CLINICAL PRACTICE GUIDELINES

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Management of Hypertension

(4th Edition)

Malaysian Society of Hypertension

Ministry of Health Malaysia

Academy of Medicine of Malaysia

STATEMENT OF INTENT

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

REVIEW OF THE GUIDELINES

This guideline was issued in 2013 and will be reviewed in 2018 or earlier if important new evidence becomes available.

This is an update to the Clinical Practice Guideline on Management of Hypertension – 3rd Edition (published 2008) and supersedes the previous.

Electronic version will be made available on the following websites:

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

DISCLOSURE STATEMENT

The panel members had completed disclosure forms. None held shares in pharmaceutical firms or acted as consultants to such firms (details are available upon request from the CPG Secretariat).

SOURCES OF FUNDING

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KEY MESSAGES

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

2. The prevalence of hypertension in Malaysians aged 18 years and above was 32.7% and for aged 30 years and above was 43.5% in 2011.

3. Hypertension is a silent disease; the majority of cases (61%) 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 pre-hypertension.

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

8. In patients with newly diagnosed uncomplicated hypertension and no compelling indications, choice of first line monotherapy includes ACEIs, ARBs, CCBs, diuretics and beta blockers. Beta blockers is now recommended based on evidence from newer meta analyses since the last edition.

9. Only 35% 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 in patients with stage II hypertension and in high risk stage I hypertension.

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

12. Renal sympathetic denervation is a treatment option for selected patients with resistant hypertension.

FOREWORD

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

In 2010 the Ministry of Health launched the National Strategic Plan for Non Communicable Diseases. Diseases of the heart and circulatory system (Cardiovascular diseases or CVD) dominates the national health landscape being the number 1 cause of morbidity and mortality for the last few decades and is projected to do so for the next few. Of all the risk factors contributing to CVD, hypertension confer the greatest disease burden. It is thus pertinent that all health care providers directly or indirectly involved with CVD knows what is latest in the management of hypertension.

I will like to record my utmost appreciation to all the members of the Working Group on Hypertension for their tireless effort in coming up with this latest edition of the Hypertension Clinical Practice Guideline (CPG). This is the fourth in the series since it was first launched in 1998. This reflects the rapid evolution of knowledge in hypertension driven by major outcome trials for which there were a few since the last edition 5 years ago. The results of the National Health Morbidity Survey of 2011 (NHMS 2011) were also instrumental in the drafting of this latest guideline. There are also important local studies quoted which is a testimony of the growing research interest on the topic nationally. I am happy to report that in some of the landmark multicentre clinical trials quoted, Malaysian researchers were actively involved. A special thanks to the Health Technology Assessment Unit of the Ministry of Health Malaysia for ensuring that the development of this CPG conforms to the high standards it had laid down.

Although the NHMS 2011 showed some improvement in important key indicators on hypertension, there is still a lot of scope for betterment. It is hoped that this latest edition of the Hypertension CPG will continue to play an important role in controlling this major CVD risk factor. It is the hope of the Working Group that the release of this new edition will be followed by concerted effort by the various stakeholders to make it implementable on the ground. By so doing, we will have contributed in a significant way to combat the scourge of CVD particularly pre mature CVD. If that happens, this CPG will have served its purpose, God Willing.

Yours Sincerely

Abdul Rashid Abdul Rahman
Chairman
Working Group on Hypertension CPG 2013

RATIONALE AND PROCESS OF GUIDELINES DEVELOPMENT

RATIONALE

The Clinical Practice Guideline on the Management of Hypertension was developed to provide a clear and concise approach to all health care providers on the current concepts in the management of hypertension. Since hypertension is managed by various levels of health care providers in Malaysia, attempts were made to ensure the different stakeholders will benefit from this CPG. This is reflected by the representation of the committee members which developed the guideline. There were three previous guidelines on hypertension; in 1998, 2002 and 2008.This edition is the fourth in the series and was deemed necessary due to new evidence which has emerged since the last edition. Prior to the publication of this edition, the National Health and Morbidity Survey 2011 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.

GUIDELINE DEVELOPMENT PROCESS

The current edition of the CPG was initiated by the Malaysian Society of Hypertension. The guideline was developed in 2012/2013. A committee was convened, comprising 4 nephrologists, 4 cardiologists, 3 family physicians, 2 obstetrician/gynaecologists, an endocrinologist, a neurologist, a general physician/ clinical pharmacologist, a paediatrician, an epidemiologist and a pharmacist. 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. Literature search was carried out at the following electronic databases: International Health Technology Assessment website, PUBMED, MEDLINE, Cochcrane Database of Systemic Reviews (CDSR), Journal full text via OVID search engine and Science Direct. The chapters were developed based on relevant clinical questions frequently asked by practitioners. The chapters were divided among the workgroup members based on their respective expertise. Literature searched were appraised by workgroup members using the Critical Appraisal Skills Programme (CASP) checklist. All statements and recommendations formulated were agreed upon by the workgroup members. Where there was insufficient evidence, the

recommendations were derived by consensus of the workgroup. Most evidence quoted especially for treatment recommendation is based on major clinical outcome trials irrespective of their year of publications. Many of these are seminal and landmark studies which has stood the test of time.

The articles quoted were graded by using the US/Canada Preventive Services Task Force level of evidence while the grading of recommendations was modified from the Scottish Intercollegiate Guideline Network (SIGN) as shown on page vi and vii below.

The guideline will be posted on the Ministry of Health Malaysia, Academy of Medicine Malaysia and the Malaysian Society of Hypertension 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 anti-hypertensive prescription for newly diagnosed cases of hypertension
2. Rate of blood pressure control among patients who are treated with anti-hypertensive drugs

Definition of control:

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

Numerator:

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

Denominator:

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

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

LEVEL OF EVIDENCE

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

Source: US/Canada Preventive Services Task Force

GRADES OF RECOMMENDATION

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

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

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

HYPERTENSION GUIDELINE WORKING GROUP

CHAIRPERSON

Dr. Abdul Rashid Abdul Rahman
Professor of Medicine & Clinical Pharmacology and Senior Consultant Physician
Cyberjaya University College of Medical Sciences and An Nur Specialist Hospital
Selangor

WORKGROUP MEMBERS

Dr. Sunita Bavanandan Consultant Nephrologist Kuala Lumpur Hospital Kuala Lumpur	**Dr. Hj. Azhari Rosman** Consultant Cardiologist & Electrophysiologist National Heart Institute Kuala Lumpur
Dr. Chia Yook Chin Professor of Primary Care Medicine and Senior Consultant Primary Care Physician University Malaya Medical Centre Kuala Lumpur	**Dr. Chua Chin Teong** Director of Medical Services and Consultant Nephrologist Ramsay Sime Darby Health Care Selangor
Dr. Ghazali Ahmad Consultant Nephrologist and Head of Department Department of Nephrology Kuala Lumpur Hospital Kuala Lumpur	**Dr. Faridah Aryani Md. Yusof** Senior Principal Assistant Director Pharmaceutical Services Division Ministry of Health (Jalan Universiti) Petaling Jaya
Dr. Khoo Ee Ming Professor of Primary Care Medicine and Senior Consultant Primary Care Physician University Malaya Medical Centre Kuala Lumpur	**Dr. Khoo Kah Lin** Consultant Cardiologist Pantai Medical Centre Kuala Lumpur
Dr. Khalid Yusoff Vice Chancellor Professor of Medicine and Senior Consultant Cardiologist UCSI University, Kuala Lumpur	**Dr. Yap Piang Kian** Consultant Physician & Endocrinologist Sime Darby Medical Centre Selangor
Dr. Robaayah Zambahari Managing Director Chief Executive Officer and Senior Consultant Cardiologist National Heart Institute Kuala Lumpur	**Dr Mimi Omar** Family Medicine Specialist Klinik Kesihatan Kelana Jaya Kelana Jaya Selangor

Dr. Zaleha Abdullah Mahdy Professor and Senior Consultant Obstetrician & Gynaecologist Pusat Perubataan Universiti Kebangsaan Malaysia Kuala Lumpur	**Dr. Yau Weng Keong** Consultant Geriatrician Kuala Lumpur Hospital Kuala Lumpur
Dr. Hj. Md. Hanip Rafi Consultant Neurologist and Head of Department Department of Neurology Kuala Lumpur Hospital Kuala Lumpur	**Dr. Feisul Idzwan Mustapha** Public Health Specialist Cardiovascular Diseases & Diabetes Unit Non-Communicable Disease Section Disease Control Division Ministry of Health, Putrajaya
Dr. Wan Jazilah Wan Ismail Consultant Paeditric Nephrologist and Head of Department Department of Paediatric Hospital Selayang Selangor	

EXTERNAL REVIEWERS

Dr. J Ravichandran Jeganathan Consultant Obstetrician & Gynaecologist & Head of Department Department of Obstetrics & Gynaecology Hospital Sultanah Aminah Johor	**Dr. Ho Bee Kiau** Family Medicine Specialist Klinik Kesihatan Kapar Klang
Dr. Husni Hussain Family Medicine Specialist Klinik Kesihatan Putrajaya Putrajaya	**Prof. Dr. Wan Azman Bin Wan Ahmad** Consultant Cardiologist University Malaya Medical Centre Kuala Lumpur
Assoc. Prof. Goh Lee Gan Department of Family Medicine National University Hospital Singapore	**Dr. Adina Abdullah** Primary Care Lecturer Primary Care Clinic (RUKA) University Malaya Medical Centre Kuala Lumpur
Prof. Dr. Hj Hamidon Basri Consultant Neurologist Universiti Putra Malaysia Serdang Selangor	**Prof. Brian Tomlinson** Professor of Medicine and Therapeutics and Honorary Consultant Physician Chinese University of Hong Kong Hong Kong SAR
Prof. Tariq Abdul Razak Dean Professor of Clinical Pharmacology Kulliyah of Medicine International Islamic University Kuantan, Pahang	

SUMMARY OF RECOMMENDATIONS

Issues	Recommendations	Grade
Measurement of Blood Pressure	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 is not recommended 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
Diagnosis and Assessment	Recommendations for follow-up is based on initial BP measurements.	C
Pre-hypertension	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.	C
Non-Pharmacological Management		
BMI or weight	As far as possible, aim for an ideal Body Mass Index [Weight (kg)/Height^2(m)] – for Asians, the normal range has been proposed to be 18.5 to 23.5 kg/m^2. However a weight loss as little as 4.5kg or 5% of baseline weight can significantly reduces BP.	C
Salt intake	An intake of <100 mmol of sodium or 6g of sodium chloride a day is recommended (equivalent to <11/4 teaspoonfuls of salt or 3 teaspoonfuls of monosodium glutamate).	A
Alcohol	Patients with hypertension should refrain from alcohol intake. For those who want to consume 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 1/2 a pint of beer or 100ml of wine or 20 ml 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 5 times a week.	A
Diet	A diet rich in fruits, vegetables and dairy products with reduced saturated and total fat can substantially lower BP (11/6mmHg 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
Pharmacological Management	**Figure 1** (page 17) outlines the management of a patient with hypertension.	C
Management of Severe Hypertension		
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 160/90mmHg.	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
Hypertension and Diabetes Mellitus	Pharmacological treatment should be initiated in patients with diabetes when the BP is persistently >140 mmHg systolic and/or >80 mmHg diastolic.	A
	SBP should be targeted to<140 and DBP <80 mmHg	A
	BP of <130/80 mmHg is recommended for younger patients without systemic complications.	C
	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
	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 maybe considered if either ACEIs or ARBs cannot be used.	A

Hypertension and Non-Diabetic Renal Disease	The combination of ACEIs and ARBs has been proven to reduce proteinuria more than monotherapy with either agent in non-diabetic renal disease. This combination should only be initiated by a nephrologist.	A
	If there is a persistent rise of serum creatinine of 30% from baseline over a two month period, 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 µmol/L, thiazide diuretics may not be effective anti-hypertensive 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 "add-on" therapy as they have an additional antiproteinuric effect.	A
Hypertension and Cardiovascular Disease	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
Hypertension and Stroke	Blood pressure is the most consistent and powerful predictor of stroke and is also the most important modifiable cause from stroke.	A
	Beta-blockers, diuretics, CCBs, ACEIs and ARBs have been shown to reduce the risk and mortality from stroke.	A
	Calcium channel blockers in particular, provided significantly better primary 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 Ischaemic 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
	In acute haemorrhagic stroke , recent evidence suggest that lowering SBP< 140mmHg is safe.	B
Hypertension in the elderly and the very elderly	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 160mmHg initially is acceptable. Subsequently, attempts should be made to reduce BP to target levels.	C

	In the very elderly (>80 years old) who can tolerate treatment, a target of <150 mmHg/90 mmHg is acceptable.	A
	Weight loss and modest salt reduction maybe especially effective in the elderly because of their greater sensitivity to sodium intake.	A
	The five major classes of drugs (diuretics, b-blockers, CCBs, ACEIs and ARBs) have been shown to reduce cardiovascular events in the elderly.	A
	In the very elderly, thiazide-like diuretics based treatment with or without ACEIs reduced not only stroke but also total mortality.	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
	Standing BP should be measured to detect postural hypotension.	C
Hypertension and Pregnancy	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 hydrallazine (2.5-5 mg bolus or infusion)or IV labetalol (10-20 mg slow bolus over 5 minutes or infusion), or oral nifedipine (10mg stat dose), may be used to lower the BP.	A
	Sublingual nifedipine is no longer recommended.	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
Hypertension and Oral Contraceptives	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

Hypertension and Hormone Replacement Therapy	All women treated with HRT should have their BP monitored every six months. Greater caution and closer monitoring is required for hypertensive patients on conjugated equine estrogen (CEE).	C C
Hypertension in Children and Adolescents	Once a child is diagnosed with hypertension, he should be referred to a paediatrician for further evaluation and management. Non-pharmacologic management particularly weightreduction in those who are obese is recommended in all children with hypertension as well as those with BP in the 90th to 95th percentile. 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 C C
Pharmaco-economics	Treating hypertension to target is very cost effective. 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.	B C
Resistant Hypertension	Patient whose BP did not reach target despite taking 3 drugs (including a diuretics) are by definition having resistant hypertension Medication non-compliance and possible secondary hypertension must be considered. Patients with eligible criteria may be considered for renal denervation.	C C C
Antiplatelet and Antilipid therapy	All hypertensive for secondary prevention must receive antiplatelet and antilipid therapy Antiplatelet for primary prevention is recommended for patient with higher baseline BP but BP must be treated to target before starting antiplatelet Statin should be intiated for primary prevention in patients with mildly elevated cholesterol (LDL-C >2.6mmol/L in high risk, >3.4mmol/L in medium risk patient)	A B A

TABLE OF CONTENTS

LIST OF TABLES & FIGURE

1.0 DEFINITION, CLASSIFICATION AND TYPES 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.

Hypertension is an increasingly important medical and public health issue. The National Health and Morbidity Survey (NHMS) 2011 has shown that the prevalence of hypertension in Malaysia for adults ≥18 years has increased from 32.2% in 2006 to 32.7% in 2011. For those >30 years old, the prevalence has increased from 42.6% to 43.5% Unfortunately, 60.6% of total hypertensive were "undiagnosed".[1] Hence BP should be measured at every opportunity.

No significant difference between gender was observed. In terms of the main ethnic groups, the Bumiputera from Sabah & Sarawak have the highest prevalence at 36.4%, followed by the Malays at 34.0%, Chinese at 32.3% and lastly the Indians at 30.6%.[1]

An analysis of NHMS 3 (2006) data has shown that 63% of Malaysians had at least one cardiovascular risk factor, 33% had two risk factors and 14% had three or more risk factors. Hypertension remains the number one risk factor with a prevalence rate of 42.6% in adults above 30 years of age, followed by central obesity (37%), hypercholesterolaemia (24%) and hyperglycaemia (15%).[2]

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

Table 1. Classification and Prevalence of Elevated Blood Pressure for Adults Age ≥18 years in Malaysia (NHMS 3, 2006)[3]

Classification*	SBP (mmHg)	DBP (mmHg)	Prevalence in Malaysia[3]
Optimal	<120 and	<80	32%
Normal	<130 and	<85	20%
High Normal	130 – 139 and/or	85 – 89	17%
Hypertension			
Stage I	140 – 159 and/or	90 – 99	20%
Stage II	160 – 179 and/or	100 – 109	8%
Stage III	≥180 and/or	≥110	4%

** Adapted from JNC VI*

- Hypertension is defined as persistent elevation of systolic BP of 140 mmHg or greater and/or diastolic BP of 90 mmHg or greater.
- This definition is based on the average of two or more properly measured, seated, BP readings on each of two or more clinic visits. When SBP and DBP fall into different categories, the higher category should be selected to classify the individual's BP.

Isolated Systolic Hypertension
Isolated systolic hypertension (ISH) is defined as SBP of ≥140 mmHg and DBP <90 mmHg. It is common after the age of 50, and carries with it a poor prognosis. Clinical trials have demonstrated that control of ISH reduces total mortality, cardiovascular mortality, stroke and heart failure events.[4,5,6]

Changing patterns of BP occur with increasing age. The rise in SBP continues throughout life in contrast to DBP, which rises until approximately age 50, tends to level off over the next decade, and may remain the same or fall later in life.[7,8] Diastolic hypertension predominates before age 50, either alone or in combination with SBP elevation. The prevalence of systolic hypertension increases with age, and above 50 years of age, systolic hypertension represents the most common form of hypertension. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important.[9]

Isolated Office ("white-coat") Hypertension
Isolated office hypertension is characterised by an elevation in clinic blood pressure but normal home or ambulatory blood-pressure values. In these subjects the clinic BP is persistently above 140/90 mmHg but the home or 24-hour ambulatory systolic/diastolic BP measurements are lower than 130/80 mmHg. It is still debatable whether isolated office hypertension is an innocent phenomenon or whether it carries an increased cardiovascular risk.[10]

Masked Hypertension
Patients with masked hypertension have normal clinic blood pressure but elevated 24-hour ambulatory or home blood-pressure load (≥135/85 mmHg). Prognosis of masked hypertension is worse than isolated office hypertension.[11]

For both isolated office and masked hypertension, once diagnosed, first-line therapeutic interventions should be non-pharmacological and aim at lifestyle changes. However, drug treatment is indicated, particularly when the patient's cardiovascular risk profile is elevated or when target-organ damage (TOD) is detected.[12] (Refer to chapter on **Diagnosis and Assessment**)

2.0 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
- electronic devices
- aneroid sphygmomanometer
- 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 for devices 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 non invasive measurement.[13] (Level III) 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:

a. The key to the reservoir should be turned open
b. The mercury meniscus should be at zero.
c. The calibrated glass tube must be clean – a dirty tube can cause inaccurate readings.
d. 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[13] too small a cuff will give a falsely higher reading and vice versa.
e. 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 beat.[13]
f. 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.[13] 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 under estimation of the SBP.
— The complete disappearance of sound (Korotkoff Phase V) should be taken as the diastolic reading.
— Check BP in both arms in the first consultation. Use the higher reading for making diagnosis.

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.

Blood Pressure should be measured in both arms on the first visit and the higher reading is taken as the systolic BP.[13] At least 3 readings preferably 1-2 minutes apart should be taken in the same arm with the patient in the same position. The first reading should be discarded and the latter two averaged.[13] Blood pressure measurements should not be done on the arm with arterio-venous fistula in haemodialysis patients.

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

The BP should be taken both lying/sitting and at least 1 minute after standing (with arm supported) to detect any postural drop, especially in the elderly and in diabetics.[13] On rising, the BP will transiently rise and then fall. A systolic drop of >20 mmHg after one minute of standing is considered a significant postural drop.[13]

2.2 ELECTRONIC BP SETS

This is now increasingly being used. The best are those validated by a reputable body, e.g., national hypertension societies such as British Hypertension Society (www.bhsoc.org) or American Association for the Advancement of Medical Instrumentation (www.aami.org). A list of validated machines is available from their websites.

These electronic machines are generally less accurate in patients with atrial fibrillation. Diastolic blood pressure also tends to be lower than mercury sphygmomanometer. They should not be used in pregnancy as the BP reading may be underestimated.

The use of home devices that measure the blood pressure in the fingers or the wrists is not recommended.

2.3 HOME BP MEASUREMENT (HBPM) USING ELECTRONIC DEVICES

Home BP measurement is a useful adjunct in the diagnosis and management of hypertension especially in selected patients. If properly performed, it has good prognostic value.[14,15 (Level II-2)]

Systematic review has shown that HBPM is superior compared to office measurements in diagnosing uncontrolled hypertension, assessing antihypertensive treatment, improving patients compliance and provides potential cost saving.[16 (Level I)]

Additionally, some studies have shown that HBPM measurements can be an alternative to ABPM and may have similar prognostic value.[17,18 (Level I)]

Indications for HBPM[19]

- At initial assessment
- To diagnose isolated office hypertension
- To diagnose masked hypertension
- To assess treatment effects
- To diagnose true resistant hypertension
- To improve compliance with long term treatment
- To optimize blood pressure control in high CV risk patients and pregnancy

HBPM Interpretation[19]

- Average BP from several monitoring days (at least 3 days) should be used
- BP values measured on the first monitoring day should be discarded
- Mean home systolic BP >135 mmHg and/or diastolic BP >85 mmHg should be considered as elevated
- Systolic and diastolic home BP <130 and <80 mmHg respectively, should be considered normal

Home BP is generally lower than clinic BP by approximately 10-20 mmHg systolic and 5-10 mmHg diastolic.

Recommendations

BP Measuring Technique

For Clinic BP, patients should be

- seated for at least 5 mins, without smoking, meal, caffeine intake or physical exercise for at least 30 mins
- seated position in a quiet room, back supported, arm supported (for example, resting on the table)
- seated with legs uncrossed, not talking and relaxed
- the correct cuff bladder must be placed at heart level

For home measurements, besides the above ;

- a minimum measurement for 3 days and ideally 7 days should be performed
- should be done at about the same time once in the morning and evening
- morning (before drug intake if treated) and evening (before meal) readings should be taken with two measurements per occasion (1–2 mins apart)
- the results must be immediately recorded in a specific logbook or stored in device memory

2.4 AMBULATORY BLOOD PRESSURE MONITORING (ABPM)

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

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

However the latest NICE Guideline suggests a possible role of ABPM in confirming the diagnosis of hypertension when the clinic blood pressure is 140/90mmHg or higher, in selected patients.[20 (Level III)]

ABPM is useful in selected clinical situations. These include[21 (Level III)]:

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

Recommendations

ABPM Technique

- 15-30 min needed for fitting and setup
- Relax patient in a quiet room
- Enter patient's details into monitor
- Measure BP in both arms
- If SBP difference <20 mmHg and/or DBP difference <10 mmHg, use non-dominant arm
- If SBP difference >20 mmHg and/or DBP difference >10 mmHg, use arm with greater pressure
- Select appropriate cuff
- Select frequency of measure (usually every 15-20 min during day and every 30 min at night, ideally every 15 min over the 24 hours)
- Give patient written instructions and a diary card
- Instruct patient how to remove and inactivate monitor after 24 hour

Table 2. Criteria for Staging Hypertension Based on Clinic, Home and Ambulatory Blood Pressure Monitoring

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

* Adapted from National Institute for Health and Clinical Excellence (NICE) Hypertension, 2011. [Available at: www.nice.org.uk/guidance/CG127 (accessed 8th September 2013)]

3.0 DIAGNOSIS AND ASSESSMENT

Evaluation of patients with documented hypertension has three objectives:

1. To exclude secondary causes of hypertension. (**Table 3**)
2. To ascertain the presence of target organ damage or complication (**Table 4**)
3. To assess lifestyle and identify other cardiovascular risk factors (**Table 5**) or coexisting condition that affect prognosis and guide treatment. (**Table 6**)

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

Table 3. Secondary Causes of Hypertension

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

Table 4. Manifestations of Target Organ Damage (TOD) / Target Organ Complication (TOC)

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

TOD = Target organ damage (LVH, retinopathy, proteinuria)
TOC = Target organ complication (heart failure, renal failure)

A complete history should include:

- duration and level of elevated BP if known
- symptoms of secondary causes of hypertension
- symptoms of target organ complications (i.e. renal failure and heart failure)
- symptoms of cardiovascular disease (e.g. CHD and cerebrovascular disease)
- symptoms of concomitant disease that will affect prognosis or treatment e.g. diabetes mellitus, heart failure, renal disease and gout

- family history of hypertension, CHD, stroke, diabetes, renal disease or dyslipidaemia
- dietary history including salt caffeine, liquorice and alcohol intake
- drug history of either prescribed or over-the-counter medication (NSAIDs, nasal decongestants) and traditional or complementary medicine treatment
- lifestyle and environmental factors that will affect treatment and outcome (e.g. smoking, physical activity, work stress and excessive weight gain since childhood)
- presence of snoring and or day time somnolence which may indicate sleep apnoea

Physical examination should include the following:

- general examination including height, weight and waist circumference
- two or more BP measurements separated by 1-2 minutes with the patient either supine or seated; and after standing for at least one minute
- take standing BP at 2 minutes and again at 5 minutes in the elderly, diabetics and other conditions where postural hypotension is frequent or suspected
- measure BP on both arms
- fundoscopy
- examination for carotid bruit, abdominal bruit, presence of peripheral pulses and radio-femoral delay
- cardiac examination
- abdominal examination for renal masses and bruit, 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)
- Ankle brachial index (where available)

The minimum initial investigations aim to screen for presence of secondary causes of hypertension, determine the presence of CV risk factors, target organ damage (TOD) and target organ complication (TOC). They should include the following:[22] (Level III)

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

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 or TOC (**Table 4**), further tests should be considered.

Table 5. Concomitant Cardiovascular Risk Factors

- Diabetes mellitus
- Dyslipidaemia
- Cigarette smoking
- Central obesity (waist circumference >90 cm for men, >80 cm for women)
- Microalbuminuria/Proteinuria
- Estimated GFR <60 mL/min/m^2
- Age (>55 years for men, >65 years for women)
- Family history of premature cardiovascular disease (men <55 years or women <65 years)
- Physical inactivity (Refer to chapter 5 on **Non-Pharmacological Management**)

According to a study in Malaysia as many as 54% patients with essential hypertension did not have their cardiovascular risks adequately assessed.[23 (Level III)]

Following initial clinical evaluation and investigations, the patient should be risk stratified. **Table 6** stratifies the risk of developing major cardiovascular events, which includes stroke, myocardial infarction and total mortality.

Table 6. Risk Stratification

Co-existing Condition / BP Levels (mmHg)	No RF No TOD No TOC	TOD or RF (1-2) No TOC	TOC or RF(≥3) or Clinical atherosclerosis	Previous MI or Previous stroke or Diabetes
SBP 130 – 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 and/or DBP >110	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 > 6.5mmol/L, family history of premature vascular disease)
Clinical atherosclerosis (CHD, carotid stenosis, peripheral vascular disease, transient ischaemic attack, stroke)

Following initial clinical evaluation, investigations and risk stratification, patients need to be re evaluated at subsequent visits as recommended below.

Table 7. Recommendations for Follow-Up Visit based on Initial Blood Pressure Measurements for Adults

Initial BP (mmHg)			Follow-up recommended to confirm diagnosis
Systolic		Diastolic	
<130	and	<85	Recheck in one year
130 – 139	and	85 – 89	Recheck within 3 – 6 months
40 – 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-VII [24 (Level III)]

4.0 PRE-HYPERTENSION

Pre-hypertension is defined as SBP of 120 to 139 or DBP 80 to 89 mmHg, based on 2 or more seated BP readings on each of 2 or more clinic visits.[24]

The term "pre-hypertension" 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.

Rationale for highlighting this category of BP include:

1. To emphasize the excess cardiovascular risk associated with BP in this range. 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.[25]

2. To increase clinical and public health awareness on the prevention of hypertension.

4.1 EPIDEMIOLOGY OF PRE-HYPERTENSION

In Malaysia, data from the National Health and Morbidity Survey (NHMS III) indicates that 37% of our population has pre-hypertension.[3]

Patients with pre-hypertension are at increased risk for progression to hypertension. In the Framingham study, the high-normal BP group conversion rate was 37% in 4 years.[26] This conversion rate was even higher in the Trial of Preventing Hypertension (TROPHY) study in which over a period of 4 years, stage I hypertension developed in nearly two thirds of patients with untreated pre-hypertension.[27] Predictors of conversion to hypertension include baseline BP, increasing age, obesity and weight gain.

Pre-hypertension tends to cluster with other CVD risk factors such as dyslipidaemia, glucose abnormalities and obesity.[28-30] However, the weight of evidence suggests that pre-hypertension itself is an independent CVD risk factor.[30,31 (Level II-2)]

4.2 MANAGEMENT OF PRE-HYPERTENSION

- Patients should be managed with non-pharmacologic interventions/therapeutic lifestyle modifications to lower BP. (Refer to **Chapter 5**). Major challenges to this approach will be the lack of clinical symptoms, the extremely long latent period before target organ damage becomes clinically apparent as well as psychological and practical barriers (time, cost, etc) to lifestyle modification.

- There should be 6-12 monthly follow-up in patients with pre-hypertension to detect and treat hypertension as early as possible.[24 (Level III)]

- Decision regarding pharmacological treatment should be based on the individual patient's global CV risk. In diabetes mellitus with proteinuria or patients with chronic kidney disease (with proteinuria >1g/day), medical treatment is required if BP is above 130/80.[32-34 (Level I)] This also applies to other high risk subjects such as those with previous CVA or CAD.[35-37 (Level I)]

- All patients with pre-hypertension should have full cardiovascular risk assessment. There is presently inadequate evidence for pharmacological intervention in pre-hypertensive patients at moderate or low total CV risk. Two trials i.e. the Trial of Preventing Hypertension (TROPHY) study[27] and the Prevention of Hypertension with the Angiotensin Converting Enzyme inhibitor Ramipril in Patients with High-normal pressure (PHARAO) study[38] have shown that treatment with either an ARB or an ACEI monotherapy significantly reduce the risk of developing hypertension.

Pre-hypertension is defined as systolic BP 120 to 139 or diastolic BP 80 to 89 mmHg, based on 2 or more seated BP readings on each of 2 or more office visits.

Recommendations

- Non-pharmacological intervention is the mainstay of management. (Grade C)
- Patient at high CV risk may require pharmacological intervention. (Grade A)

5.0 NON-PHARMACOLOGICAL MANAGEMENT

Non-pharmacological management (therapeutic lifestyle modification) plays an important role in the management of hypertension and in improving overall cardiovascular health.[39] However evidence from randomized controlled trials on lifestyle intervention and blood pressure came from small trials with short duration of intervention and poor in quality. In an overview of 98 trials including 7,993 participants, statistically significant reductions in blood pressure were found in the short term for improved diet and exercise, relaxation therapies, sodium and alcohol reduction.[20 (Level I)] When recommending lifestyle modification, it is important to know that these interventions require a concerted effort from both the patient and the doctors.

5.1 WEIGHT REDUCTION

Weight-reducing diets in overweight hypertensive persons can result in modest weight loss in the range of 3-9% of body weight [40 (Level I)] and are associated with blood pressure reduction of about 3-6 mmHg. It is advisable for overweight hypertensive patients to lose at least 5% of their weight.

5.2 SODIUM INTAKE

High salt intake is associated with significantly increased risk of stroke and total cardiovascular disease.[41 (Level I)] Evidence from published systematic review and meta analyses showed that restricting sodium intake in people with elevated blood pressure in the short term leads to reductions in blood pressure of up to 10.5 mmHg systolic and 2 mmHg diastolic.[41-43 (Level I)] 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).[44,45,46 (Level I)]

In society with a high salt intake, such as in Malaysia, salt reduction should be emphasized.[47 (Level III)]

5.3 AVOIDANCE OF ALCOHOL INTAKE

Alcohol consumption elevates BP acutely. For those who consume alcohol, intake should be restricted to no more than 21 units for men and 14 units for women per week (1 unit is equivalent to one half-pint of beer or 100 ml of wine or 20 ml of "proof whisky"). Meta analyses have shown that, interventions to reduce alcohol consumption caused a small but significant reduction (3.3/2 mmHg) in both systolic and diastolic blood respectively.[48 (Level I)] Hypertensives who are heavy drinkers are also 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.[49]

5.4 REGULAR PHYSICAL EXERCISE

Aerobic exercise is more effective than resistance training (e.g., weight lifting).[50] Exercise like walking-jogging can result in a reduction of 13/18 mmHg in SBP/DBP.[51 (Level I)] More recent evidence showed that resistant exercise is effective in lowering blood pressure among normotensives and pre-hypertensives but not among hypertensives.[52] However isometric resistant exercise can reduce BP by 10.4/6.7 mmHg as shown by a recent meta analysis.[53 (Level I)] General advice on cardiovascular health would be for modest exercise, such as brisk walking for a total of at least 150 mins per week.[54,55 (Level I)]

5.5 HEALTHY EATING

A diet rich in fruits, vegetables and low fat dairy products with reduced saturated and total fat can substantially lower BP (11/6 mmHg in hypertensive patients and 4/2 mmHg in patients with high normal BP).[55] (Level I) More recently, diet high in L-Arginine has been shown to be able to reduce BP by 5.4/2.3 mmHg[56] (Level I)

5.6 CESSATION OF SMOKING

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

5.7 RELAXATION THERAPY

Relaxation interventions were shown to be associated with statistically significant reductions in systolic and diastolic blood pressure of about 3 mmHg.[55] However, another systematic review of studies on the effect of stress reduction on blood pressure found small and non-significant effect on blood pressure.[57] (Level I) It is not recommended for routine provision in primary care.

5.8 OTHERS

These include micronutrient alterations, caffeine reduction and dietary supplementation with fish oil, potassium, calcium, magnesium and fibre. However the evidence for its beneficial effect is limited.[58-61] (Level I)

In summary while weight reducing diet, regular exercise, alcohol and salt restriction have been consistently shown to be beneficial in reducing BP in patients, the evidence thus far has not been consistent for relaxation therapies and supplementations with calcium, magnesium or potassium.[62] (Level I)

Recommendations

- Lifestyle modification must be instituted as an integral role in reducing blood pressure (Grade C)
- Patients must be advised to lose weight, do regular exercise, restrict alcohol intake and reduce salt consumption (Grade A)

6.0 PHARMACOLOGICAL MANAGEMENT

6.1 GENERAL GUIDELINES

All patients must be risk stratified to guide management. Decision to initiate pharmacologic treatment depends on the total cardiovascular risk (**Table 6**). It is the reduction of BP which provides the main benefits in the general hypertensive population.[63] (Level I) The choice of drug should be individualized. Appendix 3 shows the drugs currently available in Malaysia.

6.1a Initiating Treatment

For patients with Stage I hypertension with low cardiovascular risk, advice should be given on lifestyle modification for a period of three to six months. The patient should be seen two to three times during this period to assess the efficacy of the above intervention. Stage I patients with medium or higher risk should be offered drug treatment upon diagnosis (**Figure 1**).(Level III)

6.1b Choosing Antihypertensive Drug Treatment

In patients with newly diagnosed uncomplicated hypertension and no compelling indications, choice of first line monotherapy includes ACEIs, ARBs, CCBs and diuretics which have all been shown to reduce cardiovascular morbidity and mortality.[64-68] (Level I) Beta-blockers are not recommended as first line monotherapy in this group of patients according to the one guideline.[20] (Level III) This is mainly based on an earlier meta analysis which showed that it is not as effective in lowering blood pressure and in the prevention of stroke compared to the other anti-hypertensive agents.[69-72] However more recent meta analyses[73,74] including updated versions of earlier meta analysis[75,76] have vindicated beta-blockers even as first line agent. Aside from the NICE guideline and the latest JNC guideline [77] all other guidelines continue to recommend beta-blockers as first line agent even in uncomplicated newly diagnosed hypertension.[22,78,79] However, all guidelines recommend that beta-blockers should be considered in younger patients in particular:

- those with an intolerance or contraindication to ACE inhibitors and angiotensin receptor blockers 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 and co-morbidities (**Table 8**). Contraindications to the use of these drugs must also be considered.

In patients with stage I hypertension, treatment should be started with monotherapy at low dose. Monotherapy can lower BP to <140/90 mmHg in approximately 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

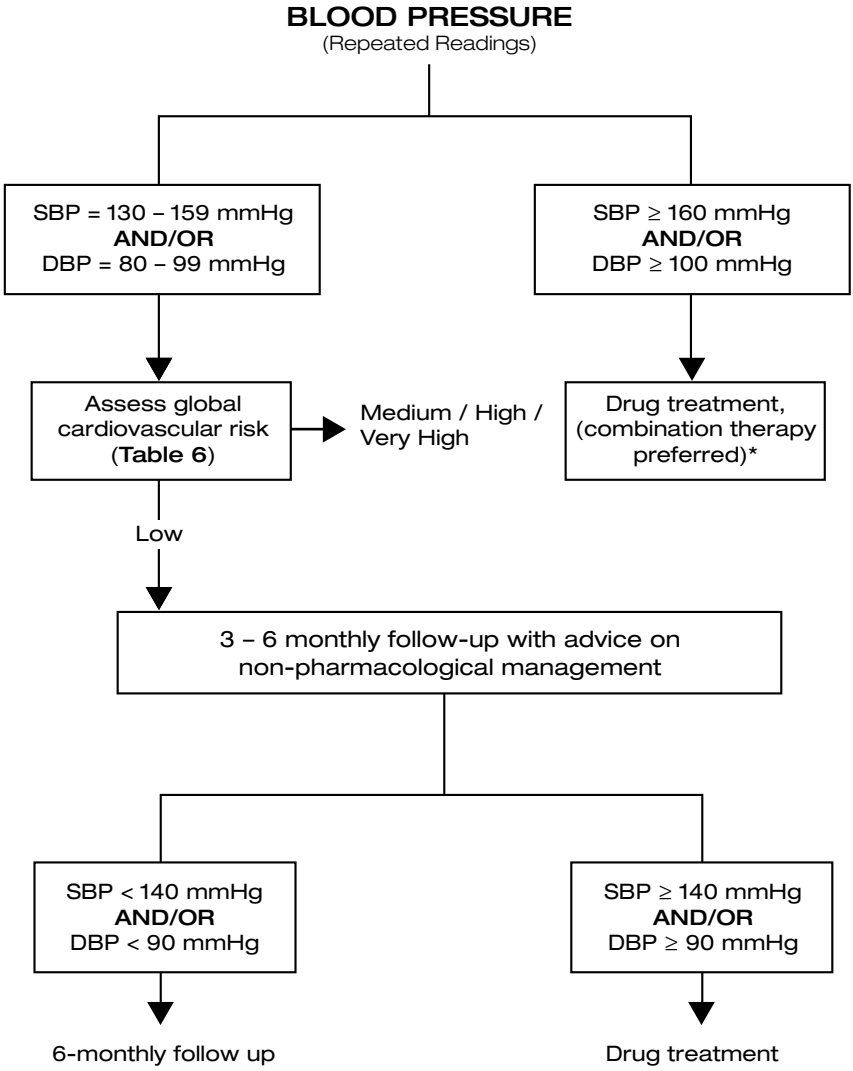
Choices of combination therapy is as shown in **Table 9 & 10**.

When target BP is not achieved after initiation of an anti-hypertensive, either increase the dose of the initial anti-hypertensive agent or add a second anti-hypertensive. The former may however give rise to dose-related adverse effects. Properly selected anti-hypertensive combinations may also mitigate the adverse effects of each other. If the patient does not show response or does not tolerate the initial drug, substituting with a drug from another class is recommended.[(Level III)] In patients presenting with stage II hypertension or beyond, combination therapy as first line is recommended.[(Level III)] (Refer to **Figure 1**)

Single Pill Combinations (SPC) is very convenient to use and promote treatment adherence [80] by reducing pill burden and simplifying the treatment regimen.[81,82] In addition, it takes less time to achieve BP control using a combination than monotherapy.[83,84 (Level I)]

It should be emphasized that simplification of the treatment regimen is only one strategy for improving adherence. For many patients, cost is a critical issue. In Malaysia, generic SPC are generally not available. Patented SPC are available but are more expensive. This may adversely affect adherence especially for self paying patients. Free drug combination is the obvious choice in such circumstances It is however worth noting than available evidence showed SPC is associated with not only improved adherence, but also lower overall health care cost.[85 (Level II-2)]

Figure 1. Algorithm for the Management of Hypertension



* either free or single pill combination

Table 8. Choice of Anti-Hypertensive Drugs in Patients with Concomitant Conditions

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

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

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

Table 9. Effective Anti-Hypertensive Combinations Used in Outcome Trials

Effective combination	Patients studied
ACEI + thiazide-like diuretics [86]	Post stroke
ARB + thiazide[87]	Hypertensive with Left Ventricular Hypertrophy
CCB + ACEIs or ß-blocker + thiazide[88]	Patients with Coronary Artery Disease
ARB + thiazide or CCB + thiazide[89]	High risk hypertensives
CCB + ACEI[90]	Medium risk hypertensives with no overt vascular diseases
ACEI + thiazide-like diuretics[91]	High risk hypertensives with diabetes
ACEI + CCB[92]	High risk hypertensives
thiazide-like diuretics + ACEI[93]	Very elderly (>80 years old)

Table 10. Drug Combinations in Hypertension:

Preferred (based on outcome trials)[86-93]
ACEI / thiazide or thiazide-like diuretics
ARB / thiazide diuretics
ACEI / CCB
ß-Blocker / thiazide diuretics
thiazide diuretics / K^+ sparing diuretics

Acceptable (no outcome trial evidence yet)
ARB / CCB
ß-Blocker / thiazide-like diuretics
DRI/diuretic

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

6.1c Target Blood Pressure

Efforts must be made to reach target BP. For patients <80 years old, the target SBP should be <140 mmHg and DBP <90 mmHg.[20,78] For patients aged 80 years and above, aim for a target of <150/90 mmHg (Refer to chapter 8 on **Hypertension in the Elderly**). For high/very high risk individuals the target is <130 or 140 mmHg / 80 mmHg (Refer to chapter 8 on **Hypertension in Special Groups**).

If BP is still >140/90 mmHg with three drugs, including a diuretic at optimal doses, there is a need to exclude medication non-compliance and isolated office hypertension. After excluding these causes of uncontrolled hypertension, the patient is then defined as having resistant hypertension[94] (Refer to chapter on **Resistant Hypertension**). A quick check on the possible causes of resistant hypertension is required. These include:

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

6.2 FOLLOW-UP VISITS

Follow up intervals should be individualised based on global CV risk, pre-treatment BP levels and drugs used. For high and very high risk patients, it is advisable to bring the BP to target within 3 to 6 months.[89] Once target BP is achieved, follow-up at three to six-month intervals is appropriate. As a rule, once the BP is controlled, most patients will require life-long treatment.

6.3 STEP-DOWN THERAPY

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

- BP well-controlled for at least 1 year on the same medication
- patients' BP must not be higher than stage I hypertension with low global CV risk
- must agree to be followed-up at least 3-6 monthly
- must be motivated to continue life-style modification

6.4 WHEN TO REFER

Most patients can be effectively managed by primary care 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
- isolated office hypertension
- children <18 years old

Recommendations

- For the majority of hypertensive patients, treatment is life-long (Grade C)
- Choice of treatment should be individualised (Grade C)
- Target BP should be SBP<140 mmHg and DBP<90 mmHg for most (Grade A)
- For high / very high risk patients, target SBP is <130 or <140 mmHg and DBP <80 mmHg (Grade A)
- Combination therapy (free or single pill) is required is most patients to achieve BP control (Grade B)

7.0 MANAGEMENT OF SEVERE HYPERTENSION

Severe hypertension is defined as persistent elevated SBP >180 mmHg and/or DBP >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, subarachnoid haemorrhage and hypertensive encephalopathy.

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.[95]

In a recent large series, only a minority of patients admitted (5.1%) had hypertensive crises. Of those more than three quarters (76.6%) constitute hypertensive emergencies.[96 (Level III)]

Management of these patients depends on the clinical presentation and laboratory investigations. The evaluation of these patients should include a thorough history and physical examination, particularly looking for signs of acute target organ damage / complication and causes of secondary hypertension. (**Table 11**)

The commonest reason of severe hypertension is long-standing poorly controlled essential hypertension.[97] Other causes are as listed in **Table 11**.

Table 11. Common Causes of Severe Hypertension

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

7.1 SPECIFIC MANAGEMENT

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

7.1.1 Asymptomatic Severe Hypertension

Admission may be necessary in the newly diagnosed, or where drug adherence may be a problem. Patients already on treatment need to have their drug regime reviewed. Oral combination therapy should be preferred.

7.1.2 Hypertensive Urgencies

These include patients with grade III or IV retinal changes (also known as **accelerated and malignant hypertension**), but no overt acute target organ damage/complication. These patients should be admitted. 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.[95,98 (Level III)] Oral drugs proven to be effective are outlined in **Table 12**. Combination therapy is necessary. There is no role for intravenous BP lowering drugs.

Table 12. Oral Treatment for Hypertensive Urgencies

Drug	Dose (mg)	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.[99,100 (Level III)]

This is best achieved with parenteral drugs. (**Table 13**)

There has been very few head to head comparative trials is the management of hypertensive crises especially hypertensive emergencies. A recent meta analysis showed that IV labetalol have comparable efficacy and safety compared to nicardipine with the later showing more predictable and consistent BP control [101 (Level I)]

Table 13. Treatment Options for Hypertensive Emergencies[98-100]

Drugs	Dose	Onset of action	Duration	Remarks
Sodium nitroprusside	0.25–10 µg/kg/min	seconds	1 – 5 min	Caution in heart failure
Labetalol	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
Nitroglycerine	5 – 100 µg /min	2 – 5 min	3 – 5 min	Preferred in acute coronary syndrome and acute pulmonary oedema
Hydralazine*	IV 5–10 mg maybe repeated after 20–30 minutes. IVI 200–300 mcg/min initially. Maintenance 50–150 µg/min	10 – 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 µg/kg/min	5 – 10 min	1 – 4 hrs	Caution in acute heart failure and coronary ischaemia
Esmolol	IV bolus 250–500 µg/kg over 1 min IVI 50–200 µg/kg/min for 4 min. May repeat sequence	1 min	10 – 20 min	Used in peri-operative situations and tachyarrhythmias

In pregnancy, 200 mg labetalol in 50 ml normal saline and start infusion at 4 ml/hour.
* In pregnancy, the initial dose is 25 µg/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.[102]

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.[103 (Level III)] However oral nifedipine retard can be used and has been recommended as first line therapy for hypertensive urgencies.[95 (Level III)]

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 chapter 8.6 on on **Hypertension and Stroke**.

Recommendations

- Do not reduce BP rapidly in asymptomatic severe hypertension. (Grade C)
- Treat hypertensive urgencies with combination oral therapy targeting BP to reduce by around 25% within 24 hours. (Grade C)
- Treat hypertensive emergencies with intravenous drugs targeting BP to reduce by around 25% within 3 to 12 hours. (Grade C)

8.0 HYPERTENSION IN SPECIAL GROUPS

8.1 HYPERTENSION AND DIABETES MELLITUS

Hypertension is common in patients with diabetes mellitus. Its presence increases the risk of morbidity and mortality. The Hypertension in Diabetes Study Group reported a 39% prevalence of hypertension among newly diagnosed patients.

Hypertension should be treated early in diabetics to prevent both microvascular, macrovascular complications and CV death.

8.1.1 Threshold for Treatment

Pharmacological treatment should be initiated in patients with diabetes when the BP is persistently >140 mmHg systolic and/or >80 mmHg diastolic.

The presence of microalbuminuria or overt proteinuria should be treated even if the BP is <140/80 mmHg. An ACEI or ARB is preferred.[104-111 (Level I)] In a proportion of patients, microalbuminuria may be normalised by high doses of ACEIs[108] or ARBs[109-110 (Level I)] even if the BP is optimally controlled. The combination of ACEI and ARBs may further reduce proteinuria but should be instituted by a specialist.[112] Normalisation of microalbuminuria is associated with a reduction in the rate of decline in glomerular filtration rate.[113]

8.1.2 Target Blood Pressure

Tight BP control should take precedence over the class of anti-hypertensive drug used.[114,115 (Level I)] This will often 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 <140 mmHg[22,91,104 (Level I)] and diastolic pressure <80 mmHg.[91 (Level I)] In a subset of patients especially the younger patients, a systolic target of <130 mmHg can be considered[116-117 (Level I)]

In the ACCORD Study, diabetic patients at high risk of cardiovascular events who were randomised to a target systolic blood pressure (SBP) of <120 mmHg, did not show a reduction in the rate of composite outcome of fatal and nonfatal major cardiovascular events as compared with <140 mmHg.[118 (Level I)]This could possibly be due to the J-curve phenomenon seen in this particular cohort of patients who had underlying cardiovascular disease at baseline. However, subgroup analysis showed the more intensive SBP-lowering group had significantly lower stroke rate. The ACCORD Study however is under powered as acknowledged by the authors.

The J-curve phenomenon was also noted in the diabetic subgroup in the INVEST Study.[119] This however is a subanalysis of the study.

There was no reported increase in cardiovascular events in the ADVANCE Study with patients whose systolic blood pressures were lowered to <120 mmHg.[91] On the other hand, renal protection was seen with baseline or achieved BP down to <120/70 mmHg. No BP threshold could be identified below which renal benefit was lost.[119]

Generally the target BP should be aimed at <140/80 mmHg and <130/80 mmHg in the younger patients. However in diabetics with known CAD further lowering BP beyond 120/80 mmHg does not confer additional cardiovascular benefit.

8.1.3 Management

The approach to managing patients with hypertension and diabetes should be along the guidelines for treatment of hypertension in general including emphasis on non-pharmacological management.

8.1.3.1 Non-pharmacological Management

This cannot be over emphasised. Dietary counselling should target at optimal body weight, glycaemic and dyslipidaemic control.

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.[115]

8.1.3.2 Pharmacological Management

The use of certain classes of anti-hypertensive drugs may be disadvantageous to the diabetic patient by virtue of their modes of action or adverse effects. Diabetic control may be compromised and various diabetic complications aggravated, for example:

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

Angiotensin-converting enzyme inhibitors are drugs of choice based on extensive data attesting to their cardiovascular and renal protective effects in patients with diabetic kidney disease.[120 (Level I)] They have also been reported to prevent the onset of nephropathy in normoalbuminuric diabetic patients with or without hypertension.[121-123 (Level I)] In addition they do not have adverse effects on lipid and carbohydrate metabolism. However it's routine use in normotensive normoalbuminuric diabetic patients is currently not recommended. If an ACEI is not tolerated, an ARB should be considered.

Angiotensin receptor blockers have been reported to be superior to conventional non-ACEI anti-hypertensive drugs in terms of slowing the progress of nephropathy at the microalbuminuric stage[109] as well as the overt nephropathy stage in type 2 diabetic patients.[110,111] In addition, ARB has been shown to prevent or delayed the onset of microalbuminuria in normoalbuminuric patients with type 2 diabetes with or without hypertension.[124,125 (Level I)] However the data is too limited for ARBs to be recommended routinely in normotensive normoalbuminuric diabetic patients.

Angiotensin receptor blockers have been shown to be of similar efficacy as ACEIs but better tolerated.[121 (Level I)] There have been no reports of adverse effects on carbohydrate and lipid metabolism.[109-111]

Thiazide and thiazide-like diuretics can be used as initial therapy or as add-on when monotherapy is inadequate. Single Pill Combinations of a thiazide-like diuretic (indapamide) with ACEI reduced overall mortality.[91]

Calcium channel blockers do not have significant adverse metabolic effects. They do not compromise glycaemic control in diabetic patients. They can be effectively combined with a RAAS blocker to lower blood pressure in general as well as in hypertensive diabetics. Combination of amlodipine with perindopril was superior to the combination of atenolol with bendroflumethiazide in the reduction of cardiovascular events in the overall study population as well as the diabetic subgroup.[90]

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.

Recommendations

- ACEIs are the agents of choice for patients with diabetes without proteinuria. For ACEI intolerant patients, ARBs should be used. (Grade A)
- ACEIs or ARBs are the agents of choice for patients with diabetes and proteinuria. (Grade A)
- Calcium channel blockers, diuretics or ß-blockers may be considered if either of the above cannot be used. (Grade B)
- Target BP in the diabetic is <140/80 mmHg for all. (Grade A)
- A target BP of <130/80 mmHg is recommended for the younger patients (Grade C)

8.2 BLOOD PRESSURE AND THE METABOLIC SYNDROME

The metabolic syndrome is a cluster of risk factors predisposing to cardiovascular disease and diabetes. Since the last guideline was formulated, several key medical organisations have agreed on a common definition.[126] However the American Diabetes Association and the European Association for the Study of Diabetes have not subscribed to it.

The diagnostic criteria are listed in the table below. More recently, the Harmonised International Diabetes Federation (IDF) has agreed that waist circumference no longer needs to be a compulsory criterion, but it should be country and ethnic-specific. The presence of any three out of the five criteria would lead to a diagnosis of the Metabolic Syndrome.[126] The IDF definition is in line with the American National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria[127] and that which is modified for Asian[128] and other populations[129] (**Table 14**).

An elevated blood pressure is one of the criteria for the diagnosis of the Metabolic Syndrome. In these high risk patients, the cut-off point has been set at 130/85 mmHg. Despite disagreement over the usefulness of making a diagnosis of the Metabolic Syndrome, the consensus is that various components of the metabolic syndrome should be treated vigorously. For blood pressure, the target should be <130/85 mmHg.[129,130] Blood pressure associated with the Metabolic Syndrome should be treated according to standard clinical practice guidelines. Drugs which are metabolically neutral, like the RAAS blockers and CCBs are preferred. ß-blockers and thiazide diuretics have the potential to increase the incidence of new onset diabetes[131,69] and thus should be used with caution in these patients.

In Malaysia, the overall prevalence of the Metabolic Syndrome using the original NCEP ATP III and the Harmonised IDF criteria was 34.3% and 42.5% respectively.[132,133] These prevalence rates are among the highest in the world. The prevalence of the Metabolic Syndrome in Malaysia was higher in urban areas, among females and those of Indian ethnicity. Among the criteria used for metabolic syndrome, abdominal obesity was most prevalent (57.4%); being higher in females (64.2%) and among Indians (68.8%). Hypertension was higher in males (56.5%) and among Malays (52.2%). In contrast, the Chinese had the highest prevalence of hypertriglyceridaemia (47.4%).

The prevalence of the Metabolic Syndrome in Malaysia is among the highest in the world.

Recommendations

- In the presence of one component of Metabolic Syndrome, other components of the syndrome must be screened for (Grade C)
- Treat each component of the Metabolic Syndrome optimally. (Grade B)
- Chose treatment which will not aggravate other components of the syndrome. (Grade C)

Table 14. NCEP ATP III and IDF Criteria for the Metabolic Syndrome [126,127]

Components of metabolic syndrome	Waist (cm)	BP (mm Hg)	FBS (mmol/L)	TG (mmol/L)	HDL (mmol/L)
NCEP 2001 3 out of 5 criteria	> 102 (M) > 88 (F)	≥130/85	≥ 5.6	≥ 1.7	< 1.0 (M) < 1.3 (F)
IDF Task Force 2009 3 out of 5 of criteria	Country and Ethnic-specific	≥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.[134,135] Renal disease is one of the commonest 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/1.73m^2 (CKD stages 3–5) have hypertension.[136] Hypertension accelerates the progression of renal disease and may lead to end stage renal disease (ESRD). Tight control of BP in patients with CKD is therefore important. The target BP should be <140/90 mmHg for patients with CKD[33,137,138 (Level I)] and <130/80 mmHg for those with proteinuria of ≥1g/24 hours.[34 (Level I)] All anti-hypertensive 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. Anti-hypertensive 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.[139] Overall 30% reduction in incidence of ESRD with ACEI can be expected.[140] The anti-proteinuric effect and reduction in ESRD was beyond that attributable to the BP lowering effect.[138,141 (Level I)] This anti-proteinuric effect of ACEI was most prominent in patients on a low sodium diet or those treated with diuretics. Patients with proteinuria >3g/24 hours benefit the most.[138,141] The advantage of ACEI is most apparent in patients with rapid progression of renal disease associated with proteinuria. ARBs are similar to ACEI in lowering BP and reducing proteinuria.[142,143] The combination of ACEIs and ARBs has also been proven to reduce proteinuria more than monotherapy.[144] However 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 and also after every increase in dose. If there is a persistent rise of serum creatinine of >30% from baseline within two months, ACEIs[145 (Level I)] or ARBs should be reduced or stopped after excluding other precipitating factors. These patients should be referred to a nephrologist or physician.

In patients with renal disease and hypertension with an elevated serum creatinine of >200 µmol/L (GFR <30 ml/min/1.73m^2), thiazide diuretics may not be effective anti-hypertensive agents and therefore loop diuretics are preferred.[146 (Level III)] Concurrent diuretic therapy will often be necessary in patients with renal insufficiency since salt and water retention is an important determinant of hypertension in this setting.

Calcium channel blockers may be used in renal disease. In those with proteinuria, the non-dihydropyridine group of CCBs namely diltiazem or verapamil are preferred, as they have an additional anti-proteinuric effect.[139 (Level I)] Dihydropyridine CCBs can be considered if optimal BP is not achieved but should not be used as monotherapy. The combination of an ACEI and a non-dihydropyridine CCB is more anti-proteinuric than either drug alone.[147]

More recently, aldosterone antagonists have been shown to have additive anti-proteinuric effects when administered with ACEI and/or ARB in patients with CKD.[148,386] However, larger randomised prospective trials are needed to confirm the efficacy and safety of aldosterone antagonists in reduction of CKD progression and mortality. Currently there is not enough evidence for these agents to be used routinely.

Recommendations

- Target BP should be <140/90 mmHg for those with proteinuria of <1g/24 hours and <130/80 mmHg for those with proteinuria of >1 g/24 hours (Grade A)
- ACEIs are recommended as initial anti-hypertensive therapy (Grade A)
- ARBs should be used in patients intolerant to ACEIs (Grade C)
- Dietary salt and protein restriction is important (Grade A)
- Concurrent diuretic therapy is useful in patients with fluid overload (Grade A)
- Non-dihydropyridine CCBs can be added on if the BP goal is still not achieved and there is persistent proteinuria (Grade A)

8.4 RENOVASCULAR HYPERTENSION

Renovascular hypertension is defined as a rise in arterial pressure attributable to reduced perfusion of the kidney(s).[149] It is important to diagnose renovascular hypertension as it is potentially reversible. Treatment also has the potential to restore or preserve renal function. The aetiology of renovascular hypertension includes the following:

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

Atherosclerotic renal artery stenosis (ARAS) is an important cause as it can lead to ESRD. 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[151,152]

The presence of a stenotic renal vessel in a patient with hypertension does not necessary equate to renovascular hypertension.

Some clinical features suggestive of renovascular hypertension includes:

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

Renal angiography including measurement of the pressure gradient remains the gold standard in the diagnosis of renovascular hypertension.[152] Non-invasive investigations commonly recommended include spiral CT angiography (CTA), and magnetic resonance angiography (MRA) in patients with normal renal function.[153]

The management of renal artery stenosis includes conservative treatment, angioplasty with or without stenting and surgery. Conservative treatment can be considered for patients with stenosis less than 70% or those with stable renal function and good BP control despite radiological evidence of stenosis >70%. These lesions should be monitored for progression using colour duplex sonography. Medical treatment of patients with ARAS include statins, low dose aspirin, cessation of smoking and management of diabetes when present.

Pharmacologic management of renovascular hypertension follows the general principles of all antihypertensive therapy but is especially dependant on effective blockade of the RAAS. Angiotensin converting enzyme inhibitors or ARB can be used in patients with suspected ARAS if renal function is carefully monitored. A persistent rise in creatinine of >30% over 2 months warrants cessation of ACEI/ARB drug therapy. This is best done under specialist's supervision.

Revascularisation has been shown in case series and non-randomised trials to alleviate renovascular hypertension as well as to salvage renal function.[154,155] It should be considered under the following circumstances.[156]

- flash pulmonary oedema
- rapidly deteriorating renal function especially if leading to dialysis
- resistant hypertension
- transplant renal artery stenosis
- fibromuscular dysplasia (FMD) associated with hypertension
- Takayasu's arteritis

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.[157] 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. For those in whom indications are uncertain, prospective randomised trials including the Stent Placement in Patients with Atherosclerotic Renal Artery Stenosis and impaired Renal Function study (STAR)[158] and Angioplasty and Stent for Renal Artery Lesions study (ASTRAL)[159] have not demonstrated compelling benefits either with endovascular stents or surgery when added to effective medical therapy. These trials are subject to several limitations including being underpowered in the former, and inconsistency in defining 'critical" vascular occlusion and the degree of stenosis in the latter. More recently, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study[160] shows renal artery stenting only achieved a modest difference in SBP favouring intervention, with no benefits in renal or cardiovascualr outcomes when added to comprehensive multifactorial medical therapy in people with atherosclerotic renal artery stenosis and hypertension or CKD.

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.[161] 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 ACEIs.[162] Given the typical patient with FMD (young female with lower angioplasty-related risks, the need for many years of anti-hypertensive treatment plus limitations of RAAS blockers during pregnancy), most clinicians would probably favour angioplasty for patients with FMD.[163] It is important to recognise that benefits of angioplasty may be limited. The chance of achieving normal BP without anti-hypertensive agents is less than 30%, although some improvement in BP may be expected in an additional 50% or more.[163]

8.5 HYPERTENSION AND HEART DISEASE

8.5.1 Hypertension and Coronary Heart Disease

Hypertension is a known risk factor for atherosclerosis. As prevention for atherosclerotic disease, blood pressure control is important especially in the presence of other risk factors. In patients with symptomatic angina, the treatment of choice should be a ß-blocker or CCB. Clinical studies have also shown that coronary events in hypertensive patients with coronary heart disease are reduced in those whose blood pressure are controlled.[164,165] Based on the many studies using different groups of antihypertensives, it appears that the benefits are achieved predominantly by lowering the blood pressure rather than the use of any specific class of antihypertensive agent. [73,166]

Following any coronary event, patients will be at high risk of subsequent events, especially if the hypertension is not controlled. There are clinical trials showing morbidity and mortality benefits of anti-hypertensive agents like ß-blockers,[167] ACEIs[168] and ARBs,[169] following myocardial infarction.

8.5.2 Hypertension and Heart Failure

Chronic, uncontrolled hypertension can cause heart failure, even in the presence of normal systolic function. Anti-hypertensive agents including ß-blockers,[170-172] ACEIs,[172] and aldosterone antagonist,[173] have shown mortality benefits and reduction in the number of hospitalizations, in patients with systolic heart failure. The evidence for ARB is less convincing[174] except for ACEI intolerant patients.[175] However for patients having heart failure with preserved systolic function, results with ARB has been mixed[176,177] while meta analysis with ACEI has shown a modest effect on diastolic dysfunction.[178] Should hypertension be persistent in spite of ACEI, ARB and/or ß-blocker, CCBs which are not negatively inotropic, such as amlodipine, can be added. These patients should also be on loop diuretics for symptomatic relief.

Recommendations

- ß-blockers, ACEIs or ARBs should be used post myocardial infarction to reduce recurrent myocardial infarction and death. (Grade A)
- ß-blockers, ACEIs and Aldosterone antagonists should be given to patients with systolic heart failure to reduce morbidity and mortality. (Grade A)
- Angiotensin receptor blockers or ACEIs should be used on heart failure patients with preserved ejection fraction. (Grade B)
- Blood pressure in post myocardial infarction and heart failure patients should be lowered to <130 / <80 mmHg. (Grade C)

8.5.3 Hypertension and Atrial Fibrillation

Hypertension is one of the risk factors for atrial fibrillation.[179] Atrial fibrillation increases the risk of thromboembolic stroke, and the role of anticoagulants to reduce this risk, is well established. Uncontrolled hypertension increases the risk of haemorrhagic stroke and hence it is imperative that patients with hypertension and atrial fibrillation should have their blood pressure well controlled, more so if they are on anticoagulant. The blood pressure target is <130 / <80 mmHg.[180]

A few small studies[181,182] and sub-analysis of larger trials[183,184] have reported that ARB can reduce the incidence of recurrent atrial fibrillation or help maintain patient in sinus rhythm. Both ARB and ACEI have been shown to reduce the incidence of atrial fibrillation in patients with paroxysmal atrial fibrillation and to prevent new onset atrial fibrillation.[185] While both ACEI and ARB can prevent onset of atrial fibrillation, there is no significant reduction in new onset atrial fibrialltion in the subset of patients with underlying hypertension.[186] However for hypertensive patients with paroxysmal atrial fibrillation, ACEI and ARB are the preferred choice. For elderly patients (>75 years old) who are on anticoagaulation for atrial fibrillation, both ACEI and ARB reduce mortality.[187] (Level II-2)

For rate-control of permanent atrial fibrillation, ß-blockers and non-dihydropiridine CCBs (verapamil and diltiazem) should be considered.[188]

8.5.4 Hypertension and Peripheral Arterial Disease

The risk factors for peripheral arterial disease (PAD) include hypertension, diabetes, current smoking and hypercholestrolaemia.[189] As atherosclerosis is a 'global' vascular disease, diffuse atherosclerosis, CAD, and renovascular disease often coexist in these patients. PAD is associated with an increased risk of death from CVD. It is appropriate that these patients are also screened for the presence of atherosclerotic disease of the other systems. Control of hypertension in patients with peripheral arterial disease is poor.[190] The aim of treatment in peripheral arterial disease is both symptom relief and prevention of cardiovascular event. There is no consensus on the treatment of choice for hypertensive patients with peripheral artery disease,[191] although sub-analysis of major trials showed benefits of ACEI in patients with both symptomatic and asymptomatic peripheral arterial disease.[36] Although ß-blockers may cause vasoconstriction and may worsen the frequency of intermittent claudication, they may be used with caution in patients with compelling indications (CHD and/or HF). Should patients present with Raynaud's phenomenon, consider a vasodilator such as CCBs. Cilostazol has been shown to be useful especially in the elderly with disabling peripheral arterial diease.[192] In addition to these medications, patients should stop smoking. Other therapy including LDL-cholesterol lowering and better control of diabetes is also recommended.

Recommendations

- Treat blood pressure in hypertensives with peripheral arterial disease to <130 / <80 mmHg (Grade C)
- Any antihypertensive can be used as first choice (Grade C)
- Give ACEI to patients with PAD to prevent vascular events (Grade B)
- Consider cilostazol in the elderly patients with symptomatic CAD (Grade B)
- Other aspects of management must include smoking cessation, optimal treatment of concurrent diabetes, dyslipidaemia and antiplatelet agent

8.5.5 Hypertension and Left Ventricular Hypertrophy (LVH)

Left Ventricular Hypertrophy is characterized by increased left ventricular mass index and may be associated with increased wall thickness. In LVH due to hypertension, the hypertrophy is usually concentric, and is sometimes associated with echocardiographic 'impaired relaxation'. This is often described as "diastolic dysfunction", and may cause heart failure with preserved systolic function. While LVH can be detected on electrocardiography (ECG), echocardiography is much more sensitive for detection of LVH. Those with LVH are at risk of premature cardiovascular events or death. Several studies have suggested that LVH regression is associated with a lower overall CVD risk. Regression of LVH can be achieved by weight reduction, salt restriction and BP lowering. For LVH regression, it is the blood pressure reduction rather than the class of anti-hypertensive that is important.[193] However, in the LIFE study, ECG LVH and cardiovascular outcome (especially stroke) was reduced significantly more by a losartan-based than atenolol-based regimen despite equivalent BP lowering.[87] This is supported by a recent meta analysis which showed that ARB has the best effect on LVH regression with ß-blockers the least.[194]

8.6 HYPERTENSION AND STROKE

High blood pressure is the most important modifiable risk factor for stroke,[195] both Ischaemic Stroke (IS) and Intracerebral Haemorrhage (ICH). Blood Pressure levels are continuously associated with the risk for stroke.[25,196] Although both SBP and DBP are associated with stroke, SBP is more predictive.[197] In the Asia Pacific region, up to 66% of CV events can be attributed to hypertension. Moreover, the burden of stroke is higher among Asian compared to Caucasian population in the region.[198]

Worldwide, 15 million people suffer from stroke annually. Of these, 5 million die and another 5 million are left permanently disabled.[199] It is presently among the top four leading causes of death in ASEAN countries.[200] In Malaysia, stroke is the fifth leading cause of death in government hospitals in 2009, accounting for 8.43 % of all deaths.[201]

8.6.1 Primary Prevention of Stroke

Systemic reviews of 17 primary prevention trials involving a total of 47,000 participants showed that lowering SBP by 10–12 mmHg and DBP by 5–6 mmHg leads to a 38% reduction in the risk of stroke. [202]

The benefits have been shown in both systolic-diastolic hypertension and in isolated systolic hypertension.[90,196,203-205] Beta-blockers, diuretics, CCBs, ACEIs and ARBs have been shown to reduce risk and mortality from stroke.[90,176,203-206] Calcium channel blockers in particular, provided significantly better protection against stroke compared with diuretics and/or ß-blockers in Asian [207] and Caucasian [204] populations.

8.6.2 Treatment of Hypertension in Acute Stroke

Treatment of elevated BP in acute stroke is still controversial.[208] Stress-related high BP values (>140/90 mmHg) are present in up to 80% of patients with acute stroke[209,210] while almost 25% of patient presents with markedly raised SBP values >180 mmHg. In a majority of patients, a decline in blood pressure without any specific medical treatment will occur within days or weeks.[211,212] A slightly higher systemic BP is required to maintain the cerebral perfusion in the situation of increased intracranial pressure, partial thrombosis and disturbed cerebral perfusion.

Current guidelines recommend that treatment of hypertension in acute IS should be delayed for several days or up to 2 weeks after an IS unless there is hypertensive encephalopathy, severe left ventricular failure, acute renal failure, acute myocardial infarction, aortic dissection, acute pulmonary oedema or repeated BP readings reveal SBP values >220 mmHg and DBP >120 mmHg.[213-214] (**Table 15**)

Current recommendations for treatment of elevated BP levels in patients with acute ICH are more aggressive than those with IS (**Table 15**). For ICH, BP levels should be maintained <180/105 mmHg.[215] However, if unable to differentiate between IS or ICH, it is recommended **NOT** to lower BP <180/105 mmHg.

In cases where acute BP reduction is indicated, BP lowering should be done cautiously targeting BP reduction of no more than 10 to 20% from baseline BP over 24 hours. More profound BP reductions (>20%) have been associated with neurological and functional worsening.[216]

Parenteral agents such as labetalol or nicardipine that are easily titrated and have minimal vasodilatory effects on cerebral blood flow are preferred. In cases with excessive DBP levels (>140 mmHg), intravenous administration of sodium nitroprusside is recommended for adequate BP control. The use of sublingual nifedipine should be avoided because of the risk of abrupt BP reduction and possible worsening ischaemia.[213,217]

Table 15. Current Guideline for the Management of Blood Pressure in Acute Phase of Ischaemic Stroke and Intracerebral Haemorrhage

Acute phase of ischaemic stroke [213,214,217]	
BP level, mmHg	**Treatment**
SBP ≤220 or DBP ≤120	defer anti-hypertensive therapy
SBP >220 or DBP 121–140	i. labetalol 10–20 mg IV over 1–2 min, may repeat or double every 10 min (maximum 300 mg) ii. nicardipine 5 mg/h IV infusion as initial dose, titrate to desired effect by increasing 2.5 mg/h every 5 min (maximum 15 mg/h) iii. captopril 6.25–12.5 mg p.o. or i.m. iv. dihydralazine 5 mg IV plus metoprolol 10 mg IV **Target:** Not more than 10–20% reduction from baseline BP over 24 hours
DBP >140	i. nitroprusside 0.5 µg/kg/min as initial dose with continuous BP monitoring ii. nitroglycerin 5 mg IV, followed by 1–4 mg/h IV **Target:** Not more than 10–20% reduction from baseline BP over 24 hours
Acute phase of intracerebral haemorrhage [217]	
SBP <180 and DBP <105	defer antihypertensive therapy
SBP 180 – 230 or DBP 105 – 140 (2 readings 20 mins apart)	i. labetalol 5–100 mg IV by intermittent bolus doses of 10–40 mg or continuous infusion drip (2–8 mg/min) ii. esmolol 500 µg/kg IV loading dose; maintenance use 50–200 µg/kg/min iii. enalapril 0.625–1.2 mg IV iv. other easily titratable IV medications (diltiazem, verapamil, nicardipine) **Target:** Not more than 10–20% reduction from baseline BP over 24 hours

SBP >230 or DBP >140 (2 readings 5 mins apart)	(i) nitroprusside 0.5–1.0 µg/kg/min IV **Target:** Not more than 10–20% reduction from baseline BP over 24 hours

Two recent studies in acute blood pressure lowering in patients with acute haemorrhagic stroke shed useful information on this controversial issue. A relatively small Japanese study showed that clinical outcome is worst if the achieved systolic blood pressure is higher.[218] A much bigger international study showed that a target SBP of <140 mmHg improves functional outcome and is safe. There was however no difference in the primary outcome of death or severe disabilities compared to achieved SBP <180 mmHg.[219]

8.6.3 Secondary Prevention of Stroke

Patients who have had a stroke or a Transient Ischaemic Attack (TIA) are at increased risk of future stroke, especially in the following few months.[220] Annual recurrence rate is 12.5% per year.[221] Survival rates decreased from 63.7%, 42.8% and 24% at 1, 5 and 10 years respectively. Of those who survived at 10 years, almost a third had poor range of clinical outcomes.[222]

Lowering BP has been shown to reduce the risk of subsequent strokes.[35,223] Meta analyses of randomized controlled trials confirm approximately 30–40% reduction in stroke risk with blood pressure lowering.[224]

Combination of ACEI and thiazide-like diuretic has been shown to reduce stroke recurrence in both normotensive and hypertensive patients when treatment was started at least two weeks after the stroke.[35]

Three additional large-scale randomized trials of anti-hypertensive medications after stroke have been published. In one such trial, patient with hypertension and a stroke or TIA within 2 years of the event were randomized to an ARB or CCB. Despite similar BP reductions, recurrent total strokes and TIAs were less frequent among those randomized to ARB. There was a reduction in primary composite events which were significantly lower with ARB, with reduction in TIAs accounting for most of the benefit of ARB.[225] However in a bigger trial, patients with Ischaemic stroke were randomized to ARB or placebo within 90 days of an event with no clear benefits of ARB in preventing recurrent stroke after 2.5 years of follow-up.[226] In another placebo control trial involving ARB, patients with IS were randomised within 30 hours following onset of symptoms.[227] At 6 months follow-up, there were no significant difference in the composite primary endpoint (stroke, myocardial infarction, or vascular death). Taken together, a specific role for ARB in secondary stroke prevention can not been confirmed.[228]

The target BP after a stroke is less clear. More recent guidelines suggested a target of <140/90 mmHg [22] but the most recent major outcome trial suggest that for patients with recent lacunar stroke, a target of <130/80 mmHg is beneficial[229] especially for prevention of intracranial haemorrhage.

Recommendations

- Lower blood pressure to prevent both primary and secondary stroke (Grade A)
- In acute ischaemic stroke, do not lower SBP <180 mmHg in the first 2 weeks unless hypertensive emergencies co-exist (Grade C)
- In acute haemorrhagic stroke lower SBP to <140 mmHg. This approach is both beneficial and safe (Grade A)
- Avoid lowering BP abruptly with sublingual nifedipine in acute stroke (Grade C)
- Blood Pressure can be safely lowered in both normotensive and hypertensive patients for secondary prevention (Grade A)
- Lower BP to <130/80 mmHg for secondary prevention in lacunar stroke (Grade A)
- The benefit seen in secondary stroke prevention is most likely due to BP lowering per se rather than specific drug effect (Grade B)

8.7 HYPERTENSION IN THE ELDERLY

The definition of hypertension in the elderly (>65 years old) is the same as in the general adult population. Hypertension in the elderly is an increasingly important public health concern as our population ages. Hypertension magnifies the risk for cardiovascular disease and dementia especially in the elderly.

Systolic BP, unlike DBP, increases linearly with age leading to an increase in prevalence of ISH in the elderly. It is a better predictor of cardiovascular events than DBP.[230] The prevalence of hypertension in the elderly in Malaysia has been reported to be 62.4% of which 55% is ISH.[1]

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.[5,64,87,90,204,207,231-235] (Level I) A more recent RCT has shown that active treatment significantly reduces the risks of death from stroke and death from any cause in very elderly (>80 years old) patients. There was also a significant reduction in stroke.[93] (Level I) A systematic review also showed that BP reduction in the elderly prevented vascular dementia.[236] (Level I)

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 1-2 mins standing, is a common problem in the elderly. Blood pressure should therefore be measured in both the seated/lying 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. In healthier patients over 80 years a target SBP of around 150 mmHg is acceptable.[93] Any further reductions need to be established in future research. In those patients with marked systolic hypertension and not tolerating treatment well, reducing SBP to below 160 mmHg initially is acceptable. (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 they are more likely to have salt sensitive hypertension.[237 (Level I)]

Pharmacological Management
The five major classes of drugs (diuretics, ß-blockers, CCBs, ACEIs and ARBs) have been shown to reduce cardiovascular events in the elderly.[5,65,68,87,207,234 (Level I)] In older patients with ISH, diuretics are preferred because they have been shown to significantly reduce multiple endpoints[5] including dementia.[236] Several trials using dihydropyridine CCBs have shown benefits particularly in stroke reduction.[90,207,210,232] Angiotensin converting enzyme inhibitors are the drugs of choice for those with concomitant left ventricular systolic dysfunction, post myocardial infarction or diabetes mellitus.[235 (Level I)] Angiotensin receptor blockers have also been shown to reduce fatal and non-fatal strokes in hypertensive patients aged 65 years or older.[87]

When initiating pharmacological treatment, the principle is to go 'slow and start low' (about half the dose that of younger patients) to minimise side effects. Drug dosage should be gradually titrated to reach BP target. Drugs which can cause or exaggerate postural hypotension, (alpha-blockers and high dose diuretics) or drugs that cause cognitive dysfunction (central alpha-2-agonists) should be used with caution. The reduction in BP should be gradual to minimise the risk of symptomatic ischaemia especially in patients with postural hypotension.

- Definition of hypertension in the elderly is similar to that of younger patients
- Prevalence of ISH increases with age
- BP measurement in the elderly should include assessment for postural hypotension

Recommendations
- Do not neglect therapeutic lifestyle modification though difficult to achieve (Grade A)
- When choosing pharmacological agent, take into account any co morbid state and contraindication especially postural hypotension (Grade C)
- Treat BP <140/90 mmHg for patients <80 years old and < 150/90 mmHg for patients >80 years old (Grade A)

8.8 HYPERTENSION IN WOMEN

8.8.1 Hypertension in Pregnancy

Hypertension in pregnancy is also defined as a systolic blood pressure (BP) ≥140 mmHg and/or a diastolic BP ≥ 90 mmHg.[238]

An increase of 15 mmHg and 30 mmHg diastolic and systolic BP levels above baseline BP respectively is no longer recognised as hypertension if absolute values are below 140/90 mmHg. Nevertheless, this warrants close observation, especially if proteinuria and hyperuricaemia are also present.[239]

Korotkoff V should now be used as the cut-off point for diastolic BP, and Korotkoff IV utilized only when Korotkoff V is absent.[238(Level III)] Measurement of BP is similar to that of the general population, as stated earlier.

8.8.1.1 Proteinuria

Significant proteinuria in pregnancy is defined as ≥300 mg protein in a 24 hour urine sample, or a spot urine protein-creatinine ratio ≥30 mg/mmol.[238] If the dipstick is the only test available, 1+ (30 mg/dl) is often, but not always, associated with ≥300 mg/day proteinuria.[238] Significant proteinuria reflects advanced disease and is associated with poorer prognosis.

8.8.1.2 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).[238,239]

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 ≥ 90 micromol/l or oliguria.
   iii. Liver disease: raised transaminases and / or severe right upper quadrant or epigastric pain.
   iv. Neurological problems: convulsions (eclampsia), hyperreflexia with clonus or severe headaches, persistent visual disturbances (scotoma).
   v. Haematological disturbances: thrombocytopenia, coagulopathy, haemolysis.
   vi. Fetal growth restriction.

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

   Oedema is no longer part of the definition of preeclampsia.[240] Excessive weight gain or failure to gain weight in pregnancy may herald the onset of preeclampsia.[241]

2. Gestational hypertension is defined as hypertension detected for the first time after 20 weeks pregnancy. The definition is changed to “transient” when pressure normalizes postpartum.

3. Chronic hypertension is 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 is diagnosed in the presence of any of the following, in a woman with chronic hypertension:

   i. De novo proteinuria after 20 week gestation
   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

8.8.1.3 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 the prevention of preeclampsia and its complications, 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 anti-hypertensive agent used pre-pregnancy.[242] (Level III) The drugs of choice in pregnancy are still methyldopa and labetalol (**Table 16**). Atenolol has been shown to lead to fetal growth restriction. The use of ARBs, ACEIs and thiazide diuretics are associated with fetal anomaly[243] and are therefore contraindicated in pregnancy.

   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.[243] Pregnant women with uncomplicated chronic hypertension should have their BP kept lower than 150/100 mmHg. In the presence of target organ damage secondary to chronic hypertension, the aim is to maintain the BP below 140/90 mmHg.[243]

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

   High risk factors for development of preeclampsia are:

   i. hypertensive disease during a previous pregnancy
   ii. chronic kidney disease
   iii. autoimmune disease such as Systemic Lupus Erythematosus (SLE) or anti-phospholipid syndrome (APS)
   iv. type 1 or type 2 diabetes mellitus, and
   v. chronic hypertension.

   High risk patients should be prescribed aspirin (75mg–100mg daily) from 12 weeks gestation until delivery.[243,244] The same treatment should also be prescribed if they have two or more of the following moderate risk factors:

   - primigravida
   - age >40 years
   - pregnancy interval >10 years
   - body mass index of >35 kg/m^2 at first visit
   - family history of preeclampsia
   - multiple pregnancy.

   For optimal effectiveness in moderate risk patients, aspirin prophylaxis must be commenced before 16 weeks gestation.[244,245] Ideally, women at moderate or high risk should be referred in the first trimester for more detailed risk assessment in a fetomaternal specialist unit.[246]

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

   In pregnant women with low dietary calcium intake (less than 600 mg day), high calcium supplementation of 1.5g/day significantly reduces the risk of eclampsia, severe gestational hypertension, and severe preeclamptic complication index.[247] A recent meta analysis of RCTs in developing countries showed that calcium supplementation produces significant reduction in the risk of gestational hypertension and preeclampsia.[248] Other supplements in pregnancy such as marine oil, garlic and pyridoxine have no proven benefits.[249-251]

   Combined vitamins C and E (i.e. tocopherol from soybean) should be avoided because they significantly increase the incidence of low birth weight without any preventive effect against preeclampsia.[252]

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

   Patient and health professional education on the importance of signs and symptoms of preeclampsia for early diagnosis and referral for further management may prevent progression to eclampsia.[253,254(Level II-2)]

8.8.1.4 Severe Preeclampsia

Severe preeclampsia must be promptly identified so that the patient can be urgently admitted to hospital for close observation and timely delivery. The Royal College of Obstetrician and Gynecology (RCOG) defines severe preeclampsia as follows:[255]

1. Systolic BP ≥170 mmHg or diastolic BP ≥110 mmHg (acute hypertensive crisis in pregnancy) on two occasions, with proteinuria of ≥1 g/day.

2. Diastolic BP ≥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/cm^3
   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

Diagnosis of severe preeclampsia should not rely precisely on the above criteria. If in doubt, it is better to over rather than under diagnose. This will prevent delay in referral.

Anti-hypertensive treatment should be initiated if diastolic BP is persistently ≥100 mmHg. The target BP to achieve is DBP between 80-100 mmHg.[243]

In the event of an acute hypertensive crisis, IV hydralazine, IV labetalol, or oral nifedipine, may be used to lower the BP.[256,257 (Level I)] Sublingual nifedipine is no longer recommended [258 (Level III)](**Table 17**).

Diuretics are generally 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.[241 (Level III)]

8.8.1.5 Anticonvulsants in Preeclampsia-Eclampsia

Parenteral magnesium sulphate is currently the drug of choice for the prevention of eclampsia and to abort an eclamptic fit [258,259] (Level I) (**Table 18**). The alternative is intravenous diazepam, bearing in mind that it is inferior in efficacy compared to magnesium sulphate. Magnesium sulphate also provides fetal neuroprotection following preterm birth with a significant reduction in the incidence of cerebral palsy.[260]

8.8.1.6 Postpartum Care

Postpartum, women with hypertensive disorders in pregnancy are advised to have their BP checked regularly at local clinics if there is a significant delay in their scheduled hospital follow-up. In these patients, the dose of anti-hypertensive should be tailed down gradually and not stopped suddenly. On average, anti-hypertensive agents are required for longer in women with preeclampsia (approximately two weeks) compared with those with gestational hypertension (approximately one week) although there is substantial variability among women that cannot be predicted reliably.[261]

De novo onset of hypertension or aggravation of BP levels during the postpartum period, can occur.[262] These patients should be promptly referred to hospital especially if there is significant proteinuria.(Level III) Eclampsia may occur in the postpartum period.

Chronic hypertension is diagnosed when the hypertension and/or proteinuria persist after three months postpartum.[238,239]

8.8.1.7 Long Term Follow-up

Evidence suggests that up to 13% of women with preeclampsia will have underlying essential hypertension that was not suspected antenatally.[255] In addition, the same factors which predispose to preeclampsia also predispose to cardiovascular disease in later life.[245] Long-term follow-up of patients with a history of hypertension in pregnancy is therefore advisable. (Level III)

8.8.1.8 Reducing Mortality

A substantial reduction in preeclampsia/eclampsia related mortality can occur in low income countries by widespread screening for hypertension and proteinuria, together with early delivery of women with severe preeclampsia. Early referral is very important.[263]

Table 16. Anti-hypertensive 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 anti-hypertensive agent used in pregnancy, with best safety profile.
Labetalol	Oral 100 mg bd, doubling every 48 hours (up to 400mg bd) until BP well controlled.
Nifedipine	Oral 10 mg tds, up to 20 mg tds, usually as second line anti-hypertensive, when BP poorly controlled despite maximum doses of methyldopa ± labetalol.

Table 17. Anti-Hypertensive Drugs for Severe Preeclampsia with Acute Hypertensive Crisis[264]

Drug	Remarks
Hydralazine*	5 mg IV bolus or IM, then 5–10 mg every 20–40 minutes up to 30 mg, or IV infusion of 0.5-10 mg per hour.
Labetalol	20 mg IV bolus, then 40 mg 10–15 minutes later, then 80 mg every 10–15 minutes, up to 220 mg; or continuous IV infusion of 1–2 mg/minute until BP stabilizes, then stop or reduce to 0.5 mg/minute. May cause fetal bradycardia.
Nifedipine	Oral 5–10 mg stat (repeat in 30 minutes if necessary), especially prior to transferring a patient from a peripheral clinic to hospital. After the initial emergency dose, 10–20 mg can be given every 3–6 hours until BP stabilizes.

* Hydralazine is no longer recommended as first line treatment for acute hypertensive crisis in pregnancy.[255]

Table 18. Anti-convulsant for Eclampsia (and Severe Preeclampsia)

Drug	Remarks
Magnesium Sulphate[265,266]	IV: 4g slow bolus over 10 minutes, followed by 1-2 g/hour maintenance infusion given via a controlled infusion pump. IM: 4g IV slow bolus over 10 minutes, followed immediately by 10g IM, then 5 g IM every 4 hours in alternate buttock. Clinical monitoring is of utmost importance, looking for signs of toxicity (especially loss of deep tendon reflexes, respiratory depression with rate <16/minute) and renal impairment (hourly urine output <30 ml/hour).
Diazepam[266]	10 mg IV bolus, followed by 40 mg in 5% dextrose slow infusion so that patient remains sedated.

Recommendations

- Diagnose and treat hypertension in pregnancy based on Korotkoff V (Grade C)
- Appropriately counsel and manage women with chronic hypertension prior to pregnancy (Grade C)
- Refer pregnant women with hypertension to the obstetrician for further management (Grade C)
- Commence aspirin in pregnant women with one or more high risk factor or two or more moderate risk factors for preeclampsia from 12 weeks onwards (Grade A)
- Provide calcium supplementation from early pregnancy to prevent preeclampsia (Grade A)
- Oral nifedipine 10 mg stat dose can be used to rapidly control BP in an acute hypertensive crisis prior to transfer to hospital (Grade C)

8.9 HYPERTENSION AND ORAL CONTRACEPTIVES

Combined oral contraceptives (COC) can induce significant increases in BP with chronic use, which is nearly always reversible after 4 weeks of discontinuation.[267] Hypertension has been reported even with low-dose-oestrogen monophasic pills.[268] A woman who develops hypertension while using COC should be advised to stop taking them and should be offered alternative forms of contraception.[269] (Level III) Low dose combined hormonal contraceptives should only be used if no other method is suitable, even for women with controlled hypertension.[270]

Drospirenone (a progestin), has anti-mineralocorticoid diuretic effects, and can lower BP when combined with oestrogen in COCs.[271] It is a recommended alternative for patients with hypertension or who developed hypertension but wish to continue oral contraception. All progestogen-only methods are appropriate except in women whose BP is higher than 160/100 mmHg. In these patients, the injectable depot medroxyprogesterone acetate (DMPA) is contraindicated, along with all oestrogen-containing contraceptives.[270]

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

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.(Level III) The decision to continue or discontinue HRT in these patients should be individualised.

Two large trials on women aged 50-79 years, concluded that the use of HRT increased cardiovascular events.[272,273] 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.(Level III) Drospirenone when used as progestin in HRT, showed improvement in BP control.[267,274]

Table 19: COC and HRT Preparations Containing Drospirenone*

Hormonal Preparation	Trade Name	Active Ingredients	
		Oestrogen	Progestin
COC	Yasmin® / Liza®	Ethinyl oestradiol 0.03 mg	Drospirenone 3 mg
	Yaz® / Liz® / Lizelle®	Ethinyl oestradiol 0.02 mg	Drospirenone 3 mg
HRT	Angeli®	Estradiol 1 mg	Drospirenone 0.5 mg

* Referenced from 132th Edition, MIMS, 2013

8.11 HYPERTENSION IN NEONATES, CHILDREN AND ADOLESCENTS

Hypertension in Neonates and Infants

The reported incidence of hypertension in neonates admitted to modern Neonatal Intensive Care Unit is 0.8%.[275] It is more common in neonates and infants with antenatal steroids, bronchopulmonary dysplasia, patent ductus arteriosus or in those with indwelling umbilical arterial catheters.[275] Catheter related hypertension is related to thrombus formation at the time of line placement.[276]

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

Standardized Protocol for BP Measurement in Neonates: [277,278]

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

A reference table for BP values after two weeks of age in infants from 26 to 44 weeks has been derived after taking into consideration gestational age at birth, postconceptional age and size for gestational age. The 95th and 99th percentile values are intended to serve as reference to identify infants with persistent hypertension that may require treatment. [277] (Refer to **Appendix 1**)

Treatment is recommended when BP is consistently above the 99th percentile. There are few published case series that used diuretics, ACEI, ß-blockers and CCB.[277]

There is concern over the use of ACEI in preterm neonates.[279] It has been reported to cause an exaggerated fall in BP and may impair the final stages of nephron maturation.[280]

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.[281,282]

> 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 (Refer to **Appendix 1**).[283] This is to allow for a more precise classification of BP and avoids mislabeling 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.

BP should be measured in all children and adolescents >3 years old at all medical encounters and in selected children <3 years old who are at high risk.[283]

To assist clinicians in the further evaluation and management of hypertensive children and adolescents, blood pressure in this group has been arbitrarily divided into normal, pre-hypertension, stage I and stage II hypertension. (**Table 20**)

Table 20. Classification and Management of Hypertension in Children and Adolescents[283]

	SBP or DBP percentile	Frequency of BP measurement	When to start pharmacologic treatment*
Normal	**< 90th**	**No data available**	**No treatment**
Pre-hypertension	> 90th to <95th or if BP > 120/80 mmHg (even if < 90th percentile) & up to 95th percentile	Recheck in 6 months	No treatment unless having compelling indications e.g., CKD, DM, heart failure
Hypertension	**SBP and/or DBP >95th percentile >3 occasions**		
Stage I hypertension	95th to 99th percentile plus 5 mmHg**)	Recheck in 1–2 wk, sooner if symptomatic, refer within 1 month	• Secondary hypertension • Symptomatic hypertension*** • Presence of TOD • Failed non-pharmacologic measures
Stage II hypertension	> 99th percentile plus 5 mmHg**	Immediately if symptomatic; refer within a week	Initiate therapy

* non-pharmacologic measures recommended in all pre-hypertensives and hypertensive children.
** To diagnose stages of hypertension, add 5 mmHg to the respective percentile value.
*** Symptoms associated with hypertension include headache, nausea, vomiting, seizures and visual disturbances.

A patient with BP levels >95th percentile in a doctor's office but who is normotensive outside a clinical setting has "isolated office hypertension". Isolated office hypertension is seen in up to 60% of children and adolescents and is not associated with target organ damage. Ambulatory blood pressure measurement is necessary to confirm hypertension in otherwise healthy children.

Identifiable causes of hypertension particularly of renal parenchymal and renovascular origin account for about 80–90% of hypertension in children <10 years of age. Children with primary hypertension tend to be obese and have positive family history of hypertension.[284]

Once a child is diagnosed with hypertension, he should be referred to a paediatrician for further evaluation and management.[285 (Level III)]

Treatment of Paediatric Hypertension

Goals of Therapy[283]

Children with uncomplicated primary hypertension without hypertensive TOD	Aim for BP <95th percentile for age, sex and height
Children with secondary hypertension, diabetes mellitus or hypertensive TOD	Aim for BP <90th percentile for age, sex and height

Non-pharmacologic Treatment

Non-pharmacologic management including dietary changes, exercise and weight reduction (if obese) is recommended in all children with hypertension as well as those with BP in the 90th to 95th percentile.[283 (Level III)]

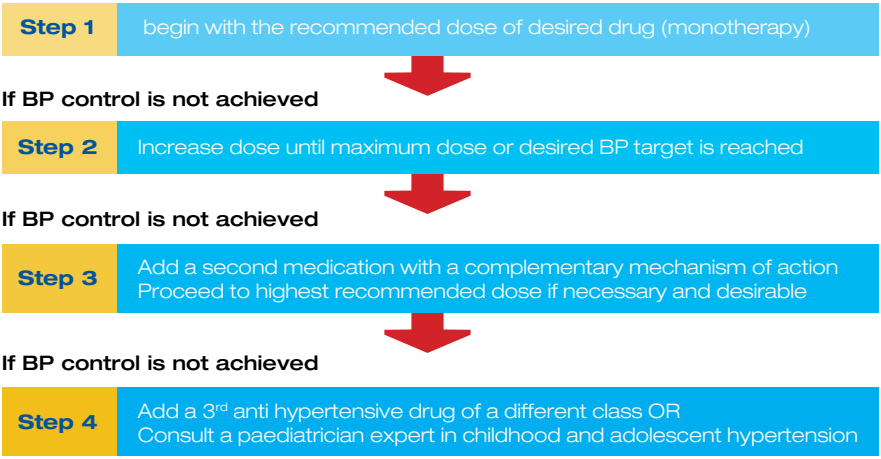
Pharmacologic Treatment

Definite indications for initiating pharmacotherapy include:[283]

- Diabetes Mellitus Type 1 and 2
- Hypertension with TOD
- Stage II hypertension
- Symptomatic Hypertension
- Secondary Hypertension
- Persistent Hypertension despite non-pharmacological measures

Stepped Care Approach
An individualised stepped care approach to the use of anti-hypertensive drugs has been recommended by the National High Blood Pressure Education Program (NHBPEP) working group.[283]

Stepped care approach:



Evidence based treatment recommendation is lacking in paediatric patients. It should not be assumed that what works for adults will work well for children and adolescents. It is probably advisable to consider several classes of agents including diuretics, ß-blocker, ACEI, ARBs and CCBs as potentially acceptable first line agents.[283,286,287]

Appendix 2 contains dosing recommendations for antihypertensive drugs used in children aged 1–17 years old.

Proteinuric Chronic Kidney Diseases[283]
NHBPEP Working group recommended ACEIs or ARBs be used preferentially in children with proteinuric CKD.

Obese Hypertensive Children[283]
The diabetogenic potential of diuretics and ß-blockers need to be considered and should probably be avoided as initial therapy in children who are obese and hypertensive.

Many drugs now have specific paediatric labelling.[288] These have been driven by initiatives to ensure that prescribed antihypertensives are efficacious, safe and contain dosing information.

9.0 PHARMACOECONOMICS OF HYPERTENSION

The public impact and economic burden of hypertension extends 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 ß-blocker in patients with hypertension and LVH. This corresponded to a reduction in the cost per patient directly related to stroke of €1141 in 2005.[289]

In Malaysia, 43% of persons aged 30 years and above were hypertensive in 2006[3] and about RM342.5 million, RM369.6 million and RM380.9 million was spent on anti-hypertensive medicines alone in year 2009, 2010 and 2011, respectively.[290] In 2010, there were 36,998 hypertension-related admissions to MOH hospitals.[291] 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 in 2005.[292] This amounts to at least RM134 million spent on managing hypertensive patients admitted to Ministry of Health hospitals. The above figures are an underestimation. They do not include the many admissions due to heart failure, myocardial infarction, stroke and renal failure where hypertension was the underlying cause.

There were 25,326 admissions for cerebrovascular diseases including stroke to government hospitals in 2010.[291] 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 in 2005.[292] Taking into account the inflation rates over the years, the total cost of managing stroke in government for the year 2010 is estimated to be at least RM101.6 million.

Admissions in MOH hospitals in 2010 for IHD which is mainly AMI were 52,145. The cost of treating acute uncomplicated ST Elevated Myocardial Infarction (STEMI) was RM17,290 using step down method.[293] This is estimated to be RM901.6 million. In another study, hypertension was present in 47% of STEMI but 70% and 73% of NSTEMI and unstable angina patients respectively.[294]

Hypertension is the second most common identifiable cause of ESRD (6%) in 2011,[295] with 5201 new cases in that year. The cost of dialysis in a MOH facility was approximately RM33,000 per patient per year in 2005.[296] The public, NGO and private sector provided 31%, 27% and 42% of overall dialysis treatment in 2011, the government provided 59% of total funding for dialysis channeled through various funding and subsidy programmes. The total cost to the country was estimated to be RM318.3 million to treat hypertensive patients that needed dialysis in year 2011.

Treating hypertension reduced strokes by approximately 40%, coronary heart disease by 16%, and resulted in fewer cases of non-fatal MI, vascular and non-vascular deaths.[297] Efforts should be focused on increasing public awareness, choice of cost effective treatment and patient drug adherence. The total drug cost incurred to the private and government sectors to manage hypertension was RM380.9 million[290] in 2010. This should translate to better rates of hypertension control and reduction in the total cost of managing its sequelae.

Recommendations

- Do not judge hypertension pharmacotherapy by the direct cost of the drug alone. (Grade C)
- The direct cost of treating hypertension is far outweighed by the cost of treating complications of hypertension. (Grade B)
- Educate patients on the cost effectiveness of taking and adhering to drug treatment. (Grade C)

10.0 TYPES OF ANTI-HYPERTENSIVE AGENTS

All stated drug dosages are referenced from MIMS 128th edition 2013[103] 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 anti-hypertensive 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 umol/L or higher), thiazides are less effective and loop diuretics should be used instead.[298]

In the elderly with no co-morbid conditions, diuretics have been shown to not only reduce the incidence of fatal and non-fatal strokes but also cardiovascular morbidity and mortality.[5,65,68,233,299]

Diuretics may be used as initial first-line therapy. They also enhance the efficacy of other classes of anti-hypertensive drugs when used in combination.[300-302]

There has been increasing debate whether pharmacologically defined thiazide diuretics (e.g. hydrochlorothiazide) and the thiazide-like diuretics (e.g. chlorthalidone and indapamide) which have previously been grouped together as "thiazide diuretics" offer comparable benefits in the treatment of hypertensive patients. Most of the outcome studies have used thiazide-like diuretics, chlorthalidone[4,68] and indapamide.[93] There are no convincing outcome data using thiazide diuretics monotherapy, in particular low dose hydrochlorothiazide. A retrospective analysis showed that chlorthalidone reduced cardiovascular events more so than hydrochlorothiazide in hypertensive patients at high risk of cardiovascular events.[303]

Indapamide has also been shown to be an effective BP-lowering agent alone or in combination with other classes of drugs.[35,93] In the very elderly patients, it reduced the incidence of fatal and non-fatal strokes as well as cardiovascular and all-cause mortality.[93]

In general, 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.

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.[304-306]

Table 21. Recommended Dosing for Diuretics

Diuretics	Starting Dose*	Recommended Maximum Daily Dose*
Hydrochlorothiazide	12.5 mg od	50 mg od
Chlorthalidone	50 mg od	100 mg od
Amiloride/hydrochlorothiazide 5 mg/50 mg	1 tablet od	2 tablets od
Indapamide SR	1.5 mg od	1.5 mg od
Indapamide	2.5 mg od	2.5 mg od

* Referenced from 132th Edition, MIMS, 2013

10.2 BETA-BLOCKERS (ß-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 ß-blockers have been shown to be beneficial in patients with heart failure. (**Table 8**)

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

They are generally well tolerated. Adverse effects reported include dyslipidaemia, masking of hypoglycaemia, an increased incidence of new onset diabetes mellitus. Despite that a recent long-term follow-up of a study in newly diagnosed type 2 diabetes showed that the benefit of ß-Blocker persisted and is even better than an ACEI.[307] (Level II-2) Other reported adverse events include erectile dysfunction, cold extremities and nightmares (especially for lipophilic ß-Blockers), increase triglyceride levels and reduce HDL levels (especially for non-selective ß-blockers). Use of ß-blockers during pregnancy is cautioned.

With the advent of newer anti-hypertensive agents with better efficacy and better safety profile, concern has been voiced over their widespread use in the treatment of hypertension.[308,309] In a major landmark study, an ARB was shown to be superior than ß-Blocker in patients with high risk hypertension and ECG LVH.[87] This prompted a meta analysis on the use of ß-blockers in the treatment of hypertension.[69] Beta-blocker therapy did not reduce the risk for first myocardial infarction compared to other drugs but was associated with a significant 16% higher risk for stroke when compared to non-ß-blocker therapy and that atenolol in particular was associated with a significant 26% increase in the risk of stroke when compared to other anti-hypertensive agents. Beta-blockers lower brachial systolic blood pressure but not the aortic pressure compared to other drugs. Heart rate is reduced but peripheral resistance is increased, thus increasing the arterial wave reflection during systole rather than diastole.[310] (Level I) Similarly, another meta analysis[71] and a systematic review also showed that ß-blockers were associated with a significant increase in their withdrawal due to side effects.[311] However a more recent meta analyses showed that ß-blocker is as effective as other drugs in improving clinical outcome.[73-76]

National Institute for Clinical Excellence (NICE) UK Guideline[20] in 2011 and JNC VIII [77] did not place ß-blockers as first line in their recommendation of anti-hypertensive therapy. It is however still recommended as first line by other guidelines.[22,78,79]

Table 22. Recommended Dosing for ß-blockers

ß-blockers	Starting Dose*	Recommended 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
Nebivolol	5 mg od	10 mg od

* Referenced from 132th Edition, MIMS, 2013

10.3 CALCIUM CHANNEL BLOCKERS (CCBs)

Calcium channel blockers are structurally and functionally heterogenous class of drug. They all cause vasodilation, which decreases peripheral resistance.

They are shown to be safe and effective in lowering blood pressure, both as first-line agents and in combination with other classes of antihypertensive drugs. 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.[203,312,313,314] They are also effective in reducing cerebrovascular event compared with other active therapies in primary prevention.[314]

For long-term use, short acting CCBs are no longer recommended and should be phased out. The use of short acting CCB should be confined to certain types of hypertensive crisis.[315] Long acting CCB is to be preferred for long term use. Its generic formulations are now widely available. Long acting CCB is particularly useful in treating hypertensive IHD.[316] This is partly because CCB improves endothelial nitric oxide and cause an increase flow mediated endothelial function.

There is a growing body of evidence to suggest that dihydropyridine CCB and RAAS blocker have additional beneficial effects when used in combination.[90,317] A landmark single pill combination trial showed that combination of ACEI and dihydropiridine CCB was more effective in preventing cardiovascular events than combination of ACEI with hydrochlorothiazide.[92]

Table 23. Recommended Dosing for CCBs

Dihydropridines	Starting Dose*	Recommended Maximum Daily Dose*
amlodipine	5 mg od	10 mg od
felodipine	5 mg od	10 mg od
isradipine	2.5 mg bd	10 mg bd
lacidipine	2 mg od	6 mg od
lercanidipine	10 mg od	20 mg od
nifedipine	10 mg tid	20 mg tid
Non-dihydropridines		
diltiazem	30 mg tid	120 mg tid
diltiazem SR	100 mg od	200 mg od
verapamil	80 mg tid	160 mg tid
verapamil SR	240 mg od	240 mg od

* Referenced from 132th Edition, MIMS, 2013

10.4 ACE INHIBITORS (ACEIs)

Angiotensin converting enzyme inhibitors are well recognised as effective antihypertensive agents which can lower cardiovascular risk and reduce mortality and morbidity in hypertensives and those at high cardiovascular risk.[36,318] They are generally well tolerated and do not have adverse effects on lipid and glucose metabolism. Their safety profile is good. Angiotensin converting enzyme inhibitors have also been shown to reduce mortality and morbidity in patients with congestive heart failure[319,320] and in post myocardial infarction patients with reduced left ventricular ejection fraction.[321-324]

In the diabetic patient, ACEIs have been shown to reduce cardiovascular mortality.[123] In addition, they have been shown to prevent the onset of microalbuminuria, reduce proteinuria and retard the progression of renal disease. Angiotensin converting enzyme inhibitors have also been shown to reduce proteinuria and retard progression of non-diabetic renal disease.[325]

In patients with established vascular disease but normal left ventricular function, ACEIs reduce mortality, myocardial infarction, stroke and new-onset congestive heart failure.[36,326] These benefits are probably 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 and potassium should be checked before initiation and during treatment. In elderly and renal impaired patients, serum creatinine and potassium should be checked within two weeks after initiation or increase in dose. Any increase in serum creatinine and/or potassium should be verified and monitored. If there is hyperkalemia (>5.6 mmol/L) or a rise of serum creatinine of more than 30% from baseline within two months, the dose of the ACEI should be reduced or discontinued.

This class of drug may increase foetal and neonatal mortality and therefore are contraindicated in pregnancy, and should be avoided in those in child-bearing age.

Table 24. Recommended Dosing for ACEIs

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

*Referenced from 132th Edition, MIMS, 2013

10.4.1 Combination Therapy with ACEI

The combination of an ACEI and a dihydropyridine CCB is preferred over the combination of an ACEI and a thiazide diuretic in patients with hypertension and high CV risk.[92] This combination is also better than combination of ß-blockers and diuretics in hypertensive patients with moderate risk and no obvious cardiovascular disease.[90]

10.5 ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

Angiotensin Receptor Blockers are drugs which specifically block angiotensin II receptors. Unlike ACEIs, persistent dry cough is less of a problem. As such ARBs are recommended in ACEI intolerant patients. As with ACEIs, they are contraindicated in pregnancy. It may be used with caution in bilateral renal artery stenosis.

Angiotensin Receptor Blockers can be recommended for moderate to high-risk patients with coronary artery disease as an alternative in ACEI intolerant patients.[327]

Angiotensin Receptor Blockers are effective in preventing progression of diabetic nephropathy[110,328] and may reduce the incidence of major cardiac events in patients with heart failure[329,330] hypertensive LVH[87] and diastolic heart failure.[176]

The Blood Pressure Lowering Treatment Trialist Collaboration (BPLTTC) in a meta analysis of 21 randomised trial[331] found that there were no clear differences between ACE inhibitors and ARBs for the outcomes of stroke and heart failure.

Table 25. Recommended Dosing for ARBs

ARBs	Starting Dose*	Recommended 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

* Referenced from 132th Edition, MIMS, 2013

The safety profiles of ARB are very similar to those of ACEI except for a lower incidence of cough. There was an initial concern of increased risk of cancer with ARB therapy. However a recent meta analysis did not provide causal evidence for an increased risk.[332,333]

ARBs and Risk of MI

There is some concern from ARB trials that there is an excess of MI[125] and total mortality[334] but none of these outcomes were statistically significant. In addition, in the largest ARB trial on CV protection, there was no statistically significant increase in MI or total mortality compared to ACEI.[326] This is supported by a recent meta analysis. This meta analysis showed that the use of ARB in hypertensive patients does not adversely affect all cause mortality. All cause mortality on the other hand was reduced with ACEI.[335]

In patients with LV dysfunction post MI, ARB has also been shown to be non-inferior to ACEI.[336]

Combination of ACEI and ARB

The combination of ACEI and ARBs is not recommended in hypertensive with normal renal function.[78,326]

This combination may be considered in hypertensive patients with significant residual proteinuria after maximal monotherapy, and will require nephrologist supervision.

10.6 DIRECT RENIN INHIBITORS (DRIs)

Direct Renin Inhibitors (DRIs) is a new class of anti-hypertensive agent. This class of drug block the RAAS at the first and rate-limiting step of the cascade by preventing renin from cleaving angiotensinogen to angiotensin I. This will result in excessive renin concentration but not in the Plasma Renin Activity (PRA).

Of this class of drugs, currently only aliskiren is orally active and has a long half-life.[337] It is therefore effective in producing a sustained lowering of BP.[338] Aliskiren was found to exhibit potency comparable with ARB and ACEI.[339]

Aliskiren may be combined with the other classes of anti-hypertensive drugs for added BP lowering. The combination of aliskiren and hydrochlorothiazide decreased seated SBP by 3.5 to 13.5 mmHg and decreased seated DBP by 2.1 to 7.3 mmHg.[340] The combination resulted in a significantly higher responder rates compared with those of the component monotherapies.[340] There was no significant difference in BP lowering between a combination of aliskiren and amlodipine 5 mg compared with amlodipine 10 mg.[341] Aliskiren is not recommended for combination with other classes of RAAS blockers for control of blood pressure.

Aliskiren has been found to be safe and well tolerated with an adverse effect profile similar to placebo. The most common side effect is diarrhea (2.3%) and is more common with doses higher than 300 mg daily. Other reported adverse effects included cough (1.1%), rash (1%), elevated uric acid (0.4%), gout (0.2%), and renal stones (0.2%).

Table 26. Recommended Dosing for DRI

DRI	Starting Dose*	Recommended Maximum Daily Dose*
Aliskiren	150 mg/day	300 mg/day

* Referenced from 132th Edition, MIMS, 2013

Doses greater than 300 mg daily result in no additional BP lowering and increased adverse effects. Dosage need not be adjusted in elderly patients.

Initial studies in humans with diabetic nephropathy[342,343] and heart failure[344] have used the addition of aliskiren on top of another RAAS blocker (ACEI or ARB). Using albuminuria reduction and BNP as surrogate markers respectively, the early results were promising. However, a later study on a larger number of patients with diabetic nephropathy using aliskiren and a ACEI or ARB was stopped prematurely because of increased adverse events compared with an ACEI or ARB alone.[345,346]

In view of the above adverse events, it is not recommended that aliskiren be added to an ACEI or an ARB in patients with diabetes.

10.7 MISCELLANEOUS DRUGS

10.7.1 The ∂-Blockers and the Combined ∂, ß-Blockers

The peripheral ∂1-adrenergic blockers lower BP by reducing peripheral resistance. They also reduce prostatic and urethral smooth muscle tone and provide symptomatic relief for patients with early benign prostatic hyperplasia (BPH).[347] They should be the treatment of choice for hypertensive patients with BPH. The use of non-specific ∂-blockers like phentolamine and phenoxybenzamine has been restricted to the treatment of phaechromocytoma.

In addition, ∂-blockers have favourable effects on lipid metabolism. However postural hypotension is a known side effect, especially at initiation of therapy.[348,349] It should be used cautiously in the elderly if indicated.

Combined ∂ and ß-blockers offer enhanced neurohormonal blockade. Labetalol has been in use for over 20 years and is safe in pregnancy (Refer to chapter 8 on **Hypertension in Pregnancy**). The intravenous formulation is useful in hypertensive emergencies, including pre-eclampsia and eclampsia.[350]

Carvedilol has been shown to be effective in hypertension and also to improve mortality and morbidity in patients with heart failure.[351-353] In addition, it has no adverse effects on insulin resistance and lipid metabolism.[354] However, its safety in pregnancy has not been established.

Table 27. Recommended Dosing for ∂-blockers

∂-blockers	Starting Dose*	Recommended Maximum Daily Dose*
Doxazosin	1 mg	16mg od
Prazosin	0.5 mg nocte	20mg in divided doses
Terazosin	1 mg	5mg od

* Referenced from 132th Edition, MIMS, 2013

Table 28. Recommended Dosing for ∂, ß-blockers

∂, ß-blockers	Starting Dose*	Maximum Dose*
Labetolol **	100 mg bd	2.4 gm 3-4 times a day
Carvedilol ***	12.5 mg od	50 mg od

* Referenced from 132th Edition, MIMS, 2013
** In the elderly start with 50 mg bd
*** The dosage of carvedilol for patients with heart failure and angina pectoris is different from the doses indicated above.

10.7.2 Centrally Acting Agents

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

Alpha-methyldopa has been in use for many years. It is the drug of choice for hypertension in pregnancy. It may be considered for resistant hypertension in combination with other classes of anti-hypertensive agents.[355]

Clonidine should **NOT** be withdrawn suddenly because rebound hypertension may occur.[356] The use of clonidine is discouraged because safer and more potent drugs are available.

Moxonidine is an orally administered imidazoline compound with selective agonist activity at imidazoline II receptors. It 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 anti-hypertensive agents. Studies have suggested that it may improve the metabolic profile of patients with impaired glucose tolerance or diabetes. Absorption is rapid and unaffected by food.[357] Rebound hypertension on cessation of the drug is less likely compared to clonidine but abrupt withdrawal is not recommended. When used with a ß-blocker the chance of a rebound is higher and it is recommended that the ß-blocker be stopped first, and moxonidine then tailed down a few days later. It has been shown to increase mortality in patients with HF and therefore contraindicated.[358]

In patients with renal impairment the dose needs to be reduced as follows:

Table 29. Recommended dosing for Centrally Acting Agent (Creatinine Clearance 30-60 ml/min):

Centrally Acting Agent	Starting Dose*	Maximum Dose*
Moxonidine	≤200 mcg in single dose	400 mcg in divided doses

* Referenced from 132th Edition, MIMS, 2013[103]

If the creatinine clearance is <30 ml/min moxonidine should not be used.

Table 30. Recommended Dosing for Centrally Acting Agents

Drug	Starting dose	Maximum dose
∂-methyldopa*	125 mg bd	500 mg tds
Clonidine	500 mcg tds	4 mg tds
Moxonidine	• 200 mcg od • To be avoided if GFR <30	• 600 mcg in divided doses • 400 mcg in divided dose (GFR 30–60) • To be avoided if GFR <30

* For dosage in pregnancy, refer to chapter on pregnancy

10.7.3 Direct Vasodilators

The direct vasodilators include hydralazine and minoxidil. Hydralazine is only available in parenteral formulation for hypertensive emergencies (Refer to **Hypertensive Emergencies** and **Hypertension in Pregnancy**). 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. Hirsuitism is a troublesome side-effect with long-term use of minoxidil. These drugs should only be prescribed by physicians familiar their usage.

Table 31. Recommended Dosing for Direct Vasodilators

Drug	Starting Dose	Maximum dose
Minoxidil	5 mg od	50 mg od
Hydralazine	10 mg qid	50 mg qid

11.0 RESISTANT HYPERTENSION

Resistant hypertension is defined as uncontrolled hypertension (>140/90 mmHg) with good medication adherence in spite of the concurrent use of three anti-hypertensive agents (including a diuretic) in adequate doses.[22,24] Based on this definition, prevalence of resistant hypertension from a survey by the Institute of Health Management, Ministry of Health is 12%.[359] A survey in primary care in Selangor also revealed a similar prevalence of around 12%.[360] In a large study, prevalence of resistance hypertension was reported to be 15%.[68] These figures are likely to be an overestimate because many of the patients are not necessarily on diuretics.

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

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

It is therefore important that a thorough review of the patient's history, physical examination and investigations be done including estimation of renal function including glomerular filtration rate (eGFR). A home or ambulatory blood pressure measurement should be done to exclude isolated office hypertension. (Refer to chapter 2 on **Measurement of Blood pressure**).The prevalence of isolated office resistant hypertension ranges from 35%– 44% [361,362]

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

Excluding Secondary Hypertension
Although the prevalence of secondary hypertension is around 5%, its prevalence is higher in patients with resistant hypertension. Depending on series, prevalence of secondary hypertension among patients with resistant hypertension can be as high as 66%, with obstructive sleep apnoea, accounting for most of it.[363,364] In two large series, primary aldosteronism was diagnosed in 11% of patients with resistant hypertension.[365,366] Subsequent investigations arranged should be guided by symptoms present, examination findings elicited and results from preliminary investigations. It is prudent that any investigations to be ordered or arranged must be rational with cost effectiveness in mind.

Treatment options in resistant primary hypertension

a. Non-pharmacological Management
Non-pharmacological approaches (therapeutic lifestyle modification) must be re-emphasised. (Refer to chapter 5 on **Non-Pharmacological Management**)

b. Pharmacological Management
A fourth drug should be added to the combination of RAAS blocker, CCB and diuretic.

Drugs tested in randomised controlled trials include spironolactone. A review of 5 prospective trials showed that spironolactone can reduce BP in patients with resistant hypertension by an additional 22/10 mmHg.[367] Alpha methyldopa has also been tested as an efficacious treatment for resistant hypertension.[368] Some patients may require more than four drugs to achieve BP control.

c. Renal Denervation

Over the last 2 years a new form of treatment has been available in the form of transluminal ablation of renal artery (renal denervation or RDN) and the treatment is now available in a few centres in Malaysia. It began with a successful proof of concept trial[369] and has been subsequently shown to be efficacious in a small randomised trial [370] and slightly bigger case report.[371] Being a new mode of invasive intervention, strict criteria needs to be observed before it can be performed.

Patients eligible for this treatment must have the following characteristics: [372]

i. absence of false resistant hypertension by doing Ambulatory Blood Pressure or Home BP Monitoring
ii. absence of secondary resistant hypertension
iii. absence of obstructive sleep apnea, high salt intake, BP raising drugs and severe obesity
iv. absence of suspicious renal vascular pathology or anomaly especially renal artery stenosis, multiple renal arteries or main renal artery diameter of less than 4mm
v. Near normal renal function (eGFR >45ml/min/1.73m^2)

It is important that a prudent approach to selecting patients for RDN be in place to avoid unnecessary procedures. A multidisciplinary team (physician, cardiologist, endocrinologist and nephrologist) is recommended that will collectively select the right patients for this procedure.

Advantages of RDN besides lowering BP, includes improving components of metabolic syndrome, sleep apnea and overall sympathetic drive. A larger clinical trial is currently being conducted in patients with resistant hypertension which include a sham procedure as a control.[373]

Recommendations

- Ensure that patients are treated with at least 3 drugs (inclusive of a diuretic) before diagnosing resistant hypertension. (Grade C)
- Consider drug non adherence and secondary hypertension before labeling a patient to have resistant hypertension. (Grade C)
- Consider referring for renal denervation in patients with true resistant hypertension. (Grade C)

12.0 ASPIRIN IN HYPERTENSION

Although the benefits of aspirin in secondary CV prevention is incontrovertible, that for primary prevention remains controversial.[374] A recent large meta analysis suggest that for primary prevention, the risk of significant bleeding outweigh the benefits of CV protection.[375] In patients with hypertension a large RCT showed that low dose aspirin (75 mg daily) reduced major CV events especially for MI but had no effect on the incidence of stroke. Non-fatal major bleeds were however twice as common with aspirin.[231] Subgroup analysis of this large trial showed that patients who benefited most are those with well treated hypertensive at higher baseline CV risk or higher baseline BP. [231] The benefits of low dose aspirin was also most convincing in patients with well controlled BP and moderate rise in serum creatinine (>114 umol/L). [376]

Recommendations

- Consider using antiplatelet in patients with higher baseline BP (Grade B)
- Treat patients BP to target once they are on antiplatelets (Grade A)

13.0 LIPID LOWERING IN HYPERTENSION

Just like for aspirin, the use of lipid lowering drugs (particularly statin) is well established in patients with high CV risk with or without hypertension. For primary prevention in hypertensive patients, the result have been mixed. In the ALLHAT study high dose pravastatin failed to show any mortality and cardiovascular benefits in high risk hypertensive with mildly elevated blood pressure.[377] The lack of benefits remains after long term follow up.[378] The level of lipid lowering achieved was however very modest. On the other hand, in the ASCOT study low dose atorvastatin in medium risk hypertensive patients with moderately elevated blood pressure showed substantially significant cardiovascular events reduction[379], although just like with pravastatin there was no mortality benefits. On long term follow up ,the benefit of atorvastatin remains, but this time the benefits include a reduction in all cause mortality, suggesting a legacy effect.[380]Taking stock of these two conflicting studies, a subsequent meta analysis including other statin trials with a large number of patients recruited showed benefits of statin therapy on cardiovascular mortality and morbidity.[381 (Level I)] in the hypertensive population.

Recommendations

- Initiate statin therapy for primary prevention in patients with concurrent hypertension and mildly elevated cholesterol. (Grade A)
- Start statin if LDL-C is > 2.6mmol/L in high risk and > 3.4 mmol/L in medium risk hypertensive patients (Grade A)
- The choice of statin is not as important as the level of cholesterol lowering achieved. (Grade B).

APPENDICES

Appendix 1: Estimated BP values after 2 weeks of age in infants from 26 to 44 weeks postconceptual age.

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

Appendix 2 : Recommended dosages for selected anti-hypertensive agents for the management of hypertension in children and adolescents

Drugs	Doses	Frequency
Angiotensin-Converting Enzyme Inhibitors		
Captopril	0.3 – 0.5 mg/kg	BD or TDS
Enalapril	0.08 – 0.6 mg/kg	Once daily or BD
Angiotensin-Receptor Blockers		
Irbesartan	6 – 12 years : 75 – 150 mg/day >13 years : 150 – 300 mg/day	Once daily
Losartan	0.7 – 1.4 mg/kg	Once daily
Calcium Channel Blockers		
Amlodipine	0.06 – 0.3 mg/kg 6 – 17 years : 2.5 – 5 mg	Once daily
Nifedipine	0.25 – 0.5 mg/kg	TDS or QID
Beta Adrenergic Blockers		
Atenolol	0.5 – 2 mg/kg	Once daily or BD
Metoprolol	0.5 – 2 mg/kg	BD
Propranolol	1 – 2 mg/kg	BD or TDS
Diuretics		
Frusemide	0.5 – 2 mg/kg	Once daily or BD
Hydrochlorothiazide	0.5 – 1 mg/kg	Once daily
Spironolactone	1 mg/kg	Once daily

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