

Clinical Practice Guidelines

# Management of Hypertension (3rd Edition)



Ministry of Health Malaysia



Academy of Medicine of Malaysia



Malaysian Society of Hypertension

## STATEMENT OF INTENT

This guideline was developed to be a guide for best clinical practice in the management of hypertension. All efforts were made to ensure references quoted were the most current at the time of printing. Specific attempts were made to use local data and publications to ensure local relevance. Adherence to this guideline does not necessarily lead to the best clinical outcome in individual patient care. Every health care provider is responsible for the care of his/her unique patient based on the clinical presentation and treatment options available locally.

### Review of the Guideline

This guideline was issued in 2008 and will be reviewed in 2012 or earlier if important new evidence becomes available.

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### Available on the following websites:

[www.moh.gov.my](http://www.moh.gov.my)  
[www.acadmed.org.my](http://www.acadmed.org.my)  
[www.msh.org.my](http://www.msh.org.my)

This is an update to the Clinical Practice Guideline on Hypertension (published 2002). This CPG supersedes the previous CPG on Hypertension (2002).

## KEY MESSAGES: CLINICAL PRACTICE GUIDELINE ON HYPERTENSION, 2008

1. Hypertension is defined as persistent elevation of systolic BP of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater.
2. The prevalence of hypertension in Malaysians aged 30 years and above was 42.6% in 2006.
3. Hypertension is a silent disease; the majority of cases (64%) in the country remain undiagnosed. Blood pressure should be measured at every chance encounter.
4. Untreated or sub-optimally controlled hypertension leads to increased cardiovascular, cerebrovascular and renal morbidity and mortality.
5. A systolic BP of 120 to 139 and/or diastolic BP of 80 to 89 mmHg is defined as prehypertension and should be treated in certain high risk groups.
6. Therapeutic lifestyle changes should be recommended for all individuals with hypertension and prehypertension.
7. Decisions on pharmacological treatment should be based on global vascular risks and not on the level of blood pressure per se.
8. In patients with newly diagnosed uncomplicated hypertension and no compelling indications, choice of first line monotherapy includes ACEIs, ARBs, CCBs and diuretics. Beta blockers are no longer recommended for first line monotherapy in this group of patients.
9. Only 26% of Malaysian patients achieved blood pressure control (<140/90 mmHg) while on treatment. Every effort should be made to achieve target blood pressure. Target blood pressure depends on specific patient groups.
10. Combination therapy is often required to achieve target and may be instituted early.

## FOREWORD

Hypertension is a major risk factor for cardiovascular, cerebrovascular and renal diseases. The third National Health and Morbidity Survey of 2006 showed that the prevalence of hypertension among adults 30 years old and above was 43%, a relative increase of 30% from that of 10 years earlier.

It is now estimated that there are 4.8 million individuals with hypertension in Malaysia. The estimated figure worldwide is a staggering 1 billion individuals. It is however alarming to note that, according to the findings of the Third National Health and Morbidity Survey of 2006, close to two thirds of individuals with hypertension in Malaysia were unaware that they have hypertension. Although there was an increase in the treatment rate among those who have been diagnosed, the control rate is still poor. The Third National Health and Morbidity Survey revealed that among patients with hypertension who were on drug treatment, only 26% of them achieved the target blood pressure. This finding is consistent with a separate survey conducted by the Institute of Health Management of the Ministry of Health on the outpatient management of hypertension in government clinics. Only 28.5% of patients treated for hypertension in government clinics achieved the target blood pressure.

Although the management of cardiovascular disease has moved away from the traditional single risk factor approach to a more comprehensive global cardiovascular risk approach, optimum management of individual risk factors must not be overlooked.

I hope this latest edition of the Clinical Practice Guideline (CPG) on Hypertension will help to address the current shortfalls in the detection, awareness, treatment and control rates of hypertension in Malaysia. I would like to thank all those who have worked hard to come out with this latest edition. I hope this CPG will be utilised optimally by health care professionals involved in the management of hypertension.

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## RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

### Rationale

The Clinical Practice Guideline on the Management of Hypertension was developed to provide a clear and concise approach to all health care providers on the current concepts in the management of hypertension. Since hypertension is managed by various levels of health care providers in Malaysia, attempts were made to ensure the different stakeholders will benefit from this CPG. This is reflected by the representation of the committee members which developed the guideline.

There were two previous guidelines on hypertension; in 1998 and 2002. This edition is the third in the series and was deemed necessary due to new evidence which has emerged since the last edition. Prior to the publication of this edition, the Third National Health and Morbidity Survey was completed and the results have since been made available. The results of the survey showed that the prevalence of hypertension has increased with very little difference in awareness rate and rate of blood pressure control in the hypertensive population. The rate of blood pressure control remained poor despite an increase in the prevalence of diagnosed patients who were prescribed antihypertensive medication. This may reflect the fact that clinicians are still not clear of the target blood pressure to achieve in their patients while on treatment. It is hoped that this CPG will contribute towards reversing this worrying trend.

### Process

The current edition of the CPG was initiated by the Malaysian Society of Hypertension. The guideline was developed in 2006/2007. A committee was convened, comprising four nephrologists, 4 cardiologists, 2 family physicians, 2 obstetrician/gynaecologists, an endocrinologist, a general physician/clinical pharmacologist, a paediatrician, an epidemiologist and a pharmacist (pharmacoeconomist). The involvement of a pharmacist (an expert in pharmacoeconomy) and an epidemiologist is unique, making this CPG more comprehensive in terms of committee membership. Besides being experts in their own fields, some of the members hold important positions in relevant non-governmental organizations and government agencies dealing with hypertension.

The development of this guideline adheres closely to the methodology outlined in the Guidelines for Clinical Practice Guideline 2003 by the Medical Development Division of the Ministry of Health. All attempts were made to ensure references quoted were current and relevant to the issues discussed. Whenever clinical recommendations were made, the best available evidence was used to support the recommendations.

The guideline was posted on both the Ministry of Health Malaysia and Academy of Medicine, Malaysia websites for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

## OBJECTIVES, QUESTIONS AND TARGETS

### OBJECTIVES

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

1. Diagnose hypertension
2. Assess and investigate a patient with hypertension

This guideline is intended to provide evidence on the

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

### EXCLUSION

This guideline, however, does not cover

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

### CLINICAL QUESTIONS

The clinical questions to be addressed in this guideline include

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

### TARGET POPULATION

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

### TARGET GROUP

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

### CLINICAL INDICATORS FOR QUALITY MANAGEMENT

Treatment setting: Primary care/Secondary care

Name of indicator:

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

Definition of control:

<140/90 mmHg for all, <130/80 mmHg for patients with diabetes/ischaemic heart disease/cerebrovascular disease/renal impairment and <125/75 mmHg for patients with proteinuria of >1 gram per day.

Numerator:

1. Number of newly diagnosed cases of hypertension prescribed antihypertensive drug per month.
2. Number of patients on treatment who achieved blood pressure control.

Denominator:

1. Total number of newly diagnosed cases of hypertension per month.
2. Total number of patients who are diagnosed and on antihypertensive drug treatment per month.

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

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

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## SUMMARY OF RECOMMENDATIONS

Issues	Recommendation	Grade
<b>Measurement of Blood Pressure</b>	The mercury sphygmomanometer remains the gold standard for measurement.	C
	All of the data upon which we base our estimates of risk as well as benefits of treatment have been accumulated from casual BP readings taken in the office or clinic setting and therefore ambulatory blood pressure monitoring (ABPM) is not necessary for the diagnosis and management of most patients with hypertension.	C
	Blood pressure should be measured in both arms and the higher reading is taken as the systemic BP.	C
	Blood pressure should be taken both lying and at least one minute after standing to detect any postural drop, especially in the elderly and in diabetics.	C
	On rising, the BP will transiently rise and then fall. A systolic drop of >20 mmHg is considered a significant postural drop.	C
	The data provided by ABPM does not influence therapeutic decisions in the vast majority of patients and as a result has not been recommended by the JNC-7, WHO-ISH and NICE guidelines as a routine procedure in the initial evaluation of the hypertensive patient.	C
	Home BP measurement can be useful in monitoring control of BP. It empowers the patient with the control of his condition and may improve compliance.	C
<b>Diagnosis and Assessment</b>	Refer to page 9 for recommendations for follow-up based on initial BP measurements for adults.	C
<b>Prehypertension</b>	There should be yearly follow-up in patients with prehypertension to detect and treat hypertension as early as possible.	C

	Decisions regarding pharmacological treatment should be based on the individual patient's global CVD risk. In diabetes mellitus or chronic kidney disease, medical treatment is required if BP is above 130/80 mmHg.	A
	Similarly, in other high risk subjects such as those with previous CVA or CAD, the threshold for commencing hypertension treatment should be lowered.	A
<b>Non-Pharmacological Management</b>		
BMI or weight	As far as possible aim for an ideal Body Mass Index [Weight (kg)/Height <sup>2</sup> (m)] – for Asians, the normal range has been proposed to be 18.5 to 23.5 kg/m <sup>2</sup> . However a weight loss as little as 4.5 kg significantly reduces BP.	C
Salt intake	An intake of <100 mmol of sodium or 6g of sodium chloride a day is recommended (equivalent to <1¼ teaspoonfuls of salt or 3 teaspoonfuls of monosodium glutamate).	A
Alcohol	Standard advice is to restrict intake to no more than 21 units for men and 14 units for women per week (1 unit equivalent to ½ a pint of beer or 100ml of wine or 20ml of proof whisky).	C
Exercise	General advice on cardiovascular health would be for “milder” exercise, such as brisk walking for 30 – 60 minutes at least 3 times a week.	A
Diet	A diet rich in fruits, vegetables and dairy products with reduced saturated and total fat can substantially lower BP (11/6 mmHg in hypertensive patients and 4/2 mmHg in patients with high normal BP).	A
Smoking	Cessation of smoking is important in the overall management of the patients with hypertension in reducing cardiovascular risk.	C
<b>Pharmacological Management</b>	Figure 1 (page 14) outlines the management of a patient with hypertension.	C

<b>Management of Severe Hypertension</b>		
Hypertensive Urgencies	Initial treatment should aim for about 25% reduction in BP over 24 hours but not lower than 160/90 mmHg.	C
Hypertensive Emergencies	The BP needs to be reduced rapidly. It is suggested that the BP be reduced by 25% depending on clinical scenario over 3 to 12 hours but not lower than 160/90 mmHg.	C
Rapid reduction of Blood Pressure	Several serious side effects have been reported with the administration of sublingual fast-acting nifedipine and therefore this is no longer recommended.	C
<b>Hypertension and Diabetes Mellitus</b>	Pharmacological treatment should be initiated in patients with diabetes when the BP is persistently >130 mmHg systolic and/or >80 mmHg diastolic.	A
	SBP should be targeted to <130 mmHg and DBP <80 mmHg.	A
	The presence of microalbuminuria or overt proteinuria should be treated even if the BP is not elevated. An ACEI or ARB is preferred.	A
	In a proportion of patients, microalbuminuria may be normalised by higher doses of ACEIs and ARBs.	A
	Tight BP control should take precedence over the class of antihypertensive drug used.	A
	The BP should be lowered even further to <125/75 mmHg in the presence of proteinuria of >1 g/24 hours.	A
	ACEIs are drugs of choice based on extensive data attesting to their cardiovascular and renal protective effects in diabetic patients.	A
	If an ACEI is not tolerated, an ARB should be considered.	A
	Beta-blockers, diuretics or calcium channel blockers may be considered if either ACEIs or ARBs cannot be used.	A

<b>Hypertension and Non-Diabetic Renal Disease</b>	The combination of ACEIs and ARBs has also been proven to reduce the rate of doubling of serum creatinine and ESRD more than monotherapy with either agent in nondiabetic proteinuric renal disease.	A
	If there is a persistent rise of serum creatinine of $\geq 30\%$ from baseline within two months, ACEIs should be stopped. Similar caution should be exercised with the use of ARBs.	C
	In patients with renal disease and hypertension with an elevated serum creatinine of $>200$ $\mu\text{mol/L}$ , thiazide diuretics may not be effective antihypertensive agents and therefore loop diuretics are preferred.	C
	In those with proteinuria, the non-dihydropyridine group of calcium channel blockers (CCBs) namely diltiazem or verapamil are preferred, as they have an additional antiproteinuric effect.	A
<b>Hypertension and Cardiovascular Disease</b>	In post-infarction patients, ACEIs and beta-blockers especially in patients with LV dysfunction, help to reduce future cardiac events which include cardiac failure, cardiac mortality and morbidity.	A
<b>Hypertension and Stroke</b>	Blood pressure is the most consistent and powerful predictor of stroke and high blood pressure is the most important modifiable cause of stroke.	C
	Beta-blockers, diuretics, CCBs, ACEIs and ARBs have been shown to reduce the risk and mortality of stroke.	A
	Calcium channel blockers in particular, provided significantly better protection against stroke compared with diuretics and/or beta-blockers in Asian and Caucasian populations.	A
	Combination of an ACEI and diuretic has been shown to reduce stroke recurrence in both normotensive and hypertensive patients when treatment was started at least two weeks after the stroke.	A
	The morbidity and mortality from further strokes were also shown to be significantly lower in patients receiving ARBs compared to CCBs for the same level of BP control.	A
	In haemorrhagic stroke, in general, it is best to avoid lowering BP in the first few days after a stroke unless there is evidence of accelerated hypertension or patients presenting concurrently with hypertensive emergencies.	C

<b>Hypertension in the Elderly</b>	The goals of treatment in older patients should be the same as in younger patients.	A
	In those patients with marked systolic hypertension and not tolerating treatment well, reducing SBP to below 160 mmHg initially is acceptable. Subsequently, attempts should be made to reduce BP to target levels.	C
	Weight loss and modest salt reduction may be especially effective in the elderly because of their greater sensitivity to sodium intake.	A
	The five major classes of drugs (diuretics, $\beta$ -blockers, CCBs, ACEIs and ARBs) have been shown to reduce cardiovascular events in the elderly.	A
	Angiotensin converting enzyme inhibitors are the drugs of choice for those with concomitant left ventricular systolic dysfunction, post myocardial infarction or diabetes mellitus.	A
<b>Hypertension in Pregnancy</b>	Standing BP should be measured to detect postural hypotension.	C
	Korotkoff V should now be used as the cut-off point for diastolic BP, and Korotkoff IV utilized only when Korotkoff V is absent.	C
	Pregnant women with hypertension should be referred to an obstetrician for further management.	C
	Early diagnosis and referral to an obstetrician for further management may prevent progression to eclampsia.	B
	The drugs of choice in pregnancy are still methyldopa and labetalol.	C
	In the event of an acute hypertensive crisis, IV hydralazine (2.5-5 mg bolus, or infusion) or IV labetalol (10-20 mg slow bolus over 5 minutes, or infusion), or oral nifedipine (10 mg stat dose), may be used to lower the BP.	A
	Sublingual nifedipine is no longer recommended and its use is confined to acute pulmonary edema.	C

	Parenteral magnesium sulphate is currently the drug of choice for the prevention of eclampsia and to abort an eclamptic fit.	A
	Pregnant women who are at high risk of developing preeclampsia should be referred to an obstetrician. Specialist management will include doppler ultrasonography and aspirin pharmacoprophylaxis.	A
	High calcium supplementation of 1.5 g/day significantly reduces the risk of eclampsia, severe gestational hypertension and severe preeclamptic complication index in pregnant women with low dietary calcium intake.	A
<b>Hypertension and Oral Contraceptives</b>	A woman who develops hypertension while using combined oral contraceptives (COC) should be advised to stop taking them and should be offered alternative forms of contraception.	C
	Blood pressure should be reviewed regularly, at least every six months.	C
<b>Hypertension and Hormone Replacement Therapy</b>	All women treated with HRT should have their BP monitored every six months.	C
	Greater caution and closer monitoring is required for hypertensive patients on conjugated equine estrogen (CEE).	C
<b>Hypertension in Children and Adolescents</b>	Once a child is diagnosed with hypertension, he should be referred to a paediatrician for further evaluation and management.	C
	Non-pharmacologic management particularly weight reduction in those who are obese is recommended in all children with hypertension as well as those with BP in the 90th to 95th percentile.	C
	The goal of pharmacologic therapy is to reduce BP to lower than 95th percentile in uncomplicated primary hypertension and <90th percentile for children with TOD, CKD and diabetes mellitus.	C
<b>Pharmacoeconomics</b>	Hypertension pharmacotherapy should not be judged by the direct cost of the drug alone.	B
	Public education should include information on cost effectiveness and drug compliance.	C

## TABLE OF CONTENTS

1. DEFINITION AND CLASSIFICATION OF HYPERTENSION	1
2. MEASUREMENT OF BLOOD PRESSURE	2
3. DIAGNOSIS AND ASSESSMENT	5
4. PREHYPERTENSION	10
5. NON-PHARMACOLOGICAL MANAGEMENT	11
6. PHARMACOLOGICAL MANAGEMENT	12
7. MANAGEMENT OF SEVERE HYPERTENSION	17
8. HYPERTENSION IN SPECIAL GROUPS:	
8.1 Hypertension and Diabetes Mellitus	20
8.2 Hypertension and the Metabolic Syndrome	22
8.3 Hypertension and Non-Diabetic Renal Disease	23
8.4 Renovascular Hypertension	24
8.5 Hypertension and Cardiovascular Disease	26
8.6 Hypertension and Stroke	28
8.7 Hypertension in the Elderly	29
8.8 Hypertension in Pregnancy	31
8.9 Hypertension and Oral Contraceptives	35
8.10 Hypertension and Hormone Replacement Therapy	36
8.11 Hypertension in Children and Adolescents	36
9. PHARMACOECONOMICS	38
10. TYPES OF ANTIHYPERTENSIVE AGENTS	
Diuretics	39
Beta-blockers	40
Calcium Channel Blockers	41
ACE Inhibitors	41
Angiotensin Receptor Blockers	42
Miscellaneous Drugs	43
REFERENCES	45
APPENDIX 1 List of British Hypertension Society-validated electronic BP sets	62
APPENDIX 2 Cockcroft–Gault Formula	63
APPENDIX 3 Antihypertensive drugs currently available in Malaysia	63
APPENDIX 4 Normative tables of BP based on age and sex adjusted for height percentiles	64
LIST OF ABBREVIATIONS	68
ACKNOWLEDGEMENTS	69
DISCLOSURE STATEMENT	69
SOURCES OF FUNDING	69
LEVELS OF EVIDENCE & GRADES OF RECOMMENDATIONS	69

## LIST OF TABLES

Table 1.	Classification of blood pressure for adults age 18 and older	1
Table 2.	Secondary causes of hypertension	6
Table 3.	Cardiovascular risk factors	6
Table 4.	Manifestations of target organ damage (TOD)/ target organ complication (TOC)	8
Table 5.	Risk stratification	8
Table 6.	Recommendations for follow-up based on initial blood pressure measurements for adults	9
Table 7.	Choice of antihypertensive drugs in patients with concomitant conditions	15
Table 8.	Effective antihypertensive combinations	15
Table 9.	Common causes of severe hypertension	17
Table 10.	Oral treatment for hypertensive urgencies	18
Table 11.	Treatment options for hypertensive emergencies	19
Table 12.	NCEP ATP III and IDF criteria for the metabolic syndrome	23
Table 13.	Antihypertensive drugs commonly used in pregnancy	35
Table 14.	Classification of hypertension in children and adolescents with measurement frequency and recommended therapy	37
Table 15.	Diuretics commonly used for the treatment of hypertension in Malaysia	39
Table 16.	Beta-blocker commonly used for the treatment of hypertension in Malaysia	40
Table 17.	CCBs commonly used for the treatment of hypertension in Malaysia	41
Table 18.	ACEIs commonly used for the treatment of hypertension in Malaysia	42
Table 19.	ARBs commonly used for the treatment of hypertension in Malaysia	43
Table 20.	$\alpha$ -blockers	43
Table 21.	$\alpha$ , $\beta$ -blockers	43
Table 22.	Centrally-acting agents	44
Table 23.	Direct vasodilators	44

## 1. DEFINITION AND CLASSIFICATION OF HYPERTENSION

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

There is a positive relationship between systolic blood pressure (SBP), diastolic blood pressure (DBP) and the risk of developing cardiovascular, cerebrovascular and renal diseases. Therefore the main aim of identifying and treating high BP is to reduce these risks. Hence BP should be measured at every clinic encounter.

The classification of high BP, although arbitrary, is useful as clinicians must make treatment decisions based on the measured BP and the patients' associated cardiovascular/cerebrovascular risks and comorbidities. Table 1 provides a classification of BP for adults (age 18 and older). The WHO-ISH guidelines in principle have adopted a similar classification.<sup>1</sup> These criteria are for subjects who are not on any antihypertensive medication and who are not acutely ill.

Table 1. Classification of blood pressure for adults age 18 and older

Category	Systolic (mmHg)	Diastolic (mmHg)	Prevalence in Malaysia <sup>2</sup>
Optimal	<120	and <80	32%
Prehypertension	120-139	and/or 80-89	37%
Hypertension			
Stage 1	140-159	and/or 90-99	20%
Stage 2	160-179	and/or 100-109	8%
Stage 3	≥180	and/or ≥110	4%

The classification is based on the average of two or more readings taken at two or more visits to the doctor. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's BP.

Doctors should explain to patients the significance of their BP readings. The need for follow-up and treatment if necessary should be emphasized. Table 6 on page 9 provides follow-up recommendations based on the initial set of BP measurements.

### 1.1 Isolated office (“white-coat”) hypertension

Isolated office (“white-coat”) hypertension is a condition noted in patients whose BP is consistently elevated in the physician’s clinic but normal at other times. In these subjects the clinic BP is persistently above 140/90 mmHg but the home or ambulatory systolic/diastolic BP measurements are 125/80 mmHg or lower.<sup>3</sup>

Isolated office hypertension accounts for 10 – 15% of hypertensive patients.<sup>4</sup> Clinicians should aim to identify this whenever clinical suspicion is raised, by use of home or ambulatory measurements.<sup>5</sup> There is also a potential impact of this phenomenon on the cost-benefit ratio of anti-hypertensive treatment.

It is still debatable whether isolated office hypertension is an innocent phenomenon or whether it carries an increased cardiovascular risk. The decision to initiate treatment should be based on the individual patient’s overall risk factors and the presence of target organ damage (TOD). If a decision is made not to treat then close follow-up is warranted.

### 1.2 Isolated systolic hypertension

Isolated systolic hypertension is defined as SBP of >140 mmHg and DBP <90 mmHg. It should be staged appropriately. Treatment of this condition is effective in reducing cardiovascular risk.<sup>6</sup>

## 2. MEASUREMENT OF BLOOD PRESSURE

Blood pressure should be measured correctly. It can be measured directly or indirectly. There are four common devices used for the indirect measurement of BP namely:

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

There are many calibrated electronic or ambulatory BP devices available in the market. Only professionally validated electronic models should be used.

Various countries have their own validating bodies, e.g. British Hypertension Society, American Association for the Advancement of Medical Instrumentation (AAMI) and German Hypertension Society. The mercury sphygmomanometer remains the gold standard for measurement.<sup>7(Level III)</sup> However, it is gradually being replaced by the electronic blood pressure measurement device due to environmental and health concerns.

### 2.1 The mercury column sphygmomanometer

The following points should be noted when using this:

- i) The key to the reservoir should be turned open
- ii) The mercury meniscus should be at zero
- iii) The calibrated glass tube must be clean – a dirty tube can cause inaccurate readings.

- iv) The cuff size should be appropriate

Both the length and width of the inflatable bladder are important. The bladder length should encircle at least 80% of the circumference whilst the width should be at least 40% of the circumference of the arm. Standard bladder size is 13 cm x 24 cm.<sup>8</sup> Too small a cuff will give a falsely higher reading and vice versa.

- v) Inflation-deflation bulb

It is important to ensure that inflation-deflation device functions properly. The following may indicate malfunction of the device:

- Failure to achieve a pressure of 40 mmHg above the estimated SBP or 200 mmHg after 3–5 seconds of rapid inflation.
- The inability of the equipment to deflate smoothly at a rate of 1 mmHg per second or at each pulse.<sup>8</sup>

- vi) Auscultatory measurement of systolic and diastolic pressures  
The following technique is recommended for the measurement of BP using a sphygmomanometer:

- Patients should be adequately rested and seated with their arms supported.
- The cuff and the mercury reservoir should be at the level of the heart.
- They should not have smoked or ingested caffeine within 30 minutes of measurement.
- The SBP should be estimated initially by palpation. While palpating the brachial/ radial artery, the cuff is inflated until the pulse disappears. The cuff should then be inflated to a further 20 mmHg. The cuff is then slowly deflated and the pressure at which the pulse is palpable is the estimated SBP.
- The bladder is again inflated to 20 mmHg above the previously estimated SBP and the pressure reduced at 1-2 mmHg per second whilst auscultating with the bell of the stethoscope.<sup>9</sup> The bell should not be placed under the cuff. The point at which repetitive, clear tapping sounds first appears (Korotkoff Phase I) gives the SBP.
- Phase I sounds sometimes disappear as pressure is reduced and reappears again at a lower reading (the auscultatory gap), resulting in underestimation of the SBP.
- The complete disappearance of sound (Korotkoff Phase V) should be taken as the diastolic reading.

In some groups, e.g. anaemic or elderly patients, the sounds may continue until the zero point. In such instances the muffling of the repetitive sounds (Korotkoff Phase IV) is taken as the diastolic pressure. The point of muffling is usually higher than the true arterial diastolic pressure. If Korotkoff Phase IV is used, this should be clearly recorded.

BP should be measured in both arms and the higher reading is taken as the systemic BP.<sup>(Level III)</sup>

If the difference in BP between the two arms is >20/10 mmHg, there may be an arterial anomaly which requires further evaluation.

The BP should be taken both lying and at least one minute after standing to detect any postural drop, especially in the elderly and in diabetics.<sup>(Level III)</sup> On rising, the BP will transiently rise and then fall. A systolic drop of >20 mmHg is considered a significant postural drop.<sup>(Level III)</sup>

Blood pressure measurement can also be done from the thigh:-

- The patient must be supine.
- The correct size cuff must be chosen.
- The marker must be placed behind the knee, approximately 2 finger widths above the popliteal fossa.
- The popliteal artery must be palpated.
- The subsequent steps are similar to measuring blood pressure from the arm.

## 2.2 Ambulatory blood pressure monitoring (ABPM)

All of the data upon which we base our estimates of risk as well as benefits of treatment have been accumulated from casual BP readings taken in the office or clinic setting and therefore ABPM is not necessary for the diagnosis and management of most patients with hypertension.<sup>9 (Level III),10</sup>

The data provided by ABPM does not influence therapeutic decisions in the vast majority of patients and as a result has not been recommended by the JNC-7<sup>11</sup>, WHO-ISH<sup>1</sup> and NICE guidelines<sup>12</sup> as a routine procedure in the initial evaluation of the hypertensive patient.<sup>(Level III)</sup>

Furthermore the expense of this procedure is not justifiable at the present time.

ABPM is useful in selected research and clinical situations. These include:

- “white coat hypertension”
- borderline hypertension/labile hypertension
- resistant hypertension (BP >140/90 mmHg on a regimen of three or more anti-hypertensive drugs), one of which must be a diuretic
- evaluation of suspected hypotensive symptoms
- establishing the duration of action of new drugs in clinical trials

There is increasing evidence that damage to target organs, e.g. heart, kidney, brain and large arteries correlates better with out-of-office measurements including those of ABPM, and home BP measurements than with office measurements.<sup>13</sup>

## 2.3 Electronic BP sets

This is now increasingly being used. In the US, mercury sphygmomanometers are already withdrawn. It is important to realize that not all of the machines are accurate. The best are those validated by a reputable body, e.g. national hypertension societies such as British Hypertension Society or American Association for the Advancement of Medical Instrumentation (AAMI). A list of validated machines is listed in Appendix 1.

These machines should be serviced and calibrated every six months to maintain accuracy or at least compared with the readings taken by a mercury sphygmomanometer.

These electronic machines are generally less accurate in patients with atrial fibrillation. They should not be used in pregnancy as the BP reading may be underestimated.

Auscultatory electronic BP sets similar to the mercury sets but with a digital instead of mercury column will be available in the future.

## 2.4 Home blood pressure measurement

Home BP measurement may be useful in the diagnosis and monitoring of selected patients.

There is less extensive data on clinical correlation of home BP measurement compared to ABPM. Information obtained from this approach should only be regarded as supplementary to conventional measurements and not as a substitute. The decision to treat should finally be based upon the total risk stratification of the patient.

The recordings should be done at about the same time once in the morning and evening. Home BP is generally lower than clinic BP by approximately 10-20 mmHg systolic and 5-10 mmHg diastolic. The use of home devices that measure BP in the fingers or the wrists is not recommended.

Home BP measurement can be useful in monitoring control of BP. It empowers the patient with the control of his condition and may improve compliance.<sup>(Level III)</sup>

## 3. DIAGNOSIS AND ASSESSMENT

Evaluation of patients with documented hypertension has three objectives:

- (1) To exclude secondary causes of hypertension (Table 2).
- (2) To ascertain the presence or absence of target organ damage.
- (3) To assess lifestyle and identify other cardiovascular risk factors (Table 3) or concomitant disorders that affect risk factors, prognosis and guide treatment.

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

**Table 2. Secondary causes of hypertension**

Sleep apnoea
Drug-induced or drug-related
Chronic kidney disease
Primary aldosteronism
Renovascular disease
Chronic steroid therapy and Cushing syndrome
Phaeochromocytoma
Acromegaly
Thyroid or parathyroid disease
Coarctation of the aorta
Takayasu Arteritis

**Table 3. Cardiovascular risk factors**

<b>Major risk factors</b>
Hypertension
Cigarette smoking
Central obesity (waist circumference >90 cm for men, >80 cm for women)
Physical inactivity
Dyslipidaemia
Diabetes mellitus
Microalbuminuria
Estimated GFR* <60 mL/min
Age (>55 years for men, >65 years for women)
Family history of premature cardiovascular disease (men <55 years or women <65 years)
<b>Target Organ Damage</b>
Heart
• Left ventricular hypertrophy
• Angina or prior myocardial infarction
• Prior coronary revascularisation
• Heart failure
Brain
• Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

\*GFR, glomerular filtration rate.

Cockcroft-Gault formula: See Appendix 2

A complete history should include:

- duration and level of elevated BP if known
- symptoms of secondary causes of hypertension
- symptoms of target organ damage, e.g. coronary heart disease (CHD) and cerebrovascular disease
- symptoms of concomitant disease that will affect prognosis or treatment, e.g. diabetes mellitus, renal disease and gout
- family history of hypertension, CHD, stroke, diabetes, renal disease or dyslipidaemia
- dietary history including salt, fat, caffeine and alcohol intake
- drug history of either prescribed or over-the-counter medication (NSAIDs, nasal decongestants) and herbal treatment
- lifestyle and environmental factors that will affect treatment and outcome, e.g. smoking, physical activity, work stress and excessive weight gain since childhood

The physical examination should include the following:

- general examination including height, weight and waist circumference
- two or more BP measurements separated by two minutes with the patient either supine or seated; and after standing for at least one minute
- measure BP on both arms
- fundoscopy
- examination for carotid bruit, abdominal bruit, presence of peripheral pulses and radio-femoral delay
- cardiac examination
- chest examination for evidence of cardiac failure
- abdominal examination for renal masses, aortic aneurysm and abdominal obesity
- neurological examination to look for evidence of stroke
- signs of endocrine disorders, e.g. Cushing syndrome, acromegaly and thyroid disease

The initial investigations aim to exclude secondary causes of hypertension, determine the presence of risk factors and assess the extent of target organ damage (TOD). They should include the following: <sup>(Level III)</sup>

- Full blood count
- Urinalysis
- Measurement of urine albumin excretion or albumin/creatinine ratio
- Renal function tests (urea, creatinine, serum electrolytes and uric acid)
- Fasting blood sugar
- Lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides)
- Electrocardiogram (ECG)
- Chest X-ray

If the examination or investigations suggest the presence of a secondary cause, the patient should be referred for specialist evaluation. If there is evidence of TOD (Table 4), further tests should be considered.

A local study has revealed that as high as 53% patients with essential hypertension did not have their cardiovascular risks adequately assessed.<sup>14</sup>

**Table 4. Manifestations of target organ damage (TOD)/ target organ complication (TOC)**

Organ system	Manifestations
Cardiac	Left ventricular hypertrophy, coronary heart disease, heart failure
Cerebrovascular	Transient ischaemic attack, stroke
Peripheral vasculature	Absence of one or more major pulses in extremities (except dorsalis pedis) with or without intermittent claudication
Renal	GFR <60 ml/min / 1.73 m <sup>2</sup> , proteinuria (1+ or greater), microalbuminuria (2 out of 3 positive tests over a period of 4-6 months)
Retinopathy	Haemorrhages or exudates, with or without papilloedema

Table 5 stratifies the risk of a patient with hypertension developing a major cardiovascular event, which includes cardiovascular death, stroke or myocardial infarction. This classification is a useful guide for therapeutic decisions.

**Table 5. Risk stratification**

Co-existing Condition BP Levels (mmHg)	No RF No TOD No TOC	TOD or RF (1-2), No TOC	TOD or RF (≥3) or Clinical atherosclerosis	Previous MI or Previous Stroke or Diabetes
SBP 120 – 139 and/or DBP 80 – 89	Low	Medium	High	Very High
SBP 140 – 159 and/or DBP 90 – 99	Low	Medium	High	Very High
SBP 160 – 179 and/or DBP 100 – 109	Medium	High	Very High	Very High
SBP 180 – 209 and/or DBP 110 – 119	High	High	Very High	Very High
SBP ≥210 and/or DBP ≥120	Very High	Very High	Very High	Very High
Risk Level	Risk of major CV Event in 10 years	Management		
Low	<10%	Lifestyle changes		
Medium	10 – 20%	Drug treatment and lifestyle changes		
High	20 – 30%	Drug treatment and lifestyle changes		
Very high	>30%	Drug treatment and lifestyle changes		

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

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

RF = additional risk factors (smoking, TC >6.5 mmol/L, family history of premature vascular disease)

Clinical atherosclerosis (CHD, carotid stenosis, peripheral vascular disease, transient ischaemic attack, stroke)

Following initial clinical evaluation, investigation and risk stratification, patients needs to be re-evaluated as recommended below.

**Table 6. Recommendations for follow-up based on initial blood pressure measurements for adults.**

Initial BP (mmHg)		Follow-up recommended to confirm diagnosis and/or review response to treatment
Systolic	Diastolic	
<130	and <85	Recheck in one year
130-139	and 85-89	Recheck within 3-6 months
140-159	and/or 90-99	Confirm within two months
160-179	and/or 100-109	Evaluate within one month and treat if confirmed
180-209	and/or 110-119	Evaluate within one week and treat if confirmed
≥210	and/or ≥120	Initiate drug treatment immediately

Modified from JNC-7 report<sup>11 (Level III)</sup>

## 4. PREHYPERTENSION

It replaces former categories “high-normal” (130-139/85-89 mmHg) and “above optimal” (120-129/80-84 mmHg). The term “borderline hypertension” is discouraged from use as it is imprecise and inconsistently defined.

### Definition of prehypertension

Prehypertension is defined as systolic BP (SBP) 120 to 139 or diastolic BP (DBP) 80 to 89 mmHg, based on 2 or more properly measured seated BP readings on each of 2 or more office visits.<sup>11</sup>

#### 4.1 Epidemiology of prehypertension

Based on the Third National Health and Nutrition Examination Survey (NHANES-III; 1999-2000) the prevalence of prehypertension in the US population is 31% with no apparent difference by race or ethnicity.<sup>15</sup>

In Malaysia, data from the National Health and Morbidity Survey (NHMS) 1996 indicates that 37% of our populations has prehypertension.<sup>2 (Level II-2)</sup>

Patients with prehypertension are at increased risk for progression to hypertension. In the Framingham study, the high-normal BP group conversion rate was 37% in 4 years.<sup>16</sup> This conversion rate was even higher in the Trial of Preventing Hypertension (TROPHY) study in which over a period of 4 years, stage 1 hypertension developed in nearly two thirds of patients with untreated prehypertension ( the control group).<sup>17</sup> The level of BP and age of the subject are major determinants of this risk, with a higher rate of conversion associated with older individuals and those with higher BP levels. Obesity and weight gain also contribute to the progression of prehypertension to hypertension.

Prehypertension tends to cluster with other CVD risk factors such as dyslipidaemia, glucose abnormalities and obesity.<sup>18-20</sup> However, the weight of evidence suggests that the raised level of BP itself is an independent CVD risk factor.<sup>20-21</sup>

Rationale for the shift/redefinition of this category of BP

1. To emphasize the excess cardiovascular risk associated with BP in this range
  - For individuals aged 40-70 years, the risk of CVD rises progressively beginning at 115/75 mmHg<sup>22</sup>
  - It has been estimated that almost a third of BP-related deaths from coronary heart disease occur in individuals with SBP between 110 and 139 mmHg<sup>23</sup>
2. To focus increased clinical and public health attention on prevention of hypertension

#### 4.2 Management of prehypertension

- All patients should be managed with non-pharmacologic interventions/therapeutic lifestyle modifications to lower BP. (see Chapter 5)
- There should be yearly follow-up in patients with prehypertension to detect and treat hypertension as early as possible. <sup>(Level III)</sup>
- Decisions regarding pharmacological treatment should be based on the individual patient's global CVD risk. In diabetes mellitus or chronic kidney disease, medical treatment is required if BP is above 130/80 mmHg.<sup>25-27 (Level I)</sup> Similarly, in other high risk subjects such as those with previous CVA or CAD, the threshold for commencing hypertension treatment should be lower in patients with prehypertension.<sup>28-31 (Level I)</sup>

There is presently inadequate evidence for pharmacological intervention in prehypertensive patients at moderate or low total CV risk. The TROPHY study<sup>17</sup> assessed the effects of the angiotensin receptor blocker candesartan versus placebo on prevention of the onset of hypertension in subjects with BP in the previous “high-normal” range. While 2 years of active therapy reduced the incidence of hypertension, after withdrawal of candesartan the BP differences between groups narrowed, resulting in an overall minimal benefit.

## 5. NON-PHARMACOLOGICAL MANAGEMENT

Non-pharmacological management (therapeutic lifestyle modification) plays an important role in the management of hypertension.<sup>32</sup> It may be the only treatment necessary in Stage 1 hypertension. Unfortunately data from cross-sectional studies showed that non-pharmacological treatment for patient with hypertension is still inadequate. A high degree of motivation is also needed to sustain the benefits of non-pharmacological treatment. In the Treatment of Mild Hypertension Study (TOMHS), non-pharmacological intervention led to a fall of BP in the order of 9/9 mmHg and a reduction in the requirement for additional drugs in patients already on monotherapy.<sup>33</sup> It is also important to remember that lifestyle modification requires a concerted effort and reinforcement on behalf of the practitioner. Untreated patients with pre- and mild hypertension responded better to behavioural intervention on lifestyle modification than just passive advice on lifestyle modification.<sup>34</sup>

#### 5.1 Weight reduction

Weight reduction is most beneficial in patients who are more than 10% overweight. As far as possible aim for an ideal Body Mass Index [Weight (kg)/Height<sup>2</sup> (m)] – for Asians, the normal range has been proposed to be 18.5 to 23.5 kg/m<sup>2</sup>.<sup>35 (Level III)</sup> A practical target for overweight patients is a minimum reduction of 5% in body weight. However a weight loss as little as 4.5 kg significantly reduces BP.<sup>36-37 (Level I)</sup> Overweight patients on monotherapy receiving lifestyle intervention have significantly lower BP than those without such intervention.<sup>38</sup>

## 5.2 Sodium intake

The effect of sodium restriction in hypertensives can be variable. Elderly subjects are more sensitive to sodium intake. On average, a reduction of 4 mmHg systolic and 2 mmHg diastolic is achievable with sodium restriction. An intake of <100 mmol of sodium or 6g of sodium chloride a day is recommended (equivalent to <1¼ teaspoonfuls of salt or 3 teaspoonfuls of monosodium glutamate).<sup>36-37, 39 (Level I), 40</sup>

## 5.3 Avoidance of alcohol intake

Alcohol has an acute effect in elevating BP. The standard advice is to restrict intake to no more than 21 units for men and 14 units for women per week (1 unit equivalent to ½ a pint of beer or 100ml of wine or 20ml of proof whisky).<sup>(Level III)</sup> Hypertensives who are heavy drinkers are more likely to have hypertension resistant to drug treatment. The only way to reduce these patients' BP effectively is by reducing or stopping their alcohol intake.<sup>41 (Level I), 42</sup>

## 5.4 Regular physical exercise

Aerobic type exercise is more effective than exercise which involves resistance training, (e.g. weightlifting). The effect of at least six months of exercise on BP reduction amongst patients with hypertension is however very modest. General advice on cardiovascular health would be for "milder" exercise, such as brisk walking for 30 – 60 minutes at least 3 times a week.<sup>43-44 (Level I)</sup>

## 5.5 Healthy eating

A diet rich in fruits, vegetables and dairy products with reduced saturated and total fat can substantially lower BP (11/6 mmHg in hypertensive patients and 4/2 mmHg in patients with high normal BP).<sup>45 (Level II-1)</sup> This type of diet also has a beneficial effect on overall cardiovascular health.

## 5.6 Cessation of smoking

This is important in the overall management of the patients with hypertension in reducing cardiovascular risk.<sup>(Level III)</sup> Smoking can also acutely increase BP. The effect of chronic smoking per se on BP is not clear.

## 5.7 Others

These include stress management, micronutrient alterations and dietary supplementation with fish oil, potassium, calcium, magnesium and fibre. However, they have limited or unproven efficacy.<sup>(Level III)</sup>

# 6. PHARMACOLOGICAL MANAGEMENT

## 6.1 General guidelines

There are many drugs available for the treatment of hypertension. The ideal drug must be efficacious, free from side-effects, able to prevent all the complications of hypertension, easy to use and affordable. It may not matter which class of drug is used, it is the reduction of BP which provides the main benefits in the general hypertensive population.<sup>46</sup> Appendix 3 lists the drugs currently available in Malaysia.<sup>7</sup>

For patients with Stage 1 hypertension, an observational period of three to six months is recommended unless target organ involvement is already evident. During this period, appropriate advice should be given on lifestyle modification. Follow-up at this juncture should be about two monthly so that there will be between one to three visits over the period. Efficacy of the above intervention should be assessed. Figure 1 outlines the management of a patient with hypertension.<sup>(Level III)</sup>

In patients with newly diagnosed uncomplicated hypertension and no compelling indications, choice of first line monotherapy includes ACEIs, ARBs, CCBs and diuretics. Beta-blockers are no longer recommended for first line monotherapy in this group of patients.<sup>48 (Level I)</sup> A recent meta-analysis has shown that it is not as effective in lowering blood pressure and in the prevention of stroke compared to the other antihypertensive agents.<sup>48</sup> Incidence of new-onset diabetes is also higher compared to the other drugs.<sup>49</sup> However, beta-blockers may be considered in younger people, particularly:

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

Ideally, individualisation should be based on scientific evidence of reduction in endpoints (Table 7). Otherwise, theoretical benefits may determine the choice of drugs. Contraindications to the use of these drugs must also be considered. Whilst numerous controlled trials have shown that a diuretic and/or a beta-blocker reduce cardiovascular morbidity and mortality, recent trials have reported similar benefits with ACEIs and CCBs.<sup>50-54</sup>

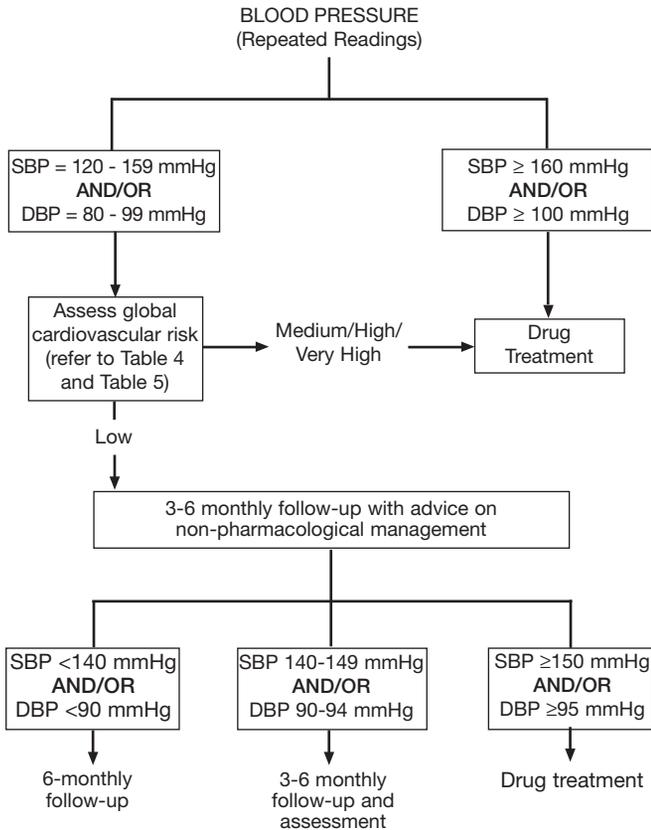
In patients with stage 1 hypertension, treatment should be started with a single drug at low dose. Monotherapy can lower BP to <140/90 mmHg in approximately 40 – 60% of patients with mild to moderate hypertension. If after a sufficient period of treatment (up to six weeks) with monotherapy BP is still not controlled, three options are available

- the dose of the initial drug can be increased
- the drug can be substituted with another class of drug
- a second drug can be added (Table 9).

Increasing the dose of the initial antihypertensive agent or adding a second agent is preferred if the patient shows response to the initial drug but target BP is not achieved. The former, however, may give rise to dose-related adverse effects. Properly selected antihypertensive combinations may also mitigate the adverse effects of each other. To improve compliance, a fixed-dose combination drug may be considered. If the patient does not show response or does not tolerate the initial drug, drug substitution is recommended.<sup>(Level III)</sup>

In patients presenting with stage 2 hypertension or beyond, combination therapy is recommended.<sup>(Level III)</sup>

**FIGURE 1. Algorithm for the Management of Hypertension**



**Table 7. Choice of antihypertensive drugs in patients with concomitant conditions**

Concomitant disease	Diuretics	β-blockers	ACEIs	CCBs	Peripheral β-blockers	ARBs
Diabetes mellitus (without nephropathy)	+	+/-	+++	+	+/-	++
Diabetes mellitus (with nephropathy)	++	+/-	+++	++*	+/-	+++
Gout	+/-	+	+	+	+	+
Dyslipidaemia	+/-	+/-	+	+	+	+
Coronary heart disease	+	+++	+++	++	+	+
Heart failure	+++	+++ <sup>#</sup>	+++	+ <sup>@</sup>	+	+++
Asthma	+	-	+	+	+	+
Peripheral vascular disease	+	+/-	+	+	+	+
Non-diabetic renal impairment	++	+	+++	+*	+	++
Renal artery stenosis	+	+	++ <sup>\$</sup>	+	+	++ <sup>\$</sup>
Elderly with no co-morbid conditions	+++	+	+	+++	+/-	+

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

+/- Use with care

- Contraindicated

\* Only non-dihydropyridine CCB

<sup>#</sup> Metoprolol, bisoprolol, carvedilol – dose needs to be gradually titrated

<sup>@</sup> Current evidence available for amlodipine and felodipine only

<sup>\$</sup> Contraindicated in bilateral renal artery stenosis

**Table 8. Effective antihypertensive combinations**

Effective combination	Comments
β-blockers + diuretics However, may	Benefits proven in the elderly, cost-effective. increase risk of new onset diabetes
β-blockers + CCBs	Relatively cheap, appropriate for concurrent CHD
CCBs + ACEIs/ARBs	Appropriate for concurrent dyslipidaemias and diabetes mellitus
ACEIs + diuretics mellitus and	Appropriate for concurrent heart failure, diabetes stroke
ARBs + diuretics diabetes	Appropriate for concurrent heart failure and mellitus

Efforts must be made to reach target BP. For patients <65 years old, the target BP should be <140/85<sup>55</sup> mmHg and <130/80 mmHg for diabetics.<sup>25</sup> For elderly patients >65 years old, refer to section 8.7. In general once the BP is controlled, most patients will require life-long treatment. If BP is still >140/90 mmHg with three drugs, including a diuretic at near maximal doses, patients by definition have resistant hypertension.<sup>56</sup> A quick check on the possible causes of resistant hypertension is required. These include:

- non-compliance
- secondary hypertension
- white coat hypertension
- excessive sodium intake, excessive liquorice intake and drug interactions.
- complications of long standing hypertension such as nephrosclerosis, loss of aortic distensibility and atherosclerotic renal artery stenosis

### 6.2 Follow-up visits

Recommended duration of follow up is as shown in Table 6. Once target BP is achieved, follow-up at three to six-month interval is appropriate.

### 6.3 Step-down therapy

An effort to decrease the dosage and number of antihypertensive drugs should be considered after hypertension has been controlled effectively for at least 1 year. The reduction should be made in a deliberate, slow and progressive manner. Step down therapy is more often successful in patients who also are making lifestyle modifications. Patients whose drugs have been discontinued should have scheduled follow-up visits because BP usually rises again to hypertensive levels, sometimes months or years after discontinuance, especially in the absence of sustained improvements in lifestyle.

### 6.4 When to refer

Most patients can be effectively managed by their own family practitioners, patients with the following conditions should be referred to the appropriate specialist for further assessment:

Indications for referral to the appropriate specialist include:

- accelerated or malignant hypertension
- suspected secondary hypertension
- resistant hypertension
- recent onset of target organ damage
- pregnancy
- children <18 years old

#### Recommendations

- Target BP should be <140/85 mmHg for most<sup>55</sup>
- Target BP for patients with Diabetes Mellitus or Chronic Kidney Disease should be <130/80 mmHg
- Treatment should be individualised
- For patients with stage 1 hypertension, start with a single drug at the lowest dosage
- For patients with stage 2 and beyond, consider combination therapy

## 7. MANAGEMENT OF SEVERE HYPERTENSION

Definition of severe hypertension:

Severe hypertension is defined as BP >180/110 mmHg.

These patients may present in the following manner:

- incidental finding in an asymptomatic patient
- non-specific symptoms like headache, dizziness, lethargy
- symptoms and signs of acute target organ damage. These include acute heart failure, acute coronary syndromes, acute renal failure, dissecting aneurysm, hypertensive encephalopathy and stroke

Management of these patients depends on the clinical presentation and laboratory investigations. The evaluation of these patients should include a thorough history and physical examination, particularly looking for signs of acute target organ damage and causes of secondary hypertension. (Table 9)

Table 9. Common causes of severe hypertension\*

Cause	Example
Renal parenchymal disease	Chronic pyelonephritis Primary glomerulonephritis Tubulointerstitial nephritis
Systemic disorders with renal involvement	Systemic lupus erythematosus Systemic sclerosis Vasculitides
Renovascular	Atherosclerotic disease Fibromuscular dysplasia Polyarteritis nodosa
Endocrine	Phaechromocytoma Conn syndrome (primary hyperaldosteronism) Cushing syndrome
Drugs	Cocaine Amphetamines Cyclosporin Clonidine withdrawal Phencyclidine
Coarctation of Aorta	-
Pre-eclampsia/eclampsia	-

\* The most common cause of severe hypertension is still long-standing poorly controlled essential hypertension.<sup>57</sup>

Patients are then categorised as having:

- a) asymptomatic severe hypertension,
  - b) hypertensive urgencies, or
  - c) hypertensive emergencies
- (b) and (c) are also referred to as hypertensive crises.<sup>58</sup>

## 7.1 Specific management

The aim of drug therapy in patients with severe hypertension is to reduce BP in a controlled, predictable and safe manner in order to avoid acute coronary, cerebral or renal ischaemia; or if ischaemia is already present, to avoid aggravating the situation.

### 7.1.1 Asymptomatic severe hypertension

Admission may be necessary in the newly diagnosed, or where compliance may be a problem. Patients already on treatment need to have their drug regime reviewed.<sup>59 (Level III)</sup>

### 7.1.2 Hypertensive urgencies

These include patients with grade III or IV retinal changes (also known as accelerated and malignant hypertension respectively), but no overt organ failure. These patients may need admission. BP measurement should be repeated after 30 minutes of bed rest. Initial treatment should aim for about 25% reduction in BP over 24 hours but not lower than 160/90 mmHg.<sup>60-61 (Level III)</sup> Oral drugs proven to be effective are outlined in Table 10. Combination therapy is often necessary.

Table 10. Oral treatment for hypertensive urgencies

Drug	Dose	Onset of action (hr)	Duration (hr)	Frequency (prn)
Captopril	25 mg	0.5	6	1 – 2 hrs
Nifedipine	10 – 20 mg	0.5	3 – 5	1 – 2 hrs
Labetalol	200 – 400 mg	2.0	6	4 hrs

### 7.1.3 Hypertensive emergencies

These include patients with complications of severe hypertension such as acute heart failure, dissecting aneurysm, acute coronary syndromes, hypertensive encephalopathy, subarachnoid haemorrhage and acute renal failure. These may occur in patients with BP <180/110 mmHg, particularly if the BP has risen rapidly.

All these patients should be admitted. The BP needs to be reduced rapidly. It is suggested that the BP be reduced by 25% depending on clinical scenario over 3 to 12 hours but not lower than 160/90 mmHg.<sup>62-64 (Level III)</sup>

This is best achieved with parenteral drugs. (Table 11)

Table 11. Treatment options for hypertensive emergencies<sup>47</sup> (References are from Malaysia Index of Medical Specialties (MIMS), 108th edition, 2007)

Drugs	Dose	Onset of action	Duration	Remarks
Sodium nitroprusside	0.25 – 10 µg/kg/min	seconds	1 – 5 min	Caution in renal failure
Labetalol <sup>†</sup>	IV bolus 50 mg (over at least 1 minute) repeating if necessary at 5 minute intervals to a max of 200 mg then 2 mg/min IVI	≤5 min	3 - 6 hrs	Caution in heart failure
Nitrates	5 – 100 µg /min	2 – 5 min	3 – 5 min	Preferred in acute coronary syndromes and acute pulmonary oedema
Hydralazine*	IV 5–10 mg maybe repeated after 20 - 30 minutes IVI 200-300 mcg/min initially. Maintenance 50-150 mcg /min	10 – 20 min 20 – 30 min	3 – 8 hrs	Caution in acute coronary syndromes, cerebrovascular accidents and dissecting aneurysm
Nicardipine	IV bolus 10-30 mcg/kg over 1 minute IVI 2–10 mcg/kg/min	5 – 10 min	1 – 4 hrs	Caution in acute heart failure and coronary ischaemia
Esmolol	IV bolus 1 – 2 min 250–500 mcg/kg over 1 min IVI 50–200 mcg/kg/min for 4 min. May repeat sequence	3 – 10 min	Used in peri-operative situations	and tachy-arrhythmias

# In pregnancy, 200mg labetalol in 50 ml normal saline and start infusion at 4 ml/hour.

\* In pregnancy, the initial dose is 25 g/min IV infusion (25 mg in 500 ml normal saline at 30 ml/hour).

## 7.2 Dangers of rapid reduction in blood pressure

Rapid reduction of BP (within minutes to hours) in asymptomatic severe hypertension or hypertensive urgencies is best avoided as it may precipitate ischaemic events.<sup>65</sup>

Oral or sublingual drugs with rapid onset of action can result in an uncontrolled BP reduction. Several serious side effects have been reported with the administration of sublingual fast-acting nifedipine and therefore this is no longer recommended.<sup>66 (Level II-2),67</sup>

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

For management of patients with severe hypertension and stroke, refer to section on Hypertension and Stroke.

## 8. HYPERTENSION IN SPECIAL GROUPS

### 8.1 Hypertension and diabetes mellitus

Hypertension is a common problem in patients with diabetes mellitus. Its presence increases the risk of morbidity and mortality. In type 1 diabetes, the incidence of hypertension increases from 5% at 10 years to 33% at 20 years and 70% at 40 years, and appears to be closely related to diabetic renal disease. In type 2 diabetes, hypertension is even more prevalent. The Hypertension in Diabetes Study Group reported a 39% prevalence of hypertension among newly diagnosed patients, and in approximately half of them the elevated BP predated the onset of microalbuminuria and was strongly associated with obesity.<sup>68-69</sup> In type 2 diabetes, hypertension is frequently present as a component of the metabolic syndrome. (Section 8.2)

Hypertension should be detected and treated early in the course of diabetes mellitus to prevent cardiovascular disease and to delay the progression of renal disease and diabetic retinopathy. Diabetic patients should also be screened for proteinuria or microalbuminuria. The presence of microalbuminuria strongly predicts overt nephropathy and cardiovascular disease.

#### 8.1.1 Threshold for treatment

Pharmacological treatment should be initiated in patients with diabetes when the BP is persistently >130 mmHg systolic and/or >80 mmHg diastolic.<sup>1,25,70 (Level I)</sup>

The presence of microalbuminuria or overt proteinuria should be treated even if the BP is not elevated. An ACEI or ARB is preferred.<sup>71-77 (Level I)</sup> In a proportion of patients, microalbuminuria may be normalised by higher doses of ACEIs<sup>74</sup> and ARBs.<sup>75-76 (Level I)</sup> Normalisation of microalbuminuria is associated with a reduction in the rate of decline in glomerular filtration rate.<sup>78</sup>

#### 8.1.2 Target blood pressure

Tight BP control should take precedence over the class of antihypertensive drug used.<sup>79-80 (Level I)</sup> This often will require combination therapy. There are suggestions that a lower target BP may be necessary to maximally protect against the development and progression of cardiovascular and diabetic renal disease. In general, the SBP should be targeted to <130 mmHg and diastolic pressure <80 mmHg.<sup>81 (Level I)</sup> The BP should be lowered even further to <125/75 mmHg in the presence of proteinuria of >1 g/24 hours.<sup>1,25,26,57,70 (Level I)</sup>

#### 8.1.3 Management

The approach to the treatment of hypertension in diabetes should be very much along the guidelines for treatment of hypertension in general. Nonetheless, a few important issues concerning non-pharmacological management and drug treatment need to be highlighted.

### Non-pharmacological management

This cannot be over emphasised. Dietary counselling should target at optimal body weight and take into consideration glycaemic control and the management of concomitant dyslipidaemia.

Moderate dietary sodium restriction is advisable. It enhances the effects of BP lowering drugs especially ACEIs and the ARBs. Further sodium restriction, with or without a diuretic, may be necessary in the presence of nephropathy or when the BP is difficult to control.<sup>82</sup>

### Pharmacological management

The use of certain classes of antihypertensive drugs may be disadvantageous to the diabetic patient by virtue of their modes of action or adverse effects. (Table 7) Diabetic control may be compromised and various diabetic complications aggravated.<sup>82</sup>

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

ACEIs are drugs of choice based on extensive data attesting to their cardiovascular and renal protective effects in diabetic patients.<sup>83-84 (Level I)</sup>  
<sup>1)</sup> In addition they do not have adverse effects on lipid and carbohydrate metabolism. If an ACEI is not tolerated, an ARB should be considered.<sup>85 (Level I)</sup>

ARBs have been reported to be superior to conventional non-ACEI antihypertensive drugs in terms of slowing the progress of nephropathy at the microalbuminuric stage as well as the overt nephropathy stage in type 2 diabetic patients. They have been shown to be of similar efficacy as ACEIs but better tolerated.<sup>85 (Level I)</sup> There have been no reports of adverse effects on carbohydrate and lipid metabolism.<sup>75-77</sup>

Diuretics can be used as initial therapy or added on when monotherapy is inadequate. The lowest possible dose should be used to minimise adverse metabolic effects. However, adverse metabolic effects with higher doses of diuretics have also been reportedly reduced when used in combination with an ACEI or an ARB.<sup>85</sup>

CCBs do not have significant adverse metabolic effects or compromise diabetic control. Some studies suggest that non-dihydropyridine CCBs may be superior to dihydropyridine CCBs in reducing proteinuria in diabetic nephropathy.<sup>86</sup>

Beta-blockers may be used when ACEIs, ARBs or CCBs cannot be used or when there are concomitant compelling indications. However, they should be used with caution, especially in patients with type 1 diabetes.<sup>86</sup>

Peripheral alpha blockers do not have adverse effects on carbohydrate or lipid metabolism. Orthostatic hypotension due to autonomic neuropathy may be aggravated with their use.

#### Recommendations

- ACEIs are the agents of choice for patients with diabetes without proteinuria
- ACEIs or ARBs are the agents of choice for patients with diabetes and proteinuria
- Beta-blockers, diuretics or CCBs may be considered if either of the above cannot be used.

## 8.2 Hypertension and the metabolic syndrome

The metabolic syndrome began life as “Syndrome X” in 1988 when Reaven gave the Banting Lecture at the annual meeting of the American Diabetes Association. Following this it was given a variety of labels – the Insulin Resistance Syndrome, Plurimetabolic Syndrome, Dysmetabolic Syndrome and Cardiometabolic Syndrome before settling on its current designation.

In essence, it is a cluster of risk factors predisposing to cardiovascular disease and diabetes. The problem was coming to a consensus on the diagnostic criteria. Various organisations have come out with their proposals, among them the WHO<sup>1</sup>, the European Group on Insulin Resistance, and the American Association of Clinical Endocrinologists. The most widely applied (and practical) criteria are the National Cholesterol Education Programme Adult Treatment Panel (NCEP ATP) III<sup>87</sup> and International Diabetic Federation (IDF)<sup>88</sup> criteria. The IDF criteria are also known as the IDF Consensus. The NCEP criteria have been modified for Asians by changing the waist circumference to the Asian standard.

Hypertension is one of the criteria for the diagnosis of the metabolic syndrome. In the original WHO<sup>1</sup> criteria the cut-off point was 140/90 mm Hg but in the current guidelines this has been lowered to 130/85 mmHg. The others include the waist circumference, blood sugar, HDL-cholesterol and triglyceride levels. (Table 12)

Controversy recently arose as to the usefulness of the metabolic syndrome as a predictor of cardiovascular disease and diabetes, and this debate is still ongoing.<sup>89-90</sup>

Notwithstanding this, all parties agree that the various components of the metabolic syndrome should be treated separately.<sup>89-91</sup> Hypertension associated with the metabolic syndrome should therefore be treated according to standard clinical practice guidelines.

Beta-blockers and thiazide diuretics have the potential to increase the incidence of new onset diabetes<sup>92,49</sup> and this should be taken into consideration when choosing drugs for patients diagnosed with the metabolic syndrome.

Table 12. NCEP ATP III and IDF criteria for the metabolic syndrome<sup>87-88</sup>

Components of metabolic syndrome	Waist (cm)	BP (mmHg)	FBS (mmol/L)	TG (mmol/L)	HDL (mmol/L)
<b>NCEP 2004</b> <i>3 out of 5 criteria</i>	>90 (M) >80 (F)	≥130/85	≥5.6	≥1.7	<1.0 (M) <1.3 (F)
<b>IDF 2005</b> <i>Waist criterion + 2 out of 4 criteria</i>	COMPULSORY >90 (M) >80 (F)	≥130/85	≥5.6	≥1.7	<1.0 (M) <1.3 (F)

## 8.3 Hypertension and non-diabetic renal disease

Hypertension may be a cause or consequence of renal failure.<sup>93-94</sup> Renal disease is the most important cause of secondary hypertension.

Hypertension in renal disease is often associated with an elevated serum creatinine, proteinuria and/or haematuria. Approximately 50-75% of individuals with GFR<60 ml/min/1.72m<sup>2</sup> (CKD stages 3-5) have hypertension.<sup>95</sup> Hypertension accelerates the progression of renal disease and may lead to end stage renal disease (ESRD). Tight control of BP is therefore important. The target BP should be < 130/80 mmHg for those with proteinuria of < 1g/24 hours and < 125/75 mmHg for those with proteinuria of > 1g/24 hours.<sup>26,57 (Level I)</sup> All antihypertensive drug classes can be used to achieve this goal.

In the management of hypertension in renal disease, control of BP and proteinuria are the most important factors in terms of retarding the progression of renal disease. Antihypertensive agents that reduce proteinuria thus have an advantage. Meta-analyses of comparative trials concluded that ACEI conferred an anti-proteinuric effect greater than other anti-hypertensive drugs.<sup>96</sup> Overall 30% reduction in incidence of ESRD with ACEI can be expected.<sup>97</sup> The anti-proteinuric effect and reduction in ESRD was beyond that attributable to the BP lowering effect.<sup>98-99</sup> This anti-proteinuric effect of ACEI was most prominent in patients on a low sodium diet or those treated with diuretics. Patients with proteinuria >3g/24 hours benefited the most.<sup>100-101</sup> The advantage of ACEI is most readily apparent in patients with rapid progression of renal disease associated with proteinuria. ARBs are similar to ACEI in lowering BP and reducing proteinuria.<sup>102-103</sup> The combination of ACEIs and ARBs has also been proven to reduce the rate of doubling of serum creatinine and ESRD more than monotherapy with either agent in nondiabetic proteinuric renal disease.<sup>104 (Level I)</sup> Consultation with a specialist is advised prior to initiation of this combination.

Renal insufficiency should not be a contraindication to starting ACEI or ARB therapy, nor should it be a reason for discontinuing therapy. Serum creatinine level should be checked within the first two weeks of initiation of therapy. If there is a persistent rise of serum creatinine of  $\geq 30\%$  from baseline within two months, ACEIs should be stopped. Similar caution should be exercised with the use of ARBs.<sup>(Level III)</sup>

In patients with renal disease and hypertension with an elevated serum creatinine of  $>200$   $\mu\text{mol/L}$ , thiazide diuretics may not be effective antihypertensive agents and therefore loop diuretics are preferred.<sup>(Level III)</sup> Concurrent diuretic therapy will often be necessary in patients with renal insufficiency since salt and water retention is an important determinant of hypertension in this setting.

CCBs may be used in renal disease. In those with proteinuria, the non-dihydropyridine group of CCBs namely diltiazem or verapamil are preferred, as they have an additional antiproteinuric effect.<sup>96 (Level I, 106)</sup> The combination of an ACEI and a non-dihydropyridine CCB is more anti-proteinuric than either drug alone.<sup>105-106</sup> More recently, aldosterone antagonists have been shown to have additive antiproteinuric effects when administered with ACEI and/or ARB in patients with CKD.<sup>107</sup> However, larger randomised prospective trials are needed to confirm the efficacy and safety of aldosterone antagonists on proteinuria and CKD progression.

#### Recommendations

- Target BP should be  $<130/80$  mmHg for those with proteinuria of  $<1\text{g}/24$  hours and  $<125/75$  mmHg for those with proteinuria of  $>1\text{g}/24$  hours
- ACEIs are recommended as initial anti-hypertensive therapy
- ARBs should be used in patients intolerant to ACEIs
- Dietary salt and protein restriction is important
- Concurrent diuretic therapy is useful in patients with fluid overload
- Non-dihydropyridine CCBs can be added on if the BP goal is still not achieved

#### 8.4 Renovascular hypertension

It is important to diagnose renovascular hypertension as it is potentially reversible. The aetiology of renovascular hypertension includes the following:

- atherosclerotic renovascular disease
- fibromuscular dysplasia
- Takayasu arteritis
- transplant renal artery stenosis

Atherosclerotic renal artery stenosis (ARAS) is an important cause as it can lead to ESRD. It is also associated with coronary heart disease, cerebrovascular disease and peripheral vascular disease. In patients with ARAS older than 60 years, the five-year-survival is 45% in patients with bilateral ARAS and 18% in those requiring dialysis therapy.<sup>108-109</sup>

The coexistence of a stenotic renal vessel and hypertension does not equate to renovascular hypertension. Renovascular hypertension is present if a cure or improvement of hypertension can be demonstrated following revascularisation.

Some clinical features associated with renovascular hypertension include:

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

Renal angiography including measurement of the pressure gradient remains the gold standard in the diagnosis of renovascular hypertension. Non-invasive investigations<sup>110</sup> include spiral CT angiography (CTA),<sup>111</sup> colour coded duplex sonography (CDS), captopril enhanced radionuclide renal scan (CR) and magnetic resonance angiography (MRA).<sup>110</sup>

Revascularisation has been shown to alleviate renovascular hypertension as well as to salvage renal function.<sup>112-113</sup> It should be considered under the following circumstances.<sup>114-115</sup>

- flash pulmonary oedema
- rapidly deteriorating renal function especially if leading to dialysis
- stenosis  $>70\%$
- refractory hypertension
- transplant renal artery stenosis
- fibromuscular dysplasia associated with hypertension
- Takayasu arteritis

The management of renal artery stenosis include conservative treatment, angioplasty with or without stenting and surgery. Conservative treatment can be considered for patients with stenosis less than 70%. These lesions should be monitored for progression using colour duplex sonography. Medical treatment of patients with ARAS will include statins, low dose aspirin and cessation of smoking. Angiotensin converting enzyme inhibitors and ARB can be used in patients with suspected ARAS if renal function is carefully monitored. A persistent rise in creatinine of  $>30\%$  warrants cessation of drug therapy. This is best done under specialist's supervision.

Ostial ARAS is best treated with angioplasty with stenting due to problem of recoil post angioplasty. In patients with deteriorating renal function or global obstructive atherosclerotic renovascular disease, renal artery stenting improves or stabilizes renal function and preserves kidney size.<sup>116-118</sup> Patients with complex renovascular disease such as renal artery aneurysm or failed endovascular procedures may benefit from renal artery surgery.

Doctors have to distinguish patients with a high likelihood of treatment benefit from those with incidental ARAS. The presence of refractory hypertension, recent deterioration of renal function and evidence of progression of the stenotic lesion will help to determine the plan of management for these patients.

Duplex Doppler examination is ideal for screening and follow-up monitoring of patients with renal transplant artery stenosis. These lesions should only be treated if there is a recent worsening of renal function as there is a possibility of spontaneous reversal of stenosis.<sup>119</sup> Percutaneous Renal Angioplasty (PTRA) is the treatment of choice where indicated. Further studies comparing intervention and conservative treatment are needed. Patients with fibromuscular dysplasia rarely have excretory dysfunction, and hypertension in these patients generally responds to ACE inhibitors. Revascularisation is indicated for patients with refractory hypertension.

## **8.5 Hypertension and cardiovascular disease**

Hypertension is one of the major risk factors for atherosclerosis and cardiovascular disease.

### **8.5.1 Left ventricular dysfunction**

The early effects of hypertension on the myocardium are stiffness and subsequently left ventricular hypertrophy. These would result in abnormalities in left ventricular function manifested initially as diastolic dysfunction and later as systolic dysfunction. In diastolic dysfunction, left ventricular size and ejection fraction remain normal but the left ventricular end diastolic pressure is increased and this may result in pulmonary venous congestion presenting as dyspnoea. When systolic dysfunction occurs, the left ventricle is dilated and ejection fraction is reduced. This will lead to an increase in left ventricular end diastolic pressure with ensuing pulmonary venous congestion. Both diastolic and systolic left ventricular dysfunction can cause congestive cardiac failure and death.<sup>120</sup>

### **8.5.2 Left ventricular hypertrophy**

Left ventricular hypertrophy (LVH) is diagnosed on echocardiography or electrocardiography (ECG).<sup>121</sup> Echocardiography is more sensitive than ECG and can also be used to assess progression of LVH<sup>122</sup> but its usage may be limited due to cost considerations and availability.

Left ventricular hypertrophy can vary from isolated septal thickening to concentric LVH. Left ventricular hypertrophy increases the risk of LV dysfunction, ventricular arrhythmias and death.<sup>123</sup> Treatment of hypertension will lead to regression of LVH, improvement of LV function and reduction of cardiovascular morbidity.<sup>124</sup> All classes of antihypertensive agents have been shown to cause regression of LVH.<sup>125</sup> In patients with diastolic heart failure, ARB has been shown to reduce morbidity but not mortality.<sup>126</sup>

### **8.5.3 Coronary heart disease**

Hypertension is a major risk factor for coronary atherosclerosis. With LVH, there is increased oxygen demand and perfusion defects have been demonstrated on radionuclear myocardial perfusion studies, even in the absence of obstructive coronary artery disease. With decreased supply from coronary atherosclerotic obstruction, there is further imbalance to the increased demands of a hypertrophied left ventricle. This will lead to myocardial ischaemia and myocardial infarction, which can result in further deterioration of left ventricular function, congestive heart failure and death.

Hypertensive patients are more prone to silent myocardial ischaemia, myocardial infarction and sudden death.<sup>127-128</sup>

Beta-blockers, ACEIs and long-acting CCBs are the preferred antihypertensives. Short-acting CCBs, especially nifedipine in high doses<sup>129</sup> should be avoided as they are associated with increased cardiac events.<sup>130</sup> These agents should also be avoided in patients with unstable angina.<sup>131</sup> In post-infarction patients, ACEIs and beta-blockers especially in patients with LV dysfunction, help to reduce future cardiac events which include cardiac failure, cardiac mortality and morbidity.<sup>131-134 (Level I)</sup>

### **8.5.4 Congestive heart failure**

In congestive heart failure, diuretics, aldosterone antagonists, beta-blockers, ACEIs and ARBs have been shown to be beneficial.<sup>135</sup>

### **8.5.5 Peripheral vascular disease**

Hypertension is a major risk factor for peripheral vascular disease (PVD). Care should be taken with beta-blockers in patients with intermittent claudication. Its presence suggests an increased likelihood of generalized atherosclerosis including coronary artery disease.

### Recommendations

- Hypertensive patients with LVH should receive an ARB as the first line treatment<sup>128</sup>
- In CHD, beta-blockers<sup>138</sup>, ACEIs<sup>127</sup> and long acting CCBs<sup>31</sup> are the drugs of choice
- Beta-blockers, ACEIs and aldosterone antagonists should be considered in patients with CHD especially in post myocardial infarction and when associated with LV dysfunction
- Beta-blockers need to be cautiously used in patients with peripheral vascular disease. They are contraindicated in patients with severe PVD
- Diuretics, ACEIs, beta-blockers, ARBs and aldosterone antagonists are drugs of choice for heart failure

## 8.6 Hypertension and stroke

Blood pressure is the most consistent and powerful predictor of stroke<sup>136</sup> and high blood pressure is the most important modifiable cause of stroke.<sup>137 (Level III)</sup> BP levels are continuously associated with the risk for stroke.<sup>138-139</sup> Although both SBP and DBP are associated with stroke, SBP is more predictive.<sup>140</sup> In the Asia Pacific region, up to 66 % of strokes can be attributed to hypertension.<sup>141</sup>

Worldwide 15 million people suffer from stroke annually, of these 5.5 million people die and another 5 million are left permanently disabled.<sup>137</sup> In Malaysia, stroke is the fourth leading cause of death in government hospitals in 2005, accounting for 8.19% of all deaths.<sup>142</sup>

### 8.6.1 Primary prevention of stroke

Both observational studies and meta-analyses of randomised control trials have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP in hypertensive patient can lead to a 34% reduction in the risk of stroke.<sup>144-145</sup> The benefits have been shown in both systolic-diastolic hypertension and in isolated systolic hypertension.<sup>138,145-147,6</sup> Beta-blockers, diuretics, CCBs, ACEIs and ARBs have been shown to reduce risk and mortality of stroke.<sup>125,127,145-147,6(LLevel I)</sup> Calcium channel blockers in particular, provided significantly better protection against stroke compared with diuretics and/or beta-blockers in Asian and Caucasian populations.<sup>136, 148-149 (Level I)</sup>

### 8.6.2 Secondary prevention of stroke

In patients who have suffered a cerebrovascular event, BP lowering has been shown to reduce the risk of subsequent strokes.<sup>28,150-151</sup> Combination of an ACEI and diuretic has been shown to reduce stroke recurrence in both normotensive and hypertensive patients when treatment was started at least two weeks after the stroke.<sup>28 (Level I)</sup> The morbidity and mortality from further strokes were also shown to be significantly lower in patients receiving ARBs compared to CCBs for the same level of BP control.<sup>152 (Level I)</sup>

### 8.6.3 Treatment of hypertension in acute stroke

Treatment of elevated BP in acute stroke is still controversial.<sup>153</sup> In general, it is best to avoid lowering BP in the first few days after a stroke unless there is evidence of accelerated hypertension or patients presenting concurrently with hypertensive emergencies.<sup>154 (Level III)</sup>

### Recommendations

- Lowering blood pressure is the key to both primary and secondary prevention of stroke
- In acute stroke, lowering BP is best avoided in the first few days unless hypertensive emergencies co-exist
- In primary prevention, a CCB-based therapy is preferred
- In secondary prevention, the benefits of BP lowering is seen in both normotensive and hypertensive patients
- ACEI- or ARB- based treatment is preferred in secondary prevention

## 8.7 Hypertension in the elderly

The definition of hypertension in the elderly is the same as the general adult population.

Hypertension in the elderly (i.e., above age 65) is an increasingly important public health concern as our population ages. Hypertension further magnifies the risk for cardiovascular disease in the elderly compared with younger populations. Systolic BP, unlike DBP, increases linearly with age leading to an increase of isolated systolic hypertension in elderly. Systolic BP is a better predictor of cardiovascular events than DBP especially in the elderly.<sup>154</sup>

Recently it has also become clear that a widened pulse pressure (SBP minus DBP) of >40 mm Hg, suggesting increased stiffness in large arteries, may be an even better marker of increased cardiovascular risk than either SBP or DBP alone.<sup>155-156,2</sup> The prevalence of hypertension in the elderly in Malaysia has been reported to be 62.4% of which 55% is isolated systolic hypertension.<sup>157</sup>

Several randomized controlled trials have shown that treatment of hypertension in the elderly up to the age of 84 years reduces cardiovascular morbidity and mortality, particularly stroke.<sup>6,36,50,55,124,136,147-149,157-158,163-165</sup> For those above the age of 85 years, the results of ongoing trials are awaited.<sup>163</sup>

### 8.7.1 Detection and evaluation

Recommendations for BP measurements in the elderly patients are similar to those for the general population. Postural hypotension, i.e. a drop in systolic BP of >20 mmHg upon standing, is a common problem in the elderly. Blood pressure should therefore be measured in both the seated/supine and standing positions. If there is a significant postural drop, the standing BP is used to guide treatment decisions.

Evaluation of elderly patients with hypertension should not differ from that of younger adult populations. Particular attention should be paid to detect atheromatous renal artery disease as the cause of secondary hypertension.

### 8.7.2 Treatment

The goals of treatment in older patients should be the same as in younger patients.<sup>149</sup> (Level I) In those patients with marked systolic hypertension and not tolerating treatment well, reducing SBP to below 160 mmHg initially is acceptable. Subsequently, attempts should be made to reduce BP to target levels.<sup>154</sup> (Level III)

#### Non-pharmacological management

Attempts at lifestyle modifications while beneficial may not be practical in the elderly. However weight loss and modest salt reduction may be especially effective in the elderly because of their greater sensitivity to sodium intake.<sup>36</sup> (Level I)

#### Pharmacological management

The five major classes of drugs (diuretics,  $\beta$ -blockers, CCBs, ACEIs and ARBs) have been shown to reduce cardiovascular events in the elderly.<sup>6,50,53,124,149,164</sup> (Level I) In older patients with isolated systolic hypertension, diuretics are preferred because they have been shown to significantly reduce multiple endpoints.<sup>9</sup> Several trials using dihydropyridine CCBs have shown benefits particularly in stroke reduction.<sup>147,148-149,136</sup> Angiotensin converting enzyme inhibitors are the drugs of choice for those with concomitant left ventricular systolic dysfunction, post myocardial infarction or diabetes mellitus.<sup>165</sup> (Level I) Angiotensin receptor blockers have also been shown to reduce fatal and non-fatal strokes in hypertensive patients aged 65 years or older.<sup>124</sup>

The starting dose in older patients should be at the lowest available. Drugs that exaggerate postural changes in BP (peripheral adrenergic-blockers, alpha-blockers and high dose diuretics) or drugs that cause cognitive dysfunction (central alpha-2-agonists) should be used with caution.

### 8.7.3 Special considerations

In the treatment of hypertension in the elderly, certain considerations should be taken into account. The elderly tends to be on many other concomitant medications. They are also more vulnerable to side effects and treatment therefore should follow the adage “start low and go slow”. In order to maximise compliance, the drug regime should be as simple as possible.<sup>124</sup>

#### Recommendations

- Isolated Systolic hypertension is particularly common in the elderly and should be recognized and treated
- Standing BP should be measured to detect postural hypotension
- Decreasing dietary salt intake is particularly useful
- When prescribing drugs, remember to start low and go slow

## 8.8 Hypertension in pregnancy

### 8.8.1 Definition

#### *Hypertension*

Hypertension in Pregnancy is defined as a systolic blood pressure (BP)  $\geq 140$  mm Hg and/or a diastolic BP  $\geq 90$  mmHg.<sup>166</sup>

An increase of 15 mmHg and 30 mmHg diastolic and systolic BP levels above baseline BP is no longer recognized as hypertension if absolute values are below 140/90 mmHg. Nevertheless, this warrants close observation, especially if proteinuria and hyperuricaemia are also present.<sup>167-168</sup>

Korotkoff V should now be used as the cut-off point for diastolic BP, and Korotkoff IV utilized only when Korotkoff V is absent.<sup>166</sup> (Level III) Measurement of BP is similar to that of the general population, as stated earlier.

#### *Proteinuria*

Significant proteinuria in pregnancy is defined as  $\geq 300$  mg protein in a 24 hour urine sample, or a spot urine protein-creatinine ratio  $\geq 30$  mg/mmol<sup>166</sup>. If the dipstick is the only test available, 1+ (30 mg/dl) is often, but not always, associated with  $\geq 300$  mg/day proteinuria.<sup>166</sup> Significant proteinuria reflects advanced disease, associated with poorer prognosis.

### 8.8.2 Classification

There are various classifications for Hypertension in Pregnancy. The most recent is by the Australasian Society for the Study of Hypertension in Pregnancy (ASSHP) and endorsed by the International Society for the Study of Hypertension in Pregnancy (ISSHP).<sup>166-167</sup>

1. Preeclampsia-eclampsia: clinically diagnosed in the presence of de novo hypertension after gestational week 20, and one or more of the following:
  - i. Significant proteinuria.
  - ii. Renal insufficiency: serum creatinine  $\geq 90$   $\mu$ mol/l or oliguria.
  - iii. Liver disease: raised transaminases and/or severe right upper quadrant or epigastric pain.
  - iv. Neurological problems: convulsions (eclampsia), hyperreflexia with clonus or severe headaches, persistent visual disturbances (scotoma).
  - v. Haematological disturbances: thrombocytopenia, coagulopathy, haemolysis.
  - vi. Fetal growth restriction.

This is followed by normalisation of the BP by three months postpartum.

Oedema is no longer part of the definition of preeclampsia.<sup>169</sup> Either excessive weight gain or failure to gain weight in pregnancy may herald the onset of preeclampsia.<sup>170</sup>

2. Gestational hypertension: hypertension alone, detected for the first time after 20 weeks pregnancy. The definition is changed to “transient” when pressure normalizes postpartum.
3. Chronic hypertension: hypertension diagnosed prior to gestational week 20; or presence of hypertension preconception, or *de novo* hypertension in late gestation that fails to resolve postpartum.
4. Preeclampsia superimposed on chronic hypertension: This can be diagnosed by the appearance of any of the following in a woman with chronic hypertension:
  - i) *De novo* proteinuria after gestational week 20
  - ii) A sudden increase in the severity of hypertension
  - iii) Appearance of features of preeclampsia-eclampsia, and
  - iv) A sudden increase in proteinuria in women who have pre-existing proteinuria early in gestation

### 8.8.3 Key points in primary care practice

Although women with hypertensive disorders of pregnancy should be managed by an obstetrician, the primary care physician plays an important role in preventing, detecting, monitoring and managing preeclampsia and its complications to a certain extent, both during the preconceptional and antenatal periods:

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

Women with chronic hypertension may require a change in the type of antihypertensive agent used pre-pregnancy.<sup>171 (Level III)</sup> The drugs of choice in pregnancy are still methyldopa and labetalol (Table 13). Atenolol has been shown to lead to fetal growth restriction. The use of ARBs & ACEIs is contraindicated in pregnancy.

In pregnancy, BP tends to drop in early pregnancy and is at its lowest mid-pregnancy. Subsequently it rises gradually to pre-pregnancy levels at term.<sup>172</sup> There is inadequate evidence for or against continuing antihypertensive treatment in women with chronic hypertension when their BP drops naturally in pregnancy.<sup>173</sup>

It should be noted that the treatment of hypertension in pregnancy is solely for maternal safety. It does not reduce the risk of development of preeclampsia or perinatal mortality, nor improve fetal growth.<sup>171</sup>

#### 2. Recognition of women at high risk of preeclampsia and referral in early pregnancy for screening and prophylaxis.

This includes women with

- a. existing chronic medical disorders such as obesity, hypertension, diabetes mellitus, renal disease, connective tissue disease and thrombophilia,
- b. previous history of preeclampsia or eclampsia or intrauterine growth restriction (IUGR) or unexplained stillbirth

- c. family history of preeclampsia or eclampsia, and
- d. extremes of reproductive age (below 20 or above 40 years old)

They should be referred for specialist assessment and management before 16 weeks of pregnancy.<sup>8</sup> Specialist management will include doppler ultrasonography and aspirin pharmacoprophylaxis.<sup>177,178 (Level I)</sup>

#### 3. Nutritional supplementation for prevention of preeclampsia and/or its complications.

High calcium supplementation of 1.5 g/day significantly reduces the risk of eclampsia, severe gestational hypertension, and severe preeclamptic complication index in pregnant women with low dietary calcium intake (less than 600 mg/day).<sup>177</sup> Other supplements in pregnancy such as marine oil, garlic and pyridoxine have no proven benefits.<sup>178-180</sup>

Combined vitamins C and E (in the form of tocopherol from soybean) should be avoided as they appear to adversely affect high risk pregnancies rather than confer any benefit.<sup>181</sup> They increase the incidence of low birth weight significantly without any preventive effect against preeclampsia.

#### 4. Prevention of eclampsia and other complications of preeclampsia

Patient education with regard to disease symptomatology, and medical staff awareness of symptoms and signs of severe disease are important. Early diagnosis and referral to an obstetrician for further management may prevent progression to eclampsia.<sup>182-183 (Level II-2)</sup>

### 8.8.4 Severe preeclampsia

Severe preeclampsia must be promptly identified so that the patient can be urgently admitted to hospital for close observation and timely delivery. The Royal College of Obstetrician and Gynecology (RCOG) defines severe preeclampsia as follows<sup>184</sup>

1. Systolic BP  $\geq 170$  mmHg or diastolic BP  $\geq 110$  mmHg (acute hypertensive crisis in pregnancy) on two occasions, with proteinuria of  $\geq 1$  g/day.
2. Diastolic BP  $\geq 100$  mmHg on two occasions, with significant proteinuria (1+ on dipstick), with two or more signs or symptoms of imminent eclampsia, which include
  - a. severe headache
  - b. visual disturbance
  - c. epigastric pain and/or vomiting
  - d. clonus
  - e. papilloedema
  - f. liver tenderness
  - g. platelet count below 100,000/cmm
  - h. abnormal liver enzymes (elevated ALT or AST)
  - i. HELLP syndrome (haemolysis, elevated liver enzymes, low platelets)
  - j. intrauterine growth restriction (IUGR)
  - k. pulmonary oedema and / or congestive cardiac failure.

In diagnosing severe preeclampsia, caution should be exercised in relying on overly precise criteria. Diagnosis should err on the side of caution.

In the event of an acute hypertensive crisis, IV hydralazine (2.5-5 mg bolus, or infusion) or IV labetalol (10-20 mg slow bolus over 5 minutes, or infusion), or oral nifedipine (10 mg stat dose), may be used to lower the BP.<sup>185-186 (Level I)</sup> Sublingual nifedipine is no longer recommended.<sup>184 (Level III)</sup>

Diuretics are, in general, contraindicated as they reduce plasma volume, may cause IUGR and may possibly increase perinatal mortality. Their only use is in the treatment of acute pulmonary oedema.<sup>170 (Level III)</sup>

Anti-hypertensive treatment should be initiated if diastolic BP is persistently  $\geq 100$  mmHg. The aim is a diastolic BP not lower than 90 mmHg so as not to compromise placental blood flow.

### 8.8.5 Anticonvulsants in preeclampsia-eclampsia

Parenteral magnesium sulphate is currently the drug of choice for the prevention of eclampsia and to abort an eclamptic fit.<sup>187-188 (Level I)</sup> The alternative is intravenous diazepam (intravenous bolus 10 mg slowly over 10-15 minutes followed by infusion), bearing in mind that it is inferior in efficacy compared to magnesium sulphate.

### 8.8.6 Postpartum care

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

*De novo* onset of hypertension or aggravation of BP levels during the postpartum period, can occur.<sup>189</sup> These patients should be promptly referred to hospital especially if there is significant proteinuria.<sup>(Level III)</sup> Eclampsia may occur in the postpartum period.

Chronic hypertension is diagnosed when the hypertension and/or proteinuria fails to disappear within three months postpartum.<sup>166-167</sup>

#### Long Term Follow-up

Evidence suggests that up to 13% of women with preeclampsia will have underlying essential hypertension that was not suspected antenatally.<sup>184</sup> In addition, the same factors that predispose to preeclampsia also predispose to cardiovascular disease in later life.<sup>173</sup> Long-term follow-up of patients with a history of hypertension in pregnancy is therefore advisable.<sup>(Level III)</sup>

**Table 13. Antihypertensive drugs commonly used in pregnancy.**

Drug	Remarks
Methyldopa	Oral 250 mg tds, doubling every 48 hours (up to 1 gm tds) until BP well controlled. Oldest antihypertensive agent used in pregnancy, with best safety profile.
Labetalol	Oral 100 mg bd, doubling every 48 hours (up to 400 mg bd) until BP well controlled. IV bolus or infusion in acute hypertensive crisis. May cause fetal bradycardia.
Nifedipine	Oral 10 mg tds, up to 20 mg tds, usually as second line antihypertensive, when BP poorly controlled despite maximum doses of methyldopa $\pm$ labetalol. Oral 10 mg stat can also be used in acute hypertensive crisis, especially prior to transferring a patient from a peripheral clinic to hospital.
Hydralazine*	IV infusion (or IM 6.25 mg to 12.5 mg stat in postpartum women) in acute hypertensive crisis.

\* The dose quoted is for dihydralazine (Nepresol®), which is no longer available in Malaysia.

#### Recommendations

- Diagnosis and treatment is based on Korotkoff V as DBP
- Pregnant women who are at high risk of developing preeclampsia should be referred to the obstetrician for screening and commencement of prophylaxis with aspirin
- Prophylactic calcium supplementation from early pregnancy is beneficial and recommended
- Pregnant women with hypertension should be referred to the obstetrician for further management
- The antihypertensives of choice are methyldopa and labetalol
- Oral nifedipine 10mg stat dose can be used to rapidly control BP in an acute hypertensive crisis prior to transfer to hospital

### 8.9 Hypertension and oral contraceptives

The incidence of hypertension is reported to be higher in women taking combined oral contraceptives (COC), especially in obese and older women.<sup>190</sup> The mechanism by which the BP rises is unknown. A woman who develops hypertension while using COC should be advised to stop taking them and should be offered alternative forms of contraception.<sup>191 (Level III)</sup> Progesterone Only Pills<sup>191</sup> and low dose COC<sup>192</sup> are not known to raise BP nor increase the risk of myocardial infarction.<sup>193</sup> They are recommended alternatives for patients with hypertension or those who develop hypertension and yet wish to continue oral contraception. A prudent approach to the use of oral contraception would be to measure baseline BP before initiating treatment. Blood pressure should be reviewed regularly, at least every six months.<sup>(Level III)</sup>

### 8.10 Hypertension and hormone replacement therapy

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

The Women's Health Initiative (WHI) trial involving 98,705 women aged 50-79 years, concluded that the use of HRT increased cardiovascular events.<sup>194-195</sup> Conjugated equine estrogen (CEE), alone or in combination with medroxyprogesterone acetate, was used in the study. In view of this, greater caution and closer monitoring is required for hypertensive patients on CEE.<sup>196 (Level III)</sup>

### 8.11 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 of individuals.<sup>197-198</sup>

The definition of hypertension in children and adolescents is based on age, gender and height. Hypertension is defined as average systolic or diastolic BP >95th percentile for age, gender and height percentiles on at least 3 separate occasions.

The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents has provided normative tables of BP based on age and gender adjusted for height percentiles from the National Centre for Health Statistics (NCHS) growth chart (Appendix 4).<sup>199</sup> This is to allow for a more precise classification of BP and avoids mislabelling children who are either too tall or too short.

Measurement of BP in children follows the same principles as set out in the section on BP measurement. Special attention needs to be paid in the selection of an appropriate cuff size in relation to the child's right upper arm.

To assist clinicians in the further evaluation and management of hypertensive children and adolescents, hypertension in this group has been arbitrarily divided into normal, prehypertension (previously classified as high normal), stage 1 and stage 2 hypertension. (Table 14)

**Table 14. Classification of hypertension in children and adolescents with measurement frequency and recommended therapy<sup>200</sup>**

	SBP or DBP percentile	Frequency of BP measurement	Pharmacologic therapy*
Normal	<90th	No data available	-
Prehypertension	90th to <95th or if BP >120/80 even if <90th percentile up to 95th percentile	Recheck 6 months	None unless compelling indications, e.g. CKD, DM, heart failure
Stage 1 hypertension	95th to 99th percentile plus 5 mmHg	Recheck in 1-2 week, sooner if symptomatic, refer within 1 month	Secondary or symptomatic hypertension, TOD or failed non-pharmacologic measures
Stage 2 hypertension	>99th percentile plus 5 mmHg	Immediately if symptomatic; refer within a week	Initiate therapy

\* nonpharmacologic measures recommended in all prehypertensives and hypertensive children.

A patient with BP levels >95th percentile in a doctor's office but who is normotensive outside a clinical setting has "white-coat hypertension" and may need referral for ambulatory BP monitoring.

Identifiable causes of hypertension particularly of renal parenchymal and renovascular origin account for about 80-90 % of hypertension in children <10 years of age. Once a child is diagnosed with hypertension, he should be referred to a paediatrician for further evaluation and management.<sup>(Level III)</sup>

Non-pharmacologic management particularly weight reduction in those who are obese is recommended in all children with hypertension as well as those with BP in the 90th to 95th percentile.<sup>198 (Level III)</sup> The recommendations for drug therapy in children are similar as for adults, with children requiring more careful dose adjustment. The goal of pharmacologic therapy is to reduce BP to lower than 95th percentile in uncomplicated primary hypertension and <90th percentile for children with TOD, CKD and diabetes mellitus.<sup>199 (Level III)</sup>

## 9. PHARMACOECONOMICS

The public impact and economic burden of hypertension extend far beyond that related to treating high blood pressure. Hypertension pharmacotherapy should not be judged by the direct cost of the drug alone. For example, ARB reduced stroke by 25% as compared to a beta-blocker in patients with hypertension and LVH. This corresponded to a reduction in the cost per patient directly related to stroke of €1141 (approximately RM5,000).<sup>200</sup>

In Malaysia, 33% of persons aged 30 years and above were hypertensive<sup>201</sup> and about RM145 million was spent on antihypertensive medicines alone in year 2004.<sup>202</sup> In 2005, there were 37,580 hypertension-related admissions to government hospitals.<sup>203</sup> The cost per admission of managing hypertension was RM2,927 for those without comorbidity and complications, RM4,248 for hypertension with comorbidity and complications, and RM4,716 for hypertension with major comorbidity and complications.<sup>204</sup> This amounts to at least RM110 million spent on managing hypertensive patients admitted to hospitals. The above figures are an underestimation. They do not include the many admissions due to heart failure, myocardial infarction and renal failure where hypertension was the underlyingly cause.

There were 17,909 admissions for stroke to government hospitals in 2005. The cost of treating stroke without complications is RM3,420, with minor complications is RM4,276, and with major complications, is RM6,129 per patient per admission.<sup>4</sup> The total cost of managing stroke in government for the year 2005 is estimated to be at least RM76 million.

Hypertension is the second most common primary cause (7%) of ESRD in 2005<sup>205</sup>, amounting to 185 cases for that year. The cost of dialysis in a MOH facility was approximately RM26,000 per patient per year<sup>206</sup>, amounting to RM5 million in 2005. Importantly, secondary hypertension is very common in CKD and is an important factor in the progression of renal disease. Up to 90% of patients entering dialysis have associated hypertension.

Treating hypertension reduced strokes approximately 40%, myocardial infarction by 25%, fewer CKD deaths and non fatal MI.<sup>207</sup> Efforts should be focused on increasing public awareness, choice of cost effective treatment and patient drug compliance. This should translate to better rates of hypertension control and reduction in the total cost of managing its sequelae.

### Recommendations

- Hypertension pharmacotherapy should not be judged by the direct cost of the drug alone
- Public education should include information on cost effectiveness and drug compliance

## 10. TYPES OF ANTIHYPERTENSIVE AGENTS

All stated drug dosages are referenced from MIMS 108th edition 2007<sup>47</sup> unless otherwise indicated.

### 10.1 Diuretics

The use of diuretics is well established in the treatment of hypertension. Thiazide diuretics are especially cheap and are one of the most widely used antihypertensive agents. When used in patients with essential hypertension and relatively normal renal function, thiazides are more potent than loop diuretics. However, in patients with renal insufficiency (serum creatinine 200 mcmol/L or higher), thiazides are less effective and loop diuretics should be used instead.<sup>209-210</sup>

Diuretics may be used as initial therapy. They also enhance the efficacy of other classes of antihypertensive drugs when used in combination.<sup>211-213</sup>

In the elderly with no co-morbid conditions, diuretics are the drugs of choice in the treatment of systolic-diastolic hypertension and isolated systolic hypertension. Diuretics not only reduce the incidence of fatal and non-fatal strokes but also cardiovascular morbidity and mortality.<sup>50,54,158,160-161,214</sup>

Diuretics should be used with care in patients with gout as they may precipitate an acute attack. Potassium-sparing diuretics may cause hyperkalaemia if given together with ACEIs or ARBs or in patients with underlying renal insufficiency. Aldosterone antagonists and potassium-sparing diuretics should be avoided in patients with serum potassium >5.0 mmol/L.<sup>215</sup>

Adverse effects are uncommon, unless high doses are used. These include increased serum cholesterol, glucose and uric acid; decreased potassium, sodium and magnesium levels and erectile dysfunction. Serum electrolytes, in particular potassium, should be closely monitored.<sup>215-218</sup>

Table 15. Diuretics commonly used for the treatment of hypertension in Malaysia

Diuretics	Starting Dose	Maximum Daily Dose
Chlorothiazide	250 mg od	500 mg od
Hydrochlorothiazide	25 mg od	200 mg od
Chlorthalidone	50 mg od	200 mg od
Amiloride/hydrochlorothiazide 5 mg/50 mg	1 tablet od	4 tablet od
Indapamide SR	1.5 mg od	1.5 mg od
Indapamide	2.5 mg od	2.5 mg od
Triamterene/hydrochlorothiazide 50 mg/25 mg	1 tablet bd	2 tablets bd

## 10.2 Beta-blockers

Beta-blockers have long been established in the treatment of hypertension. They are particularly useful in hypertensive patients with effort angina, tachyarrhythmias or previous myocardial infarction where they have been shown to reduce cardiovascular morbidity and mortality. Certain beta-blockers such as bisoprolol and long-acting metoprolol have been shown to be beneficial in patients with heart failure.

Beta-blockers are contraindicated in patients with obstructive airways disease, severe peripheral vascular disease and heart block (2nd and 3rd degree).

They are generally well tolerated. Adverse effects reported include dyslipidaemia, masking of hypoglycaemia, increased incidence of new onset diabetes mellitus, erectile dysfunction, nightmares and cold extremities.

**Table 16. Beta-blockers commonly used for the treatment of hypertension in Malaysia**

$\beta$ -blockers	Starting Dose	Maximum Daily Dose
Acebutolol	200 mg bd	400 mg bd
Atenolol	50 mg od	100 mg od
Betaxolol	10 mg od	40 mg od
Bisoprolol	5 mg od	10 mg od
Metoprolol	50 mg bd	200 mg bd
Propranolol	40 mg bd	320 mg bd

However, with the advent of newer antihypertensive agents with better efficacy and better safety profile, concern has been voiced over their widespread use in the treatment of hypertension.<sup>219-21</sup> The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study is a major landmark trial contributing to this reassessment of the use of beta-blockers in hypertension<sup>124</sup>. In this study, losartan was shown to provide clear benefit compared to atenolol in the treatment of high risk hypertensive patients with left ventricular hypertrophy. The benefit was also seen in those with higher risks, i.e. hypertensive patients with left ventricular hypertrophy and diabetes mellitus.<sup>221</sup> This prompted a meta-analysis of the use of beta-blockers in the treatment of hypertension.<sup>46</sup> Beta-blocker therapy was associated with a significant 16% higher risk for stroke when compared to non-beta-blocker therapy and that atenolol in particular was associated with a significant 26% increase in the risk of stroke when compared to other antihypertensive agents. Similar profile was also seen by another meta-analysis<sup>222</sup> which also showed that beta-blockers were associated with a significant increase in their withdrawal due to side effects. Conlin et al. documented the steady decrease in persistence of therapy with beta-blockers as compared to other antihypertensive agents.<sup>223</sup> National Institute for Clinical Excellence (NICE) Guideline<sup>12</sup> in 2006 had placed beta-blockers at Step 4 in their recommendation of antihypertensive therapy. It is therefore recommended that beta-blockers should not be the initial therapy for patients with hypertension who do not have compelling indications for beta-blockade.

## 10.3 Calcium channel blockers (CCBs)

Long-acting CCBs have been shown to be safe and effective in lowering blood pressure, both as first-line agents and in combination with other classes of antihypertensive drugs.<sup>148,225</sup> There are three major classes of CCBs (phenylalkylamines, dihydropyridines and benzothiazepines) with different characteristics and all are effective in lowering BP. With few exceptions, they have no undesirable metabolic effects and their safety profile in hypertension is good. Dihydropyridine CCBs are particularly effective in reducing isolated systolic hypertension.<sup>145-147,215</sup> They are also effective in reducing cerebrovascular events by 10% compared with other active therapies.<sup>228</sup>

Short acting CCBs are no longer recommended and should be phased out. The use of sublingual nifedipine is also discouraged.

Long acting CCBs may also be useful in treating hypertensives with coronary heart disease.<sup>54,227</sup>

Adverse effects include initial tachycardia, headache, flushing, constipation and ankle oedema. Unlike other CCBs, Verapamil may reduce heart rate and care should be exercised when used with beta-blockers.

**Table 17. CCBs commonly used for the treatment of hypertension in Malaysia**

CCBs	Starting Dose	Maximum Daily Dose
Amlodipine	5 mg od	10 mg od
Diltiazem	30 mg tds	60 mg tds
Diltiazem SR	90 mg bd	90 mg bd
Diltiazem R	100-200 mg od	100-200 mg od
Felodipine	2.5 mg od	10 mg od
Isradipine	1.5 mg bd	2.5 mg bd
Lacidipine	2 mg od	6 mg od
Lercanidipine	10 mg od	20 mg od
Nicardipine	10 mg tds	20 mg tds
Nifedipine	10 mg tds	30 mg tds
Nifedipine SR	30 mg od	120 mg od
Verapamil	80 mg bd	240 mg tds
Verapamil CR	200 mg od	200 mg bd

## 10.4 ACE inhibitors

Angiotensin-converting enzyme inhibitors (ACEIs) are generally well tolerated and do not have adverse effects on lipid and glucose metabolism. Their safety profile is good. ACEIs have been shown to reduce mortality and morbidity in patients with congestive heart failure.<sup>229-230</sup> and in post myocardial infarction patients with reduced left ventricular ejection fraction.<sup>29,231-234</sup> In patients at increased cardiovascular risk, ACEIs are been shown to reduce morbidity and mortality.

In the diabetic patient, ACEIs have been shown to reduce cardiovascular mortality.<sup>29,231</sup> In addition, they have been shown to prevent the onset of microalbuminuria, reduce proteinuria and retard the progression of renal disease. ACEIs have also been shown to reduce proteinuria and retard progression of non-diabetic renal disease.

In patients with established vascular disease but normal left ventricular function, ACEIs reduce mortality, myocardial infarction, stroke and new-onset congestive heart failure.<sup>29,30</sup> These benefits are independent of their effects on left ventricular function and blood pressure.

Adverse effects include cough and, rarely, angioedema. In patients with renovascular disease or renal impairment, deterioration in renal function may occur. Serum creatinine should be checked before initiation and repeated within one to two weeks after initiation. Any increase should be confirmed immediately and monitored. If there is a rise of serum creatinine of more than 30% from baseline within two months, ACEIs should be stopped.

ACEIs may increase foetal and neonatal mortality and therefore are contraindicated in pregnancy, and should be avoided in those planning pregnancy.

**Table 18. ACEIs commonly used for the treatment of hypertension in Malaysia**

ACEIs	Starting Daily Dose	Maximum Daily Dose
Captopril	25 mg bd	50 mg tds
Enalapril	2.5 mg od	20 mg bd
Fosinopril	10 mg od	40 mg od
Lisinopril	5 mg od	80 mg od
Perindopril	2 mg od	8 mg od
Quinapril	2.5 mg od	40 mg bd
Ramipril	2.5 mg od	10 mg od
Imidapril	2.5 mg od	10 mg od

### 10.5 Angiotensin receptor blockers (ARBs)

ARBs are drugs specifically blocked angiotensin II receptor. Unlike ACEIs, persistent dry cough is less of a problem. As such ARBs are recommended in ACEI intolerance patients. As with ACEIs, they are contraindicated in pregnancy and bilateral renal artery stenosis.

ARBs are effective in preventing progression of diabetic nephropathy<sup>76,86,235</sup> and may reduce the incidence of major cardiac events in patients with heart failure<sup>235-236</sup> hypertensive LVH<sup>124</sup> and diastolic heart failure.<sup>126</sup>

The Blood Pressure Lowering Treatment Trialist Collaboration (BPLTTC) in a meta-analysis of 21 randomised trial<sup>1236</sup> found that there were no clear differences between ACE inhibitors and ARBs for the outcomes of stroke and heart failure.

**Table 19. ARBs commonly used for the treatment of hypertension in Malaysia**

ARBs	Starting Dose	Maximum Daily Dose
Candesartan	8 mg od	16 mg od
Irbesartan	150 mg od	300 mg od
Losartan	50 mg od	100 mg od
Telmisartan	20 mg od	80 mg od
Valsartan	80 mg od	160 mg od
Olmesartan	20 mg od	40 mg od

### 10.6 Miscellaneous drugs

#### 10.6.1 The $\alpha$ -blockers and the combined $\alpha$ , $\beta$ -blockers

The peripheral  $\alpha_1$ -adrenergic blockers lower BP by reducing peripheral resistance. They also reduce prostatic and urethral smooth muscle tone and provide symptomatic relief for patients with early benign prostatic hypertrophy (BPH). They should be the logical choice for hypertensive patients with BPH. The use of non-specific  $\alpha$ -adrenergic blockers like phentolamine and phenoxybenzamine has been restricted to the treatment of pheochromocytoma.

Alpha 1-adrenergic blockers have favourable effects on lipid metabolism. However postural hypotension is a known side effect, especially at initiation of therapy.<sup>239-240</sup>

Combined  $\alpha$ ,  $\beta$ -blockers offer enhanced neurohormonal blockade. Labetalol has been in use for over 20 years and is safe in pregnancy (Section 8.8). The intravenous formulation is useful in hypertensive emergencies, including pre-eclampsia and eclampsia.<sup>241</sup>

Carvedilol has been shown to be effective in hypertension and also to improve mortality and morbidity in patients with heart failure.<sup>242-245</sup> In addition, it has no adverse effects on insulin resistance and lipid metabolism.<sup>246</sup> However, its safety in pregnancy has not been established.

**Table 20.  $\alpha$ -blockers**

$\alpha$ -blockers	Starting Dose	Maximum Daily Dose
Doxazosin	1 mg od	16 mg od
Prazosin	0.5 mg bd	10 mg bd
Terazosin	1 mg od	5 mg od

**Table 21.  $\alpha$ ,  $\beta$ -blockers**

$\alpha$ , $\beta$ -blockers	Starting Dose	Maximum Daily Dose
Labetalol®	100 mg bd	800 mg tds
Carvedilol	12.5 mg od	50 mg od

® In the elderly, start with 50 mg bd

### 10.6.2 Centrally acting agents

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

Methyldopa has been in use for many years. It is the drug of choice for hypertension in pregnancy. It may be considered for resistant hypertension in combination with other classes of antihypertensive agents.<sup>247</sup>

Clonidine should NOT be withdrawn suddenly because rebound hypertension may occur.<sup>247</sup> The use of clonidine is discouraged because safer and more potent drugs are available.

Moxonidine is an orally active imidazoline I1 receptors agonist. It acts centrally to reduce peripheral sympathetic activity, thus decreasing peripheral vascular resistance. It can be used as monotherapy in patients with mild to moderate hypertension or in combination with other antihypertensive agents. Studies have suggested that it may improve the metabolic profile of patients with impaired glucose tolerance or diabetes.<sup>249-250</sup> Rebound hypertension does not occur on cessation of the drug. Absorption is rapid and unaffected by food.<sup>251</sup>

Table 22. Centrally-acting agents

Centrally-acting agents	Starting Dose	Maximum Daily Dose
Methyldopa*	125 mg bd	1 g bd
Clonidine <sup>†</sup>	50 mcg tds	400 mcg tds
Moxonidine <sup>†</sup>	0.2 mg od	0.3 mg bd

\* For dosage in pregnancy, refer to page 35.

<sup>†</sup> Referenced from British National Formulary (BNF), Sept 2007<sup>208</sup>

### 10.6.3 Direct vasodilators

The direct vasodilators include hydralazine and minoxidil. Hydralazine is only available in parenteral formulation for hypertensive emergencies (Sections 7.1.3 and 8.8). Minoxidil is used for refractory hypertension. The usefulness of this class of drugs is limited by their side-effects including headache, compensatory tachycardia and salt and water retention. Hirsutism is a troublesome effect with long-term use of minoxidil. It should only be prescribed by doctors familiar with their usage.

Table 23. Direct vasodilators

Direct vasodilator	Starting Dose	Maximum Daily Dose
Minoxidil	5 mg od	50 mg od

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## APPENDIX 1

List of British Hypertension Society-validated electronic BP sets commonly available in Malaysia for clinical use and home/self assessment

Device/Grade	Cuff sizes (cm)	Weight (g)	Dimensions (l x w x h, mm)	Number/type of batteries
Microlife BP-3AG1 Last reading memory	Standard adult (22-32, included) Large adult (32-42)	365	130 x 105 x 52	4 x AA 1.5v included. Mains adaptor available
Microlife 3BT0-A	Standard adult (22-32, included) Large adult (32-42)	430	180 x 114 x 75	4 x AA 1.5v included. Mains adaptor available
Microlife BP A100 Pulse arrhythmia detection. Last reading memory	Standard adult (22-32, included) Large adult (32-42)	525	152 x 125 x 95	4 x AA 1.5v included. Mains adaptor available
Microlife BP 3AC1-1 60 reading memory capacity	Standard adult (22-32, included) Large adult (32-42)	510	170 x 118 x 88	4 x AA 1.5v included. Mains adaptor available
Microlife BPA 100 Plus Derivative of 3BT0-A. Automatic averaging of 3 readings, arrhythmia detection, 99 reading memory capacity.	Standard adult (22-32, included) Large adult (32-42)	565	152 x 140 x 95	4 x AA 1.5v included. Mains adaptor available
Omron T9P (HEM-759P)	Small adult (17-22) Standard adult (22-32) Large adult (32-42)	380	177 x 115 x 71	4 x AA Battery
Omron M5 (HEM-742)	Small adult (17-22) Standard adult (22-32, included) Large adult (32-42). NB Cuff depth on Small is 11cm, Standard is 15cm and Large is 17.5 cm. The Standard and Large cuffs are deeper than average.	380	177 x 135 x 112	4 x AA Battery
Omron T5/T5-M (HEM-762/752)	Small adult (17-22) Standard adult (22-32, supplied) Large adult (32-42)	420	126 x 198 x 102	4 x AA Battery
Omron IA1 (HEM-7000)	Small adult (17-22) Standard adult (22-32, supplied) Large adult (32-42)	355	152 x 122 x 79	4 x AA Battery
Omron IA1B (HEM-7000C1L)	One-Size Cuff fits 22-42	350	131 x 155 x 84	4 x AA Battery or AC/DC adaptor
Omron HEM-907 (HEM-907)	Small adult (17-22) Standard adult (22-32) Large adult (32-42)	910	203 x 139 x 131	AC Adaptor (with battery pack)

## APPENDIX 2

Cockcroft-Gault Formula

$$\text{Creatinine Clearance} = \frac{[140 - \text{Age (years)}] \times \text{Weight (kg)}}{(\text{ml/min}/1.73\text{m}^2) \times 0.812 \times \text{s. creatinine (mcmol/L)}}$$

## APPENDIX 3

Antihypertensive drugs currently available in Malaysia

<p><b>Diuretics</b> Amiloride-Hydrochlorothiazide Bumetanide Chlorothiazide Chlorthalidone Frusemide Hydrochlorothiazide Indapamide Spironolactone Triamterene-Hydrochlorothiazide</p>	<p><b>Combined alpha/beta-blockers</b> Carvedilol Labetalo</p>
<p><b>Beta-blockers</b> Acebutolol Atenolol Betaxolol Bisoprolol Esmolol Metoprolol Nadolol Nebivolo Oxprenolol Pindolol Propranolol Sotalol Timolol</p>	<p><b>Direct vasodilators</b> Hydralazine Minoxidil Nitroglycerin Sodium Nitroprusside</p>
	<p><b>ACE inhibitors</b> Captopril Enalapril Fosinopril Imidapril Lisinopril Perindopril Quinapril Ramipril</p>
	<p><b>Alpha-blockers</b> Alfuzosin Doxazosin Prazosin Terazosin</p>
<p><b>Calcium channel blockers</b> Amlodipine Diltiazem Felodipine Isradipine Lacidipine Lercanidipinel Nicardipine Nifedipine Verapamil</p>	<p><b>Angiotensin receptor blockers</b> Candesartan Irbesartan Losartan Olmesartan Telmisartan Valsartan</p>
<p><b>Centrally acting drugs</b> Alpha-methyldopa Clonidine Moxonidine</p>	<p><b>Fixed-dose combination drugs</b> Atenolol/chlorthalidone Candesartan/hydrochlorothiazide Irbesartan/hydrochlorothiazide Losartan/hydrochlorothiazide Metoprolol/chlorthalidone Oxprenolol/chlorthalidone Perindopril/indapamide Pindolol/clopamide Valsartan/hydrochlorothiazide Telmisartan/hydrochlorothiazide</p>

## APPENDIX 4

### Normative tables of BP based on age and sex adjusted for height percentiles

#### BP Levels for Boys by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg								DBP, mm Hg							
		Percentile of Height								Percentile of Height							
		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>	99 <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>	99 <sup>th</sup>
1	50 <sup>th</sup>	80	81	83	85	87	88	89	34	35	36	37	38	39	39		
	90 <sup>th</sup>	94	95	97	99	100	102	103	49	50	51	52	53	53	54		
	95 <sup>th</sup>	98	99	101	103	104	106	106	54	54	55	56	57	58	58		
	99 <sup>th</sup>	105	106	108	110	112	113	114	61	62	63	64	65	66	66		
2	50 <sup>th</sup>	84	85	87	88	90	90	92	39	40	41	42	43	44	44		
	90 <sup>th</sup>	97	99	100	102	104	105	106	54	55	56	57	58	58	59		
	95 <sup>th</sup>	101	102	104	106	108	109	110	59	59	60	61	62	63	63		
	99 <sup>th</sup>	109	110	111	113	115	117	117	66	67	68	69	70	71	71		
3	50 <sup>th</sup>	86	87	89	91	93	94	95	44	44	45	46	47	48	48		
	90 <sup>th</sup>	100	101	103	105	107	108	109	59	59	60	61	62	63	63		
	95 <sup>th</sup>	104	105	107	109	110	112	113	63	63	64	65	66	67	67		
	99 <sup>th</sup>	111	112	114	116	118	119	120	71	71	72	73	74	75	75		
4	50 <sup>th</sup>	88	89	91	93	95	96	97	47	48	49	50	51	51	52		
	90 <sup>th</sup>	102	103	105	107	109	110	111	62	63	64	65	66	66	67		
	95 <sup>th</sup>	106	107	109	111	112	114	115	66	67	68	69	70	71	71		
	99 <sup>th</sup>	113	114	116	118	120	121	122	74	75	76	77	78	78	79		
5	50 <sup>th</sup>	90	91	93	95	96	98	98	50	51	52	53	54	55	55		
	90 <sup>th</sup>	104	105	106	108	110	111	112	65	66	67	68	69	69	70		
	95 <sup>th</sup>	108	109	110	112	114	115	116	69	70	71	72	73	74	74		
	99 <sup>th</sup>	115	116	118	120	121	123	123	77	78	79	80	81	81	82		
6	50 <sup>th</sup>	91	92	94	96	98	99	100	53	53	54	55	56	57	57		
	90 <sup>th</sup>	105	106	108	110	111	113	113	68	68	69	70	71	72	72		
	95 <sup>th</sup>	109	110	112	114	115	117	117	72	72	73	74	75	76	76		
	99 <sup>th</sup>	116	117	119	121	123	124	125	80	80	81	82	83	84	84		
7	50 <sup>th</sup>	92	94	95	97	99	100	101	55	55	56	57	58	59	59		
	90 <sup>th</sup>	106	107	109	111	113	114	115	70	70	71	72	73	74	74		
	95 <sup>th</sup>	110	111	113	115	117	118	119	74	74	75	76	77	78	78		
	99 <sup>th</sup>	117	118	120	122	124	125	126	82	82	83	84	85	86	86		
8	50 <sup>th</sup>	94	95	97	99	100	102	102	56	57	58	59	60	60	61		
	90 <sup>th</sup>	107	109	110	112	114	115	116	71	72	72	73	74	75	76		
	95 <sup>th</sup>	111	112	114	116	118	119	120	75	76	77	78	79	79	80		
	99 <sup>th</sup>	119	120	122	123	125	127	127	83	84	85	86	87	87	88		
9	50 <sup>th</sup>	95	96	98	100	102	103	104	57	58	59	60	61	61	62		
	90 <sup>th</sup>	109	110	112	114	115	117	118	72	73	74	75	76	76	77		
	95 <sup>th</sup>	113	114	116	118	119	121	121	76	77	78	79	80	81	81		
	99 <sup>th</sup>	120	121	123	125	127	128	129	84	85	86	87	88	88	89		
10	50 <sup>th</sup>	97	98	100	102	103	105	106	58	59	60	61	61	62	63		
	90 <sup>th</sup>	111	112	114	115	117	119	119	73	73	74	75	76	77	78		
	95 <sup>th</sup>	115	116	117	119	121	122	123	77	78	79	80	81	81	82		
	99 <sup>th</sup>	122	123	125	127	128	130	130	85	86	86	88	88	89	90		

Age, y	BP Percentile	SBP, mm Hg								DBP, mm Hg							
		Percentile of Height								Percentile of Height							
		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>	99 <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>	99 <sup>th</sup>
11	50 <sup>th</sup>	99	100	102	104	105	107	107	59	59	60	61	62	63	63		
	90 <sup>th</sup>	113	114	115	117	119	120	121	74	74	75	76	77	78	78		
	95 <sup>th</sup>	117	118	119	121	123	124	125	78	78	79	80	81	82	82		
	99 <sup>th</sup>	124	125	127	129	130	132	132	86	86	87	88	89	90	90		
12	50 <sup>th</sup>	101	102	104	106	108	109	110	59	60	61	62	63	63	64		
	90 <sup>th</sup>	115	116	118	120	121	123	123	74	75	75	76	77	78	79		
	95 <sup>th</sup>	119	120	122	123	125	127	127	78	79	80	81	82	82	83		
	99 <sup>th</sup>	126	127	129	131	133	134	135	86	87	88	89	90	90	91		
13	50 <sup>th</sup>	104	105	106	108	110	111	112	60	60	61	62	63	64	64		
	90 <sup>th</sup>	117	118	120	122	124	125	126	75	75	76	77	78	79	79		
	95 <sup>th</sup>	121	122	124	126	128	129	130	79	79	80	81	82	83	83		
	99 <sup>th</sup>	128	130	131	133	135	136	137	87	87	88	89	90	91	91		
14	50 <sup>th</sup>	106	107	109	111	113	114	115	60	61	62	63	64	65	65		
	90 <sup>th</sup>	120	121	123	125	126	128	128	75	76	77	78	79	79	80		
	95 <sup>th</sup>	124	125	127	128	130	132	132	80	80	81	82	84	84	84		
	99 <sup>th</sup>	131	132	134	136	138	139	140	87	88	89	90	92	92	92		
15	50 <sup>th</sup>	109	110	112	113	115	117	117	61	62	63	64	65	66	66		
	90 <sup>th</sup>	122	124	125	127	129	130	131	76	77	78	79	80	80	81		
	95 <sup>th</sup>	126	127	129	131	133	134	135	81	81	82	83	84	85	85		
	99 <sup>th</sup>	134	135	136	138	140	142	142	88	89	90	91	92	93	93		
16	50 <sup>th</sup>	111	112	114	116	118	119	120	63	63	64	65	66	67	67		
	90 <sup>th</sup>	125	126	128	130	131	133	133	78	78	79	80	81	82	82		
	95 <sup>th</sup>	129	130	132	134	135	137	137	82	83	83	84	85	86	87		
	99 <sup>th</sup>	136	137	139	141	143	144	145	90	90	91	92	93	94	94		
17	50 <sup>th</sup>	114	115	116	118	120	121	122	65	66	66	67	68	69	70		
	90 <sup>th</sup>	127	128	130	132	134	135	136	80	80	81	82	83	84	84		
	95 <sup>th</sup>	131	132	134	136	138	139	140	84	85	86	87	87	88	89		
	99 <sup>th</sup>	139	140	141	143	145	146	147	92	93	93	94	95	96	97		

BP Levels for Girls by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg								DBP, mm Hg							
		Percentile of Height								Percentile of Height							
		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	50 <sup>th</sup>	83	84	85	86	88	89	90	38	39	39	40	41	41	42		
	90 <sup>th</sup>	97	97	98	100	101	102	103	52	53	54	54	55	55	56		
	95 <sup>th</sup>	100	101	102	104	105	106	107	56	57	58	58	59	59	60		
	99 <sup>th</sup>	108	108	109	111	112	113	114	64	64	65	65	66	67	67		
2	50 <sup>th</sup>	85	85	87	88	89	91	91	43	44	44	45	46	46	47		
	90 <sup>th</sup>	98	99	100	101	103	104	105	57	58	58	59	60	61	61		
	95 <sup>th</sup>	102	103	104	105	107	108	109	61	62	62	63	64	65	65		
	99 <sup>th</sup>	109	110	111	112	114	115	116	69	69	70	70	71	72	72		
3	50 <sup>th</sup>	86	87	88	89	91	92	93	47	48	48	49	50	50	51		
	90 <sup>th</sup>	100	100	102	103	104	106	106	61	62	62	63	64	64	65		
	95 <sup>th</sup>	104	104	105	107	108	109	110	65	66	66	67	68	68	69		
	99 <sup>th</sup>	111	111	113	114	115	116	117	73	73	74	74	75	76	75		
4	50 <sup>th</sup>	88	88	90	91	92	94	94	50	50	51	52	52	53	54		
	90 <sup>th</sup>	101	102	103	104	106	107	108	64	64	65	66	67	67	68		
	95 <sup>th</sup>	105	106	107	108	110	111	112	68	68	69	70	71	71	72		
	99 <sup>th</sup>	112	113	114	115	117	118	119	76	76	76	77	78	79	79		
5	50 <sup>th</sup>	89	90	91	93	94	95	96	52	53	53	54	55	55	56		
	90 <sup>th</sup>	103	103	105	106	107	109	109	66	67	67	68	69	69	70		
	95 <sup>th</sup>	107	107	108	110	111	113	113	70	71	71	72	73	73	74		
	99 <sup>th</sup>	114	114	116	117	118	120	120	78	78	79	79	80	81	81		
6	50 <sup>th</sup>	91	92	93	94	96	97	98	54	54	55	56	56	57	58		
	90 <sup>th</sup>	104	105	106	108	109	110	111	68	68	69	70	70	71	72		
	95 <sup>th</sup>	108	109	110	111	113	114	115	72	72	73	74	74	75	76		
	99 <sup>th</sup>	115	116	117	119	120	121	122	80	80	80	81	82	83	83		
7	50 <sup>th</sup>	93	93	95	96	97	99	99	55	56	56	57	58	58	59		
	90 <sup>th</sup>	106	107	108	109	111	112	113	69	70	70	71	72	72	73		
	95 <sup>th</sup>	110	111	112	113	115	116	116	73	74	74	75	76	76	77		
	99 <sup>th</sup>	117	118	119	120	122	123	124	81	81	82	82	83	84	84		
8	50 <sup>th</sup>	95	95	96	98	99	100	101	57	57	57	58	59	60	60		
	90 <sup>th</sup>	108	109	110	111	113	114	114	71	71	71	72	73	74	74		
	95 <sup>th</sup>	112	112	114	115	116	118	118	75	75	75	76	77	78	78		
	99 <sup>th</sup>	119	120	121	122	123	125	125	82	82	83	83	84	85	86		
9	50 <sup>th</sup>	96	97	98	100	101	102	103	58	58	58	59	60	61	61		
	90 <sup>th</sup>	110	110	112	113	114	116	116	72	72	72	73	74	75	75		
	95 <sup>th</sup>	114	114	115	117	118	119	120	76	76	76	77	78	79	79		
	99 <sup>th</sup>	121	121	123	124	125	127	127	83	83	84	84	85	86	87		
10	50 <sup>th</sup>	98	99	100	102	103	104	105	59	59	59	60	61	62	62		
	90 <sup>th</sup>	112	112	114	115	116	118	118	73	73	73	74	75	76	76		
	95 <sup>th</sup>	116	116	117	119	120	121	122	77	77	77	78	79	80	80		
	99 <sup>th</sup>	123	123	125	126	127	129	129	84	84	85	86	86	87	88		

Age, y	BP Percentile	SBP, mm Hg								DBP, mm Hg							
		Percentile of Height								Percentile of Height							
		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>		
11	50 <sup>th</sup>	100	101	102	103	105	106	107	60	60	60	61	62	63	63		
	90 <sup>th</sup>	114	114	116	117	118	119	120	74	74	74	75	76	77	77		
	95 <sup>th</sup>	118	118	119	121	122	123	124	78	78	78	79	80	81	81		
	99 <sup>th</sup>	125	125	126	128	129	130	131	85	85	86	87	87	88	89		
12	50 <sup>th</sup>	102	103	104	105	107	108	109	61	61	61	62	63	64	64		
	90 <sup>th</sup>	116	116	117	119	120	121	122	75	75	75	76	77	78	78		
	95 <sup>th</sup>	119	120	121	123	124	125	126	79	79	79	80	81	82	82		
	99 <sup>th</sup>	127	127	128	130	131	132	133	86	86	87	88	88	89	90		
13	50 <sup>th</sup>	104	105	106	107	109	110	110	62	62	62	63	64	65	65		
	90 <sup>th</sup>	117	118	119	121	122	123	124	76	76	76	77	78	79	79		
	95 <sup>th</sup>	121	122	123	124	126	127	128	80	80	80	81	82	83	83		
	99 <sup>th</sup>	128	129	130	132	133	134	135	87	87	88	89	89	90	91		
14	50 <sup>th</sup>	106	106	107	109	110	111	112	63	63	63	64	65	66	66		
	90 <sup>th</sup>	119	120	121	122	124	125	125	77	77	77	78	79	80	80		
	95 <sup>th</sup>	123	123	125	126	127	129	129	81	81	81	82	83	84	84		
	99 <sup>th</sup>	130	131	132	133	135	136	136	88	88	89	90	90	91	92		
15	50 <sup>th</sup>	107	108	109	110	111	113	113	64	64	64	65	66	67	67		
	90 <sup>th</sup>	120	121	122	123	125	126	127	78	78	78	79	80	81	81		
	95 <sup>th</sup>	124	125	126	127	129	130	131	82	82	82	83	84	85	85		
	99 <sup>th</sup>	131	132	133	134	136	137	138	89	89	90	91	91	92	93		
16	50 <sup>th</sup>	108	108	110	111	112	114	114	64	64	65	66	66	67	68		
	90 <sup>th</sup>	121	122	123	124	126	127	128	78	78	79	80	81	81	82		
	95 <sup>th</sup>	125	126	127	128	130	131	132	82	82	83	84	85	85	86		
	99 <sup>th</sup>	132	133	134	135	137	138	139	90	90	90	91	92	93	93		
17	50 <sup>th</sup>	108	109	110	111	113	114	115	64	65	65	66	67	67	68		
	90 <sup>th</sup>	122	122	123	125	126	127	128	78	79	79	80	81	81	82		
	95 <sup>th</sup>	125	126	127	129	130	131	132	82	83	83	84	85	85	86		
	99 <sup>th</sup>	133	133	134	136	137	138	147	90	90	91	91	92	93	93		

Source: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents<sup>2</sup>

## LIST OF ABBREVIATIONS

ABPM	ambulatory blood pressure monitoring
ACEI	angiotensin-converting enzyme inhibitor
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
BP	blood pressure
BPH	benign prostate hypertrophy
CCB	calcium channel blocker
CEE	conjugated equine estrogen
CHD	coronary heart disease
CAD	coronary artery disease
CKD	chronic kidney disease
COC	combined oral contraceptive
CVA	cerebral vascular accident
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
ECG	electrocardiogram/electrocardiography
ESRD	end-stage renal disease
FBS	fasting blood sugar
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HRT	hormone replacement therapy
LDL	low-density lipoprotein
LV	left ventricle
LVH	left ventricular hypertrophy
MI	myocardial infarction
NSAID	non-steroidal anti-inflammatory drug
PVD	peripheral vascular disease
RF	risk factor
SBP	systolic blood pressure
TG	triglycerides
TOC	target organ complication
TOD	target organ damage

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The panel members have completed disclosure forms. None of them holds shares in pharmaceutical firms or acts as consultants to such firms. (Details are available upon request from the CPG secretariat.)

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## KEY TO EVIDENCE STATEMENTS

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

*SOURCE: U.S./CANADIAN PREVENTIVE SERVICES TASK FORCE*

## GRADES OF RECOMMENDATIONS

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

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