paid to the correct technique and use of appropriate paediatric validated instruments when obtaining a BP reading in children
3. Height, gender and sex are important determinants of paediatric BP. Normative blood pressure tables based on the 2017 American Academy of Pediatrics guidelines are recommended. (Refer to **Appendix 2 & 3**)
4. 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<sup>th</sup> percentile for age, sex, and height of the patient, or is  $\geq 130/90$  mmHg (whichever is lower)
5. Children who are at risk of developing secondary hypertension should have BP reading at every medical encounter, healthy obese children should have annual BP measurements from the age of 7 years.

### **1. Hypertension in Neonates and Infants**

- The incidence of hypertension in neonates admitted to Neonatal Intensive Care Unit is 1.3%<sup>(8)</sup>.
- 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.
- Catheter related hypertension is related to thrombus formation at the time of line placement.

#### **1.1 Measurement of BP in neonate**

- Healthy term neonates rarely have hypertension
- Therefore, 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.

#### **1.2 Standardised Protocol for BP Measurement in Neonates:**

- Measure by oscillometric device
- Lie prone or supine
- Use appropriately 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

### 1.3 Definition of Hypertension in Neonates and Infants (0-1 year)

- Many factors affect BP in neonates making it hard to precisely define hypertension in this age group
- 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<sup>th</sup> and 99<sup>th</sup> percentile values are intended to serve as reference to identify infants with persistent hypertension that may require treatment. (**Appendix 1**)

### 1.4 Examination and Investigations

- Antenatal history as some antenatally detected renal tract anomalies may be associated with hypertension and maternal cocaine abuse may have undesirable effects on developing kidneys leading to hypertension.
- Hypoxic ischaemic encephalopathy, which may cause renal failure and hypertension.
- The clinical course during NICU (umbilical artery catheter, medications).
- Physical examination which should include BP measurements in the four extremities (coarctation of aorta), examination of the abdomen (renal masses) and analysis of the urine (haematuria suggesting renal vein thrombosis).
- Investigations to be directed by clinical findings<sup>(115)</sup>.

### 1.5 Treatment

- Treatment is recommended when BP is consistently above the 99th percentile
- There are few published case series that used diuretics, ACE-I,  $\beta$ -blockers and CCB.
- There is concern over the use of ACE-I in preterm neonates. It has been reported to cause an exaggerated fall in BP and may impair the final stages of nephron maturation and its use is best avoided until 44 weeks postconceptional age.

## 2. Hypertension in Children and Adolescents

- Prevalence of hypertension in children and adolescents is increasing in tandem with the increasing prevalence of obesity in this group.
- There is a 1% increase of prevalence of obesity every year among school children in Brunei Darussalam<sup>(127)</sup>.
- It is estimated that half of our school children are either obese or overweight.
- Please refer to **Table 36** and **Figure 13**.

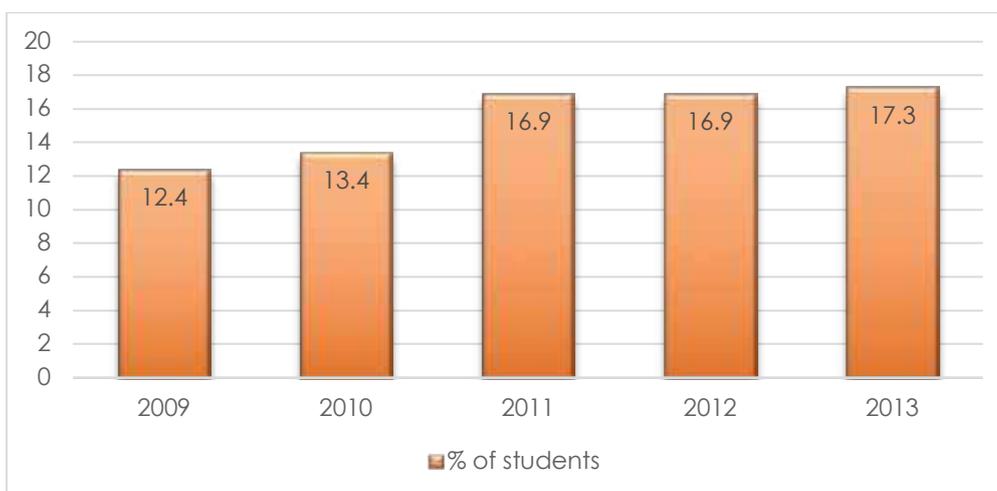
### 2.1 Primary Hypertension

- Primary hypertension is the most common cause of hypertension in children and adolescents.
- Children with suspected primary hypertension do not require extensive evaluation for secondary causes of hypertension

- Characteristics of primary hypertension in children include<sup>(116)</sup>:
  - Age  $\geq 6$  years.
  - Positive family history of hypertension in parents and grandparents
  - Overweight and obesity
  - No history or physical signs suggestive of secondary causes of hypertension
- History taking should include:
  - Nutritional History
  - Physical activity
  - Psychological factors including stress
  - Family history
- Assessment for comorbidities:
  - Cardiovascular risk factors
    - Smoking
    - Alcohol
  - Sleep history (risk of obstructive sleep apnoea).
  - Physical signs suggesting insulin resistance:
    - Truncal obesity.
    - Acanthosis nigricans

SCHOOL HEALTH (YEAR 1, 4, 6 and 8 only)	PERCENTAGE OF STUDENTS SCREENED FOR WEIGHT STATUS (%) (2009 – 2013)				
	2009	2010	2011	2012	2013
Normal weight	68.9	67.1	49.7	43.7	55.6
Overweight	14.0	14.7	11.5	12.1	13.9
Obese	12.4	13.4	16.9	16.9	17.3
Severe underweight	-	-	8.2	11.3	4.0
Underweight	4.7	4.8	13.8	15.9	9.3

**Table 36:** Weight classification of students screened from 2009-2013<sup>(127)</sup>



**Figure 13:** Percentage of obese students screened 2009-2013<sup>(127)</sup>

## 2.2 Secondary Hypertension

- All children and adolescents who do not fulfil the characteristics of primary hypertension should be evaluated for the cause of secondary hypertension<sup>(116)</sup>
- 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)

## 2.3 Isolated Office Hypertension

- A patient with BP levels  $>95^{\text{th}}$  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  $\geq 120$  cm.
- Isolated office hypertension does not require treatment but may need repeat ABPM in one- to two-year intervals to detect development of sustained hypertension.

## 2.4 Measurement of BP: Timing

### 1. Children $\geq 7$ 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:

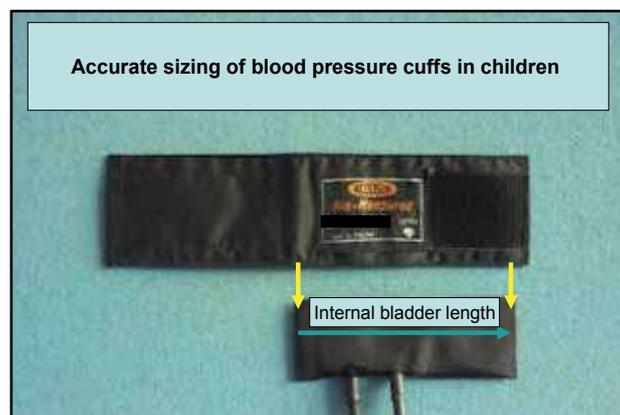
- History of complications requiring neonatal intensive care
- Congenital heart disease (repaired or unrepaired)
- Recurrent urinary tract infections, haematuria or proteinuria
- Known renal disease or urological malformation
- Family history of congenital renal disease
- Solid-organ transplant
- Malignancy or bone marrow transplant recipient
- 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<sup>(16)</sup> 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<sup>(8)</sup>.

### 3.Measuring Blood pressure in Paediatrics

#### 3.1 Method:

- Manual blood pressure measurement using a sphygmomanometer is the gold standard in children, with direct arterial BP measurement the gold standard in neonates
- Blood pressure may be measured using an automated oscillometric device or a manual cuff and auscultation
- The oscillometric device must be a calibrated machine that has been validated for use in the paediatric population.
- Oscillometric devices frequently overestimate blood pressure
- If BP >90<sup>th</sup> percentile on oscillometric device, confirmatory measurement should be obtained by auscultation techniques. Re-measure BP twice by using auscultatory technique and average these two
- The use of a Doppler technique is preferable in very young children as the Korotkoff sounds are less reliably heard in this group
- Special attention needs to be paid in selection of an appropriate cuff size in relation to the child's right upper arm (see **Figure 14**).



**Figure 14:** Size of BP cuff in children

Ideal Condition	<ol style="list-style-type: none"> <li>1. No stimulant medications or foods before measurement.</li> <li>2. Blood pressure should be measured in a relaxed environment.</li> <li>3. Allow a 5-minute rest period before measurement.</li> </ol>
Positioning	<ol style="list-style-type: none"> <li>1. Infants should be supine during BP measurement</li> <li>2. Older Child should be seated with back supported with feet on the floor.</li> <li>3. Right arm supported.</li> <li>4. Antecubital fossa at the level of the heart.</li> </ol>
Cuff Size	<ol style="list-style-type: none"> <li>1. The largest cuff which can fit on the arm should be used. The cuff should be 2/3 the length of the upper arm</li> <li>2. The bladder should be 80-100% the circumference of the arm.</li> <li>3. Errors due to too large a cuff are unlikely but if the cuff is too small blood pressure can be overestimated.</li> </ol>

**Table 37:** Measuring BP in Paediatric population

#### 4. Diagnosis and definitions of Hypertension in children and adolescents

*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<sup>th</sup> percentile for age, sex, and height of the patient, or is  $\geq 130/90$  mmHg (whichever is lower).*

- Height and gender are important determinants of paediatric BP.
- BP levels are interpreted based on gender, age and height.
- In the 2017 American Academy of Pediatrics guidelines<sup>(117)</sup>, normative table were revised by using data from normal-weight children only. (Refer to **Appendix 2 & 3**)
- There is a high rate of false-positive high BP readings at a single visit; thus, for diagnosis of hypertension use the mean of 2 consecutive BP measurements taken by auscultation repeated at 3 different visits

#### 4.1 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
<b>Normal</b>	<90 <sup>th</sup> percentile	<120 / <80 mmHg	Opportunistic	Lifestyle counselling
<b>Stage 1 Hypertension</b>	≥95 <sup>th</sup> percentile to <95 <sup>th</sup> percentile + 12 mmHg or 130/80 mmHg to 139/89 mmHg (whichever is lower)	130/80 mmHg to 139/89 mmHg	Initial	Lifestyle counselling
			Recheck in 1-2 weeks. Check upper and lower extremity BP	Diagnostic evaluation
			Recheck in 3 months Lifestyle counselling	Initiate treatment Specialist referral
<b>Stage 2 Hypertension</b>	≥95 <sup>th</sup> percentile +12 mmHg or ≥140/90 mmHg (whichever is lower)	≥140/90 mmHg	Initial Check upper & lower extremity BP	Diagnostic evaluation
			Recheck within 1 week Lifestyle counselling	Initiate treatment Specialist referral in 1 week

**Table 37:** Categories of BP in children

**4.2** Severe acute hypertension is defined as a rise in BP >30 mmHg above the 95<sup>th</sup> percentile

<b>Hypertensive urgency</b>	<ul style="list-style-type: none"> <li>• No end-organ damage</li> <li>• No or minimal symptoms</li> </ul>
<b>Hypertensive emergency</b>	<ul style="list-style-type: none"> <li>• Symptomatic with complaints such as nausea, dyspnoea, headaches and blurred vision</li> <li>• End-organ damage such as cerebral infarction, cerebral haemorrhage, encephalopathy (altered mental status, seizures), pulmonary oedema and renal failure</li> </ul>

**Table 39:** Hypertensive crises in children

- If the patient BP is symptomatic or >30 mmHg above the 95<sup>th</sup> 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.
- 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.
- The urgency of laboratory evaluation is based on the child's age, history, physical examination findings and level of BP elevation.
- **Stage 1 hypertension** allows time for evaluation before initiating treatment unless patient is symptomatic
- **Stage 2 hypertension** requires more prompt evaluation and pharmacologic therapy.

## 5. Investigations

### 5.1 Screening test and relevant population

- 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
- Investigations to assess comorbidities (the obese child)
  - Fasting blood sugar
  - HbA1c
  - AST, ALT
- Optional tests to be obtained on the basis of history and results of initial investigations
- Evaluation for left ventricular hypertrophy (LVH)

- No need to do ECG for evaluation of LVH in children with hypertension
- 2D Echocardiography: to assess for cardiac target organ damage (left ventricular mass, geometry, and function) at the time of consideration of pharmacologic treatment of hypertension.

## 6. Treatment of Paediatric Hypertension

### 6.1 Goals of therapy for children with hypertension:

- Achieve a BP level that reduces risk for target organ damage
- To reduce risk for hypertension-related cardiovascular disease in adulthood

### 6.2 Goals of therapy:

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

**Table 40:** BP targets for children

### 6.3 Lifestyle and Non-Pharmacologic Treatment

Non-pharmacologic management may be all that is required in children within the elevated blood pressure range and should be given to all children with hypertension

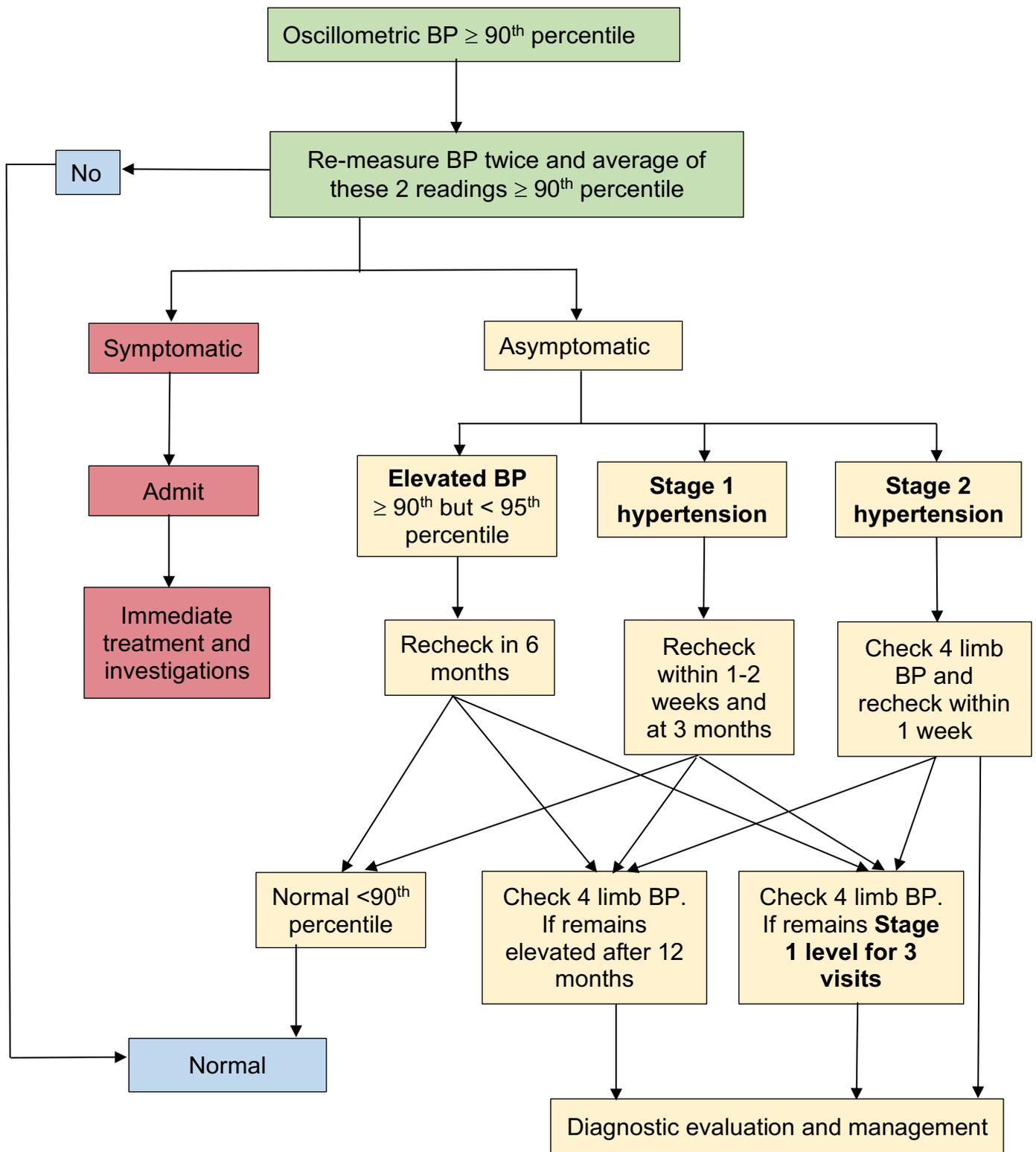
- Dietary advice regarding healthy eating (including reducing salt intake). Referral to dietician
- Physical activity. Moderate to vigorous physical activity at least 3-5 days per week (30-60 minutes per session)
- Weight reduction if overweight or obese
- Interventions to improve sleep if sleep apnoea identified.
- Stress reduction
- Good sleep habits
- Avoid smoking and alcohol

Note that lifestyle interventions are more successful if the whole family participate.

### 6.4 Pharmacologic Treatment.

Indicated in:

1. Symptomatic hypertension
2. Secondary hypertension
3. Hypertension with associated target-organ damage
4. Diabetes (types 1 and 2)

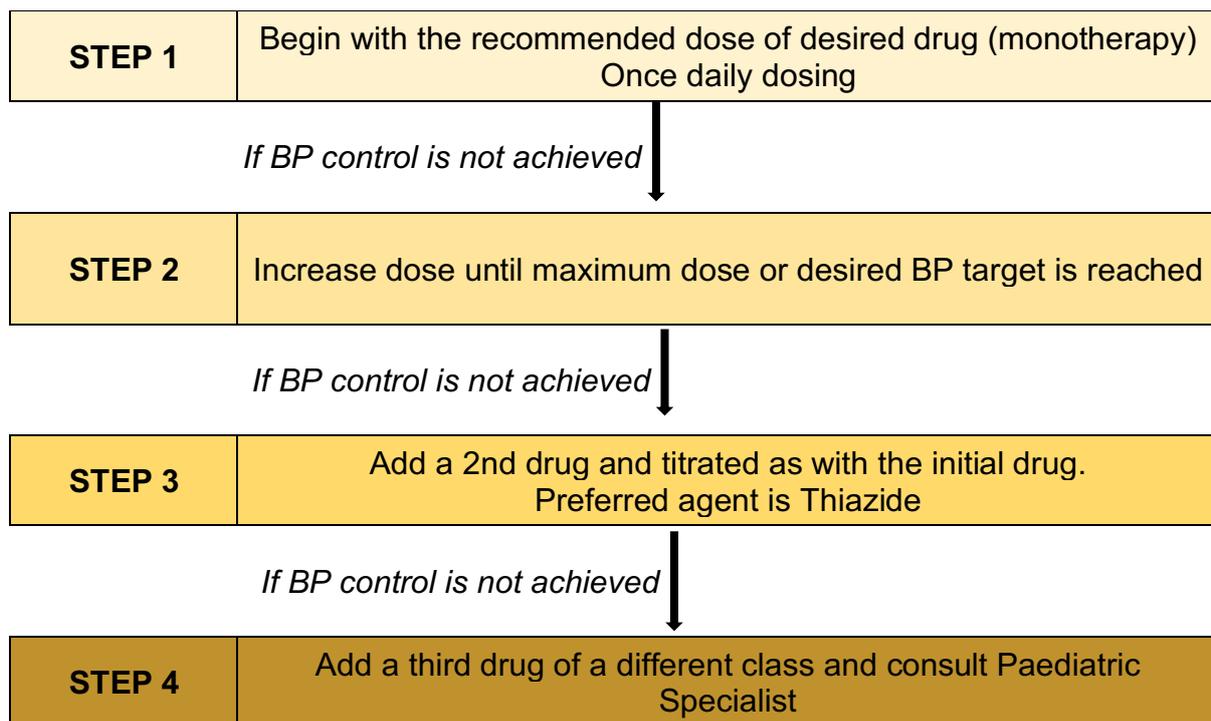


**Figure 15:** Algorithm for diagnosis of hypertension in children

## 6.5 General Principles of pharmacologic treatment

- An individualised stepped care approach to the use of anti-hypertensive drugs is recommended
- Once daily dosing regimes are preferable when possible to aid compliance
- Younger children (<1 yr) may need multiple daily dosing to increase dose flexibility e.g. propranolol rather than atenolol or captopril rather than enalapril.
- Doses should be commenced at the starting dose in the BNFC and then gradually titrated until the desired blood pressure is achieved (see goals of therapy and **Appendix 4**).
- In infants or those with impaired cardiac function it may be necessary to initiate antihypertensive medication in hospital with BP monitoring – these patients should be discussed with a paediatric specialist
- **Proteinuric Chronic Kidney Diseases** – ACE-I or ARBs are preferred in children with proteinuric CKD.
- **Obese Hypertensive Children** - Diuretics and  $\beta$ -blockers are potentially diabetogenic and hence should be avoided as initial therapy in children who are obese and hypertensive.

## 6.6 Stepped care approach



**Figure 16:** Stepwise approach in antihypertensive drug treatment in children

## 7. Appendix

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

## 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						
		5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
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

### 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						
		5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	10 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	90 <sup>th</sup>	95 <sup>th</sup>
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

## Appendix 4 Dosing Recommendation for the Initial Prescription of Antihypertensive Drugs for Outpatient Management of Chronic Hypertension in Children and Neonates

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

\* ARB and ACE-I 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.

Adapted from Malaysian Hypertension Guidelines 2018<sup>(8)</sup>

## **16: List of anti-hypertensives available in Brunei Darussalam**

The following list and related information gathered from List of Registered Medicinal Products (updated September 2018)<sup>(118)</sup>, National Standard Drug List (NSDL) 7<sup>th</sup> Edition (Updated March 2019)<sup>(119)</sup>, British National Formulary (BNF) and Malaysian Hypertension Guidelines 2018<sup>(8)</sup>.

The doses here are for guidance only, the user is advised to refer to the local formulary.

### *Angiotensin Receptor Antagonists (ARB)*

<b>Preparation Name</b>	<b>Dose</b>	<b>Starting dose</b>	<b>Recommended maximum daily dose</b>
Irbesartan	150mg	150mg od	300mg
	300mg		
Candesartan Cilexetil	8mg	8mg od	32mg
	16mg		
Valsartan	80mg	80mg bd	320mg
	160mg		
Losartan Potassium	50mg	50mg od	100mg
	100mg		
Olmesartan medoxomil	10mg	10mg od	40mg
	20mg		
	40mg		

### *ACE inhibitor (ACE-I)*

<b>Preparation Name</b>	<b>Dose</b>	<b>Starting dose</b>	<b>Recommended maximum daily dose</b>
Perindopril Tertbutylamine	4mg	4mg od	8mg
	8mg		
Perindopril erbumine	4mg		
Perindopril arginine	5mg	5mg od	10mg
	10mg		
Enalapril maleate	5mg	5mg od	40mg
	10mg		
	20mg		
Captopril	25mg	12.5mg bd	150mg

		(in elderly 6.25mg bd)	
Lisinopril	10mg	10mg od	80mg
	20mg		

### Calcium Channel Blockers (CCB)

Preparation Name	Dose	Starting dose	Recommended maximum daily dose
Amlodipine Besylate	5mg	5mg od	10mg
	10mg		
Nifedipine LA	30mg	30mg od	120mg
	60mg		
Nimodipine	30mg	60mg every 4 hours (to start within 4 days of aneurysmal subarachnoid haemorrhage and continued for 21 days)	
	0.01g/50ml (IV)	0.5mg/hour	2mg/hour, maximum 14 days (21 days if there is surgical intervention)
Diltiazem	30mg	90mg bd	360mg
Diltiazem LA	200mg	200mg	500mg
	300mg		
Verapamil HCl	40mg	80mg tds	480mg
Verapamil SR	120mg	120mg od	480mg

### $\beta$ -blockers (BB)

Preparation Name	Dose	Starting dose	Recommended maximum daily dose
Atenolol	50mg	50mg od	100mg
	100mg		
Propranolol HCl	10mg	80mg bd	320mg
	1mg/ml (syrup)		
	40mg		
	2.5mg		20mg

Bisoprolol hemifumarate	5mg	5mg od (eGFR<40ml/min/1.73m <sup>2</sup> , 2.5mg/day)	
Metoprolol Tartrate	50mg	50mg od	200mg
	5mg/5ml		
Acebutolol	200mg	200mg bd	1.2g in divided doses

*α- and β-blocker*

Preparation Name	Dose	Starting dose	Recommended maximum daily dose
Carvedilol	6.25mg	12.5mg bd	100mg
	12.5mg		
	25mg		
Labetolol HCl	100mg	100mg bd	2.4g
	25mg/5ml (IV)	Hypertension of pregnancy: 20mg/hour (to double dose after 30 minutes if necessary)	160mg/hour
		Hypertensive emergencies: Bolus injection:50mg over 1 minute, then 50mg every 5min if required IV infusion: 2mg/min	Bolus injection: 200mg  IV infusion: 200mg

*α-blocker*

Preparation Name	Dose	Starting dose	Recommended maximum daily dose
Doxazosin Mesylate	1mg	1mg od	16mg
	2mg		
	4mg		

Prazosin HCl	1mg	0.5mg bd – tds	20mg
	2mg		

*Diuretics:*

Preparation Name	Dose	Starting dose	Recommended maximum daily dose
Indapamide MR	1.5mg	1.5mg od	1.5mg
Hydrochlorothiazide BP	50mg	12.5mg od	25mg
Bendroflumethiazide	2.5mg	2.5mg od	10mg
Furosemide	40mg	40mg od	80mg
	10mg/ml		
	150ml syrup (1mg/1ml)		
Spironolactone	25mg	25mg od	25mg
Eplerenone	25mg	25mg od	50mg

*Others:*

Preparation Name	Dose	Starting dose	Recommended maximum daily dose
Methyldopa	250mg	250mg bd-tds	3000mg
Hydralazine HCl	10mg	25mg bd	100mg
	50mg		
Glyceryl trinitrate patch	5mg per 24hours	5mg	
Glyceryl trinitrate IV	1mg/ml	10-200µg/min	400µg/min
Isosorbide dinitrate	10mg/10ml (0.1%) IV	2-10mg/hour	20mg/hour
Sodium Nitroprusside	50mg/5ml (IV)	0.5-1.5 µg/kg/min, adjusted in steps of 500ng/kg/min every 5 min	

**Combination tablets:**

(for dose recommendations, please consult individual product literature)

*ARB + thiazide diuretic*

<b>Preparation name</b>
Irbesartan 150mg, Hydrochlorothiazide 12.5mg
Irbesartan 300mg; Hydrochlorothiazide 12.5mg
Irbesartan 300mg, Hydrochlorothiazide 25mg
Olmesartan Medoxomil 20mg; Hydrochlorothiazide 12.5mg
Olmesartan Medoxomil 20mg; Hydrochlorothiazide 12.5mg
Olmesartan Medoxomil 40mg; Hydrochlorothiazide 12.5mg
Perindopril tert-butylamine 4mg, Indapamide 1.25mg
Perindopril arginine 10mg (equiv. to 6.79mg perindopril); indapamide 2.5mg
Valsartan 80mg; Hydrochlorothiazide 12.5mg
Valsartan HCl 160mg; Hydrochlorothiazide 12.5mg
Valsartan 160mg; Hydrochlorothiazide 25mg
Losartan Potassium 50mg, Hydrochlorothiazide 12.5mg
Losartan potassium 100mg, Hydrochlorothiazide 25mg
Losartan Potassium 100mg, Hydrochlorothiazide 12.5mg

*CCB + ARB*

<b>Preparation name</b>
Amlodipine 10mg (as besylate); Valsartan 160mg; Hydrochlorothiazide 12.5mg
Amlodipine 10mg (as besylate); Valsartan 160mg; Hydrochlorothiazide 25mg
Amlodipine 5mg (as besylate); Valsartan 160mg; Hydrochlorothiazide 25mg
Amlodipine 10mg (as besylate); Valsartan 320mg; Hydrochlorothiazide 12.5mg
Olmesartan medoxomil 20mg and Amlodipine (as amlodipine besylate) 5mg
Olmesartan medoxomil 40mg and Amlodipine (as amlodipine besylate) 5mg
Olmesartan medoxomil 40mg and Amlodipine (as amlodipine besylate) 10mg

*CCB + ACE-I*

<b>Preparation name</b>
Perindopril arginine 5mg (equiv. to 3.395mg perindopril) and amlodipine 10mg (as besilate 13.870mg)
Perindopril arginine 10mg (equiv. to Perindopril 6.790mg); Amlodipine 5mg (as besilate 6.935mg)
Perindopril arginine 10mg (equiv to Perindopril 6.790mg); Amlodipine 10mg (as besilate 13.870mg)

*CCB + thiazide diuretic*

<b>Preparation name</b>
Indapamide 1.5mg & Amlodipine 5mg (as besilate)
Indapamide 1.5mg & Amlodipine 10mg (as besilate)
Atenolol 50mg; Chlorthalidone 12.5mg
Atenolol 100mg; Chlorthalidone 25mg

*CCB + ARB + thiazide diuretic*

<b>Preparation name</b>
Amlodipine 10mg (as besylate); Valsartan 160mg; Hydrochlorothiazide 12.5mg
Amlodipine 10mg (as besylate); Valsartan 160mg; Hydrochlorothiazide 25mg
Amlodipine 5mg (as besylate); Valsartan 160mg; Hydrochlorothiazide 25mg
Amlodipine 10mg (as besylate); Valsartan 320mg; Hydrochlorothiazide 25mg
Perindopril arginine 2.5mg (corresponding to 1.6875mg of perindopril) Indapamide 0.625mg Amlodipine besilate 6.935mg (corresponding to 5mg of amlodipine)
Perindopril arginine 2.5mg (corresponding to 1.6875mg of perindopril) Indapamide 0.625mg Amlodipine besilate 6.935mg (corresponding to 5mg of amlodipine)
Perindopril arginine 5mg (corresponding to 3.395mg of perindopril) Indapamide 1.25mg Amlodipine besilate 13.870mg (corresponding to 10mg of amlodipine)
Perindopril arginine 10mg (corresponding to 6.79mg of perindopril) Indapamide 2.5mg Amlodipine besilate 13.870mg (corresponding to 10mg of amlodipine)

*CCB + BB*

<b>Preparation name</b>
Nifedipine 20mg (SR) + Atenolol 50mg

*Neprilysin inhibitor + ARB*

<b>Preparation name</b>
Sacubitril 24.3mg & Valsartan 25.7mg
Sacubitril 48.6mg & Valsartan 51.4mg
Sacubitril 97.2mg & Valsartan 102.8mg

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