ADHERENCE TO MEDICATION AMONG HYPERTENSIVE OUTPATIENTS IN THE PENANG GENERAL HOSPITAL, MALAYSIA

AMAL KHALIL TURKI SULEIMAN

UNIVERSITI SAINS MALAYSIA
2010

ADHERENCE TO MEDICATION AMONG HYPERTENSIVE OUTPATIENTS IN THE PENANG GENERAL HOSPITAL, MALAYSIA

By

Amal Khalil Turki Suleiman

Thesis submitted fulfillment of the requirements for the degree of Doctor of Philosophy

June 2010

Acknowledgments

With profound gratitude and sincerity, I would like to acknowledge the following people. Without their help, advice, cooperation, moral support and prayers, this thesis would not have been completed.

Firstly, my deep gratitude goes to Associate Professor Dr. Syed Azhar Syed Sulaiman, who was my advisor. Without his unconditional support and thoughtful advice I would not be where I am today. I am deeply indebted to him for his tireless editing, guidance and the supportive role he has adopted throughout.

I also thank the examination committee and experts, who took the time to pose challenging questions, comments, criticism and encouragement that enabled me to finish writing this research.

I am profoundly grateful to the administration of Peneng General Hospital and hypertension outpatient clinic for the opportunity they provided to me to further my studies. I specifically thank the physicians, staff nurses and 384 hypertensive patients who participated in this thesis. My deep appreciation to them can never be adequately expressed.

Finally, my greatest thanks go to my father, mother, sisters, brothers and my husband for their prayers, inspiration and constant encouragement, which comprise my greatest motivation, and I dedicate this work to them.

TABLES OF CONTENTS

CHAPTER 3 - RESEARCH METHODOLOGY

CHAPTER 4 – RESULTS AND DISCUSSION

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

· **AC**	Active coping toward health problem
· **ACEI**	Angiotensin Converting Enzyme Inhibitor
· **AD**	Adherence
· **ADR**	Adverse drug reaction
· **AFI**	Absolute Fit Index
· **AGFI**	Adjusted Goodness-Of-Fit Index
· **AMOS**	Analysis of Moment Structures
· **AV**	Aversion towards medication
· **Bd**	Twice a day
· **BP**	Blood Pressure
· **CFA**	confirmatory Factor Analysis
· **CFI**	Comparative Fit Index
· **C.R**	Critical Ratio
· **CRC**	Clinical Research Center
· **DBP**	Diastolic blood pressure
· **DF**	Degree of Freedom
· **EFA**	Exploratory Factor Analysis
· **ER**	Emergency room
· **FBG**	Fasting Blood Glucose
· **GFI**	Goodness- of- Fit Index
· **GDP**	Gross Domestic Product
· **GOF**	Goodness of Fit
· **HDL-C**	High-Density Lipoprotein Cholesterol
· **HTN**	Hypertension
· **IFI**	Incremental Fit Index
· **ISHD**	Information System of Hypertension Department
· **JNC**	Joint National Committee
· **LA**	Lack of discipline
· **LDL-C**	Low-Density Lipoprotein Cholesterol
· **MEMS**	Medication Electronic Monitoring System
· **ML**	Maximum likelihood
· **MMAS**	Morisky Medication Adherence Scale
· **MUAH**	Maastricht Utrecht Adherence in Hypertension
· **N**	Population Size
· **n**	Sample Size
· **NCEP**	National Cholesterol Education Program
· **NCQA**	National Committee for Quality Assurance
· **NFI**	Normed Fit Index
· **Od**	Once a day
· **PA**	Positive attitude towards antihypertensive medications
· **PFI**	Parsimonious Fit Index

- **RMSEA** Root Mean Square Error of Approximation
- **SBP** Systolic blood pressure
- **S.E** Standard Error
- **SEM** Structural Equation Modeling
- **SMC** Squared Multiple Correlations
- **SMI** Special Medical Institutions
- **SRMR** Standardized Root Mean Residual
- **TC** Total Cholesterol
- **Tds** Three times a day
- **TG** Triglyceride
- **VIF** Variance inflation factor
- **WHO** World Health Organization

KEPATUHAN TERHADAP PENGAMBILAN UBAT DALAM KALANGAN PESAKIT LUAR HIPERTENSI DI HOSPITAL BESAR PULAU PINANG, MALAYSIA

ABSTRAK

Secara umumnya, kepatuhan terhadap pengambilan ubat antihipertensi tidak didokumenkan kebanyakan di negara sedang membangun. Di samping keberkesanan rawatan antihipertensi, kepatuhan terhadap pengambilan ubat adalah suboptimum dalam kalangan populasi hipertensi di Malaysia. Kajian kohort retroprospektif ini bertujuan menilai kepatuhan terhadap pengambilan ubat dan juga faktor yang mempengaruhinya. Seramai 380 pesakit hipertensi daripada klinik pesakit luar hipertensi di Hospital Besar Pulau Pinang terlibat dalam kajian ini. Skala lapor-sendiri Morisky mencatatkan bahawa 51.3% pesakit (n=195) mempunyai kepatuhan yang lemah terhadap pengambilan ubat antihipertensi yang dipreskribkan. Temu bual berstruktur mencatatkan bahawa masalah lupa, sokongan sosial yang lemah, kesan sampingan ubat, dan persepsi bahawa pengubatan jangka panjang mungkin akan menyebabkan ketagihan ubat, adalah faktor utama bagi kepatuhan yang lemah terhadap pengambilan ubat. Pemodelan persamaan berstruktur (structural equation modelling, SEM), mengenal pasti peramal hipotesis multivariat bagi kepatuhan yang lemah terhadap pengambilan ubat, mendapati bahawa kekurangan displin diri, aversi terhadap ubat, dan sikap negatif terhadap ubat, secara umumnya merupakan 75% daripada faktor yang mempengaruhi kepatuhan terhadap pengambilan ubat. ANOVA satu hala dan ujian t bebas daripada sampel bebas menunjukkan bahawa secara statistiknya tiada perbezaan yang signifikan ($p>0.05$ bagi semua) antara pesakit yang patuh dan tidak patuh,

berhubung dengan pemboleh ubah demografi, termasuklah umur, gender, sejarah hipertensi keluarga, bangsa, tahap pendidikan dan pendapatan. Perkaitan yang signifikan ditemui dimana kepatuhan akan menjadi lebih baik jika mereka meningkatkan kekerapan dos harian lebih daripada satu regimen ($p< 0.001$). Analisis regresi linear menunjukkan bahawa kepatuhan yang lemah secara signifikannya adalah peramal bebas daripada tekanan darah yang tidak terkawal. Tekanan darah yang tidak dikawal juga adalah suatu peramal bebas yang signifikan bagi ketidaknormalan profil lipid dan paras glukos ($p<0.05$). Akhirnya, perkaitan yang signifikan ditemui dalam kohort di antara kepatuhan yang lemah dan peningkatan risiko kemasukan ke hospital ($p<0.001$). Berdasarkan keputusan ini, pengamal perubatan sepatutnya menyediakan pendidikan kepada pesakit tentang kepentingan pengambilan ubat antihipertensi dan menilai tahap sokongan sosial untuk mengoptimumkan kepatuhan mereka terhadap pengambilan ubat. Pengamal perubatan juga boleh menganjurkan program yang lebih sensitif bagi disesuaikan dengan keperluan setiap pesakit. Mereka ini lebih berisiko terhadap penyakit koronari dan serebrovaskular dan juga kemasukan ke hospital Oleh itu, kepatuhan terhadap pengambilan ubat dapat dianggap sebagai satu mediator yang penting antara amalan perubatan dan hasil keputusan pesakit.

ADHERENCE TO MEDICATION AMONG HYPERTENSIVE OUTPATIENTS IN THE PENANG GENERAL HOSPITAL, MALAYSIA

ABSTRACT

Adherence to antihypertensive medications in general is not well documented in developing countries, and what is known is far from encouraging. Despite the effectiveness of antihypertensive treatment, medication adherence is often suboptimal in hypertensive Malaysian population. This retro-prospective cohort study aimed to assess the medication adherence, and factors affecting this. A cohort of 380 hypertensive patients was conveniently recruited from the outpatient hypertension clinic at Penang General Hospital, Malaysia. The Morisky self-report scale revealed that 51.3% patients (n=195) had poor adherence to prescribed antihypertensive medication. A Semi-structured interview revealed forgetfulness due to a lack of symptoms; poor social support, medication side effects, and the perception that long-term medication may be addictive were principal factors of poor adherence to medication. The structural equation modelling (SEM), which identified the multivariate hypothesized predictors of poor adherence to medication, showed that a lack of self discipline, aversion towards medication, and a negative attitude towards medication in general negatively accounted for 75% of factors affecting medication adherence. The one-way ANOVA and independent t-tests of independent samples revealed no statistically significant differences ($p>0.05$ for all) between adherent and non-adherent patients with regards to demographic variables, including age, gender, family history of hypertension, race, educational level, and income. A significant association was found between patients had significantly better adherence if they had an increased daily frequency of doses than

once daily regimens ($p<0.001$). The linear regression analysis showed that poor medication adherence was a statistically significant ($p<0.01$) independent predictor of uncontrolled blood pressure. Uncontrolled blood pressure was also a significant independent predictor of abnormalities in the lipid profile and glucose levels ($p<0.05$). Finally, a significant association was found in this cohort between poor adherence to medication and an increased risk of hospital admission ($p<0.001$). Based on these results, healthcare providers should aim to enhance the awareness of patients about the importance of antihypertensive medications and assess the level of social support to optimize their adherence to medication. The healthcare provider may tailor more sensitive interventions programs to suit the unique needs of each patient. They are more at risk of coronary and cerebrovascular diseases and are more likely to experience hospital admission. Therefore, medication adherence is one of the crucial mediators between the aims of medical practice and the ultimate outcome for patients.

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

The disease profile of the world is changing at a rapid rate. Chronic diseases, which include heart disease, stroke, cancer, hypertension, diabetes and mental illnesses, now account for 47% of the global burden of disease and 60% of all deaths (Jack, 2009). Based on World Health Organization (2003) eighty percent of these chronic disease deaths occur in the low and middle income countries, and 50% occur prematurely in people under the age of 70 years. This data disputes the long-held notion that chronic diseases mainly affect affluent countries and older individuals (World Health Organization, 2003).

In Malaysia, chronic diseases are a major health problem, accounting for many of the most prevalent and costly illnesses. Such diseases account for 71% of all deaths and 69% of the total burden of disease (Rampal et al., 2008). In fact, there is growing concern in the Malaysian Ministry of Health about the increasing prevalence of chronic diseases among its population (Lim & Morad, 2004). Healthcare professionals are considering the serious consequences of chronic illness that face the present generation, and plan for the burden that will be placed on the future generation unless appropriate action is taken (Ministry of Health Malaysia, 2006). Data from the Malaysian Ministry of Health Non-Communicable Disease Section (MOH-NCD, 2006) estimated that approximately 11.6 million of Malaysian adults aged between 25 and 64 years had at

least one risk factor for a chronic disease and only approximately 3% did not have any risk factors.

Hypertension is one of the most common chronic diseases that affect the Malaysian population (Rampal et al., 2008). It is the main reason for clinic visits to physicians, as well as the most common outpatient diagnosis (Lim et al., 1992). Worldwide, the prevalence of hypertension was around 26% in 2000, and is projected to rise to 29% by 2025 (Wu et al., 2009). According to the most recent data from the Ministry of Health Malaysia (2009), hypertension has been on the rise in Malaysia over the past 10 years and now affects an estimated 4.8 million Malaysians. This has also been reported by Rampal et al. (2008) in a recent national survey that sampled more than 16,000 Malaysians, which showed that the prevalence of hypertension amongst those aged 30 years and above had increased from 32.9% in 1996 to 40.5% in 2004, and 42.6% in 2006.

From observations on the current situation of hypertensive patients in Malaysia, Rampal reported in 2008 that the blood pressure (BP) of many treated hypertensive patients remained above the recommended target levels. This high failure rate of treatment has been ascribed largely to poor medication adherence. Martino et al. (2009) reported better control over BP levels among patients who take at least 80% of their medications compared with those who take less than 50% of their prescribed medications. The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure identified poor medication adherence as the main cause for poor control of BP.

In fact, the concept of adherence to medication was first recognized as a major public health problem by Sackett et al. (1979) who reported that only about 50% of patients adhere to their prescribed medications. Recently, this point has also been supported by Vrijens et al. (2009), who reported that approximately half of the 4,783 patients who were prescribed 43 different antihypertensive drugs, including angiotensin II receptor blockers (n=2088), calcium channel blockers (n=937), angiotensin converting enzyme inhibitors (n=665), β-blockers (n=195), and diuretics (n=155), had stopped taking prescribed antihypertensive medication within one year.

Evidently, poor adherence to medication is a serious healthcare concern and has provided challenges to healthcare providers. According to Vrijens et al. (2009) and Wu et al. (2009), adherence to treatment is a critical factor in the low rates of blood pressure control among people with hypertension. Gazmararian et al. (2010) stated that hypertension complication, such as cardiovascular and renal diseases is a major impact of poor adherence to antihypertensive medication. This point has been also expressed by Kim et al. (2010), who stated that non-adherence to antihypertensive treatment recommendations by patients remains a global problem, concluded that promoting patient medication adherence is a major clinical hurdle that is necessary to decrease the overall cardiovascular morbidity and mortality.

The seriousness of poor adherence to treatment in Malaysia was highlighted in 2006 by Hassan et al. (2006) that 55.8% (n=240) of all classes of antihypertensive medication were not taken as directed in the Hospital University Sains Malaysia, Kelantan. The authors went on to argue that when medications are used incorrectly or not taken at all,

this represents a waste of the time, effort and expertise of the healthcare providers, which may impair the quality of life of patients, make their condition more difficult to treat, and cause further complications that creates further financial strain on the healthcare system.

The information provided above enabled the formulation of six unresolved problems with regards to the adherence of patients to treatment for hypertension, which this study aimed to resolve. These six areas are outlined below.

1.2 Research Problems

This study identifies six problems as described below:

1. Patients with well-controlled blood pressure represent only a small fraction of the hypertensive Malaysian population.
2. To date, there has been a shortage of published academic and empirical research on medication adherence among hypertensive patients in Malaysia, most of the reviews of this subject were conducted in Europe or the USA.
3. Most previous studies focused on non-medication adherence from the perspective of healthcare providers, and these tend to ignore the factors that influence the patients from their perspective.
4. Inconclusive findings have been found in previous studies that investigated the relationship between adherence to antihypertensive medication and the frequency of dosages.

5. Few studies have explored the nature of the relationship between BP control and levels of plasma lipids and fasting blood glucose, and this gap has been identified as a further research.
6. Few studies have shown the benefit of medication adherence with regard to a reduction in the risk of hospitalization for hypertensive patients, and this relationship is still unclear.

1.3 Research Objectives

The main objective of this thesis was to examine the adherence to medication among hypertensive outpatients who attend the Penang General Hospital. The specific research objectives, which were based on the research problems outlined in Section 1.2, were as follows:

1. To identify patients with poor adherence to antihypertensive medication.
2. To investigate the factors that influence adherence to antihypertensive medication.
3. To examine the relationship between medication adherence and different daily dosing frequency among hypertensive patients.
4. To examine the relationship between adherence to antihypertensive medication and the control of BP.
5. To examine the relationship between BP control and lipid profile and glucose levels among hypertensive patients.
6. To examine the relationship between medication adherence and its association with hospital admission rates among hypertensive patients.

CHAPTER 2

LITERATURE REVIEW

The topics of (i) hypertension and (ii) medication adherence were reviewed and presented as follows:

2.1 Hypertension

2.1.1 Definition

Hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or greater, and/or a diastolic blood pressure (DBP) of 90 mmHg or greater (The Seventh Report of the Joint National Committee [JNC 7], 2003).

The Seventh Report of the Joint National Committee (2003) report has introduced a new classification that includes four categories: normal BP (SBP <120 mmHg and DBP <90 mmHg); pre-hypertension (SBP between 120 and 139 mmHg and/or DBP between 80 and 89 mmHg); stage I (SBP between 140 and 159 mmHg and/or DBP between 90 and 99 mmHg); and stage II (SBP >160 mmHg and/or DBP >110 mmHg).

2.1.2 Epidemiology

Hypertension is a key contributing cause for at least one third of the premature deaths that are due to heart attacks and even a higher proportion of premature deaths due to stroke (Kandiah et al., 1980). The Framingham Heart Study on the role of BP in the development of congestive heart failure showed that the dominant etiological precursor

was hypertension in 75% of cases (Kannel, 1986). There is increasing evidence that the optimal control of hypertension would reduce the incidence of coronary heart disease and cerebrovascular accidents.

Unfortunately, as Malaysia approaches attaining developed nation status by 2020, the prevalence of chronic lifestyle diseases, such as hypertension, is likely to increase. In fact, periodic national surveys have shown a steady increase over recent years in the prevalence of hypertension (Minister of Health Malaysia, 2009). The latest National Health and Morbidity Survey in 2006 showed that the prevalence of essential hypertension among Malaysian adults aged 30-years-old and above was 43%, which had increased from 33% recorded 10 years ago (Rampal et al., 2008). Moreover, among patients with hypertension who were on drug treatment, only 26% of them had achieved their target blood pressure (Ministry of Health Malaysia, 2006). This finding is consistent with a separate survey conducted by the Institute for Health Management of the Health Ministry with regards to the outpatient management of hypertension in government-funded clinics (Ministry of Health Malaysia, 2009). That survey found that only 28.5% of patients achieved the target blood pressure while receiving anti-hypertensive medication.

The estimated figure of essential hypertension worldwide is a staggering one billion individuals (Chobanian et al., 2003). It is now estimated that there are 4.8 million individuals with essential hypertension in Malaysia. It is also alarming to note that nearly two thirds of individuals with hypertension in Malaysia were unaware of their diagnosis; although there has been an increase in the proportion of individuals who

received treatment among those diagnosed, the rate of controlled hypertension remains poor (Ministry of Health Malaysia, 2009). Since the proportion of hypertensive people will increase dramatically worldwide in the years to come, the prevention, detection, treatment and control of this condition has become a major public health priority.

2.1.3 Types of hypertension

Primary hypertension, which is also termed essential or idiopathic hypertension, accounts for between 90 and 95% of the all cases of hypertension. This chronic elevation in BP occurs in the absence of evidence of any other disease processes (Chobanian et al., 2003).

Secondary hypertension, which accounts for the other 5% to 10% of cases of hypertension, is caused by other pathological states. These causes include renal diseases (for example, acute glomerulonephritis, renal tumors), endocrine disorders (for example, primary aldosteronism), vascular disorders, pregnancy related disease, such as pre-eclampsia, and drug-related disorders (for example oral contraceptive pills, steroids, and cyclosporin; Chobanian et al., 2003).

2.1.4 Signs and symptoms

In most cases, hypertension causes no symptoms. However, if the BP levels are very high, headaches, epistaxis, tinnitus, depression and dizziness can occur, but these complaints are relatively nonspecific (Mulatero et al., 2009; Kearney et al., 2005; Oparil et al., 2003).

2.1.5 Complications of hypertension

The complications of hypertension are a consequence of the degenerative vascular changes that affect several organs, such as the heart, brain, and kidneys. Patients who have uncontrolled hypertension and are non-adherent to anti-hypertensive medications may proceed to develop the following complications (JNC, 2003):

i) Heart failure, myocardial ischemia, and myocardial infarction are common complications of hypertension (Uren & Rutherford, 2010). Hypertension precedes left ventricular failure due to its increased work because of the increased resistance in the systemic vascular system. In the first stage of this process, the left ventricle becomes hypertrophic. In the longer term, the myocardium loses contractility, which causes a gradual expansion and loss of efficiency of the left ventricle. The myocardium will eventually become dilated and congestive heart failure occurs with a high associated mortality and morbidity (Beulens et al., 2007).

ii) Chronic hypertension can lead to the formation of aneurysms within the arterial walls in the brain, which causes the artery to lose its contractility (Mancia et al., 2008). When blood pressure increases further, the aneurysm may rupture, resulting in intracerebral hemorrhage or stroke. There is a high incidence of stroke in individuals with essential hypertension in Western countries, with high rates of morbidity and even mortality depending on the size and location of the stroke unless patients receive immediate specialized treatment (Agarwal et al., 2008).

iii) The rate of onset of renal failure in a hypertensive individual is directly proportional to the level of BP and the rate that the glomerular filtration rate (GFR) deteriorates (Uren & Rutherford, 2010). The GFR commonly declines by 4 and 8 ml/min per year if the SBP remains uncontrolled (Alan, 2010). Uncontrolled hypertension can induce arteriosclerosis in multiple vessels, including the renal artery, which leads to renal failure and uremia. The retention of urine is common urological problem and highly toxic due to accumulation of urine in the bladder. The increase in pressure in the bladder can also prevent urine entering from the ureters or even cause urine to pass back up the ureters and get into the kidneys, causing hydronephrosis, possibly pyonephrosis, kidney failure, sepsis, and if remain untreated may result in impaired consciousness and death (Beulens et al., 2007).

iv) Vascular complications of hypertension include embolism, thrombosis and hemorrhage. The presence of atherosclerotic plaques leads to ineffective blood circulation and a reduction in the blood supply to the high-risk target organs, which include the heart, brain and kidney. Eventually, these result in organ dysfunction, such as in the development of exertional angina, memory impairment and renal dysfunction (Uren & Rutherford, 2010).

v) The risk of blindness increases due to the thickening of the walls of the retinal arteries, which can lead to hemorrhage. Blood is toxic to the optic nerve, and vision becomes gradually more impaired (Alan, 2010).

2.1.6 Management of hypertension

The goal of the management of hypertension is to reduce cardiovascular, cerebrovascular, renal and optical morbidity and mortality. High BP can be controlled within the safe range of normal, as stated in by Section 2.1.3, by non-pharmacological management alone or in combination with pharmacological management.

2.1.6.1 Non-pharmacological management

Based on the report by the JNC-7 in 2003, non-pharmacological management plays an important role in the treatment of hypertension. It involves lifestyle modifications, such as dietary adaptations, exercise, and smoking cessation, amongst others that will be discussed below (Malaysian Index of Medical Specialties, 2007).These strategies should form the basis for the initial advice given to most patients with primary hypertension. Such measures may comprise the only treatment that is necessary in Stage 1 of hypertension and can reduce blood pressure by an average of 10 mmHg (SBP) and 8 mmHg (DBP) (Mancia et al., 2008).

Non-pharmacological management strategies:

a) Weight reduction

Overweight (body mass index > 25 kg/m 2) has been seen in epidemiologic studies to be an important risk factor for higher blood pressure, and there seems to be a linear relation between body weight and blood pressure. Clinical trials have shown that weight loss, especially when combined with dietary sodium restriction, lowers blood pressure in hypertensive and also in normotensive patients (Morgan, 2000).

The Hypertension Prevention Trial showed that a 4% reduction in body weight over 3 years was associated with a 2.4 mmHg reduction in systolic and a 1.8 mmHg reduction in diastolic blood pressures (Morgan, 2000). It is therefore important that all patients be advised to maintain weight near optimal by reducing calorie intake and increasing physical activity.

b) Avoidance of excessive alcohol intake

Alcohol has an acute effect in elevating BP. The standard advice is to restrict the intake of alcohol to no more than 21 units for men and 14 units for women per week (Mancia et al., 2008). Hypertensive patients who are heavy drinkers are more likely to be resistant to drug treatment. The only way to reduce BP effectively in this scenario is by planning a reduction or cessation strategy for their alcohol intake (Malaysian Index of Medical Specialties, 2007).

c) Sodium intake

Dietary salt intake has a linear association with blood pressure. Reduced sodium intake to approximately 100 mmol/ day can prevent hypertension, can facilitate blood pressure control in patients on medication and can potentially prevent cardiovascular events in overweight individuals (Uren & Rutherford, 2010). The Trials of Hypertension Prevention, showed that sodium reduction, alone or combined with weight reduction, can reduce the incidence of hypertension by approximately 20%. The data from these trials led to current recommendations to limit salt intake to 6 g/day, (100 mmol of sodium or 2.4 g per day) (Morgan, 2000).

To reduce salt intake, individuals should consume foods low in salt and limit the amount of salt added to food. Food rich in salt, like pickles, processed foods, chips and chutneys, should be avoided.

d) Regular physical exercise

Increasing aerobic physical activity such as brisk walking, jogging, swimming or bicycling has been shown to lower BP (Morgan, 2000). Significantly; this reduction is independent of any concomitant weight loss. A meta-analysis of 54 randomized controlled trials showed a net reduction of 3.8 mmHg in systolic and 2.6 mmHg in diastolic BP in individuals performing aerobic exercises, compared to controls (Agarwal et al., 2008). General advice on cardiovascular health would be for "milder" exercise, such as brisk walking for 30 – 60 minutes at least three times a week.

e) Cessation of smoking

This is important in the overall management of the patients with hypertension in reducing cardiovascular risk. Smoking can also acutely increase BP (Malaysian Index of Medical Specialties, 2007). Smoking injures blood vessel walls and speeds up the process of hardening of the arteries atherosclerosis (Morgan, 2000). Moreover, the nicotine in cigarettes and other tobacco products raise blood pressure by constricting the blood vessels. This occurs because the oxygen in blood decreases and because nicotine directly stimulates the production of a hormone, epinephrine (adrenaline), in the adrenal gland. Epinephrine raises blood pressure by constricting blood vessels. After tobacco use raises blood pressure, smoker at risk of all the medical consequences of high blood

pressure, not to mention diseases associated with smoking, such as mouth and lung cancer (Malaysian Index of Medical Specialties, 2007).

f) Healthy eating

Appel et al. (1997) demonstrated that a diet rich in fruits, vegetables and dairy products with reduced saturated and total fat content can lower BP significantly (11/6 mmHg in hypertensive patients and 4/2 mmHg in patients with a BP in the higher end of the normal range). This type of diet also has a beneficial effect on overall cardiovascular health (Malaysian Index of Medical Specialties, 2007).

2.1.6.2 Pharmacological management

When pharmacological management is instituted, antihypertensive drugs will be given in a sequence, depending on the response of the patient. Firstly, if there is no indication of a specific drug intervention, such as the presence of heart failure, diabetes mellitus, and renal disease, diuretic drugs are the first choice of drug as a monotherapy for stage I hypertensive patients. Combined antihypertensive drugs are recommended for stage II hypertensive patients; diuretic drugs in combination with other drug groups are habitually used as the first choice of drug. Secondly, if the first drug group is not effective for adequate BP control to reach a normal level, other antihypertensive drug groups or adding a higher dosage of diuretic should be added, provided that the patient can tolerate the potential side effects (Chobanian et al., 2003). The major classes of antihypertensive agents are as follows:

Diuretics

Diuretics are among the most commonly used drugs in the management of hypertension. They act by diminishing sodium chloride reabsorption at different sites in the nephron, thereby increasing urinary sodium chloride and water losses. The diuretics are generally divided into three major classes, which are distinguished by the site at which they impair sodium reabsorption:

1. Loop diuretics act in the thick ascending limb of the loop of Henle.
2. Thiazide-type diuretics in the distal tubule and connecting segment (and perhaps the early cortical collecting tubule).
3. Potassium-sparing diuretics in the aldosterone-sensitive principal cells in the cortical collecting tubule.

Diuretics are usually used as an initial therapy. They also enhance the efficacy of other classes of antihypertensive drugs when used in combination with other medications. In the elderly patient who has no comorbid conditions, diuretics are the drugs of choice in the treatment of combined systolic and diastolic hypertension and isolated systolic hypertension. The use of diuretics has been shown to reduce the incidence of fatal and non-fatal strokes as well as cardiovascular morbidity and mortality (Davis et al., 2003).

Adverse effects with use of diuretics are uncommon, unless high doses are used. Adverse effects 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 (Chobanian et al., 2003). However,

diuretics should be used with care in patients with gout, as they may precipitate an acute attack because diuretics are supposed to have a direct effect on ion exchanger proteins at the proximal tubule lumen membrane in the kidney which enhances the urate reabsorption, resulting in higher blood levels of uric acid. These higher levels reach a supersaturation level, and this is followed by shedding and precipitation of urate crystals into joints or subcutaneous tissues. The joint precipitation activates cellular signal transducers and induces inflammatory mediators, resulting in gouty synovitis (Davis et al., 2003).

Thiazide diuretics are cheap and are one of the most widely-used antihypertensive agents. When used in patients with essential hypertension and relatively normal renal function, thiazides are more potent than loop diuretics. However, in patients with renal insufficiency with a serum creatinine ≥200 μmol/L, thiazides are less effective and loop diuretics should be used instead (Vasavada et al., 2003).

Potassium-sparing diuretics may cause hyperkalemia if given together with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), or are given in patients with underlying renal insufficiency. Aldosterone antagonists and potassium-sparing diuretics should be avoided in patients with serum potassium levels greater than 5.0 mmol/L (Chobanian et al., 2003).

Table 2.1: Diuretics commonly used for the treatment of hypertension in Malaysia

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

Source: Malaysian Index of Medical Specialties (2007)

β-blockers

Beta blockers, also known as beta-adrenergic blocking agents, are drugs that block norepinephrine and epinephrine (adrenaline) from binding to beta receptors on nerves. There are three types of beta receptors and they control several functions based on their location in the body.

- Beta-1 (β1) receptors are located in the heart, eye, and kidneys;
- Beta (β2) receptors are found in the lungs, gastrointestinal tract, liver, uterus, blood vessels, and skeletal muscle; and
- Beta (β3) receptors are located in fat cells.

β-blockers have long been established agents for the treatment of hypertension. They are particularly useful in hypertensive patients with exertional angina, tachyarrhythmias or previous myocardial infarction where they have been shown to reduce cardiovascular morbidity and mortality (Zhang et al., 2006).

Certain β-blockers, such as bisoprolol and long-acting metoprolol have been shown to be beneficial in patients with heart failure. β-blockers are contraindicated in patients with

obstructive airways disease, severe peripheral vascular disease and second and third degree heart block (Zhang et al., 2006).

They are generally well-tolerated medications. Adverse effects that have been reported include dyslipidemia, the masking of hypoglycemia, and an increased incidence of new-onset diabetes mellitus, erectile dysfunction, nightmares and cold extremities.

Table 2.2: Beta-blockers commonly used for the treatment of hypertension in Malaysia

Beta-blockers	Starting dose	Maximum daily dose
Acebutolol	200 mg bd	400 mg bd
Atenolol	50 mg od	100 mg od
Betaxolol	10 mg od	40 mg od
Bisoprolol	5 mg od	10 mg od
Metoprolol	50 mg bd	200 mg bd
Propranolol	40 mg bd	320 mg bd

Source: Malaysian Index of Medical Specialties (2007)

Calcium channel blockers (CCBs)

Calcium channel antagonists block the inward movement of calcium by binding to the L-type calcium channels in the heart and in smooth muscle of the peripheral vasculature. CCB's dilate coronary arteries and peripheral arterioles, but not veins. They also decrease cardiac contractility (negative inotropic effect), automaticity at the SA node and conduction at the AV node. Dilation of the coronary arteries increases myocardial oxigen supply

Long-acting CCBs have been shown to be safe and effective in lowering blood pressure, both as first-line agents and in combination with other classes of antihypertensive drugs

(Julius et al., 2004).There are three major classes of CCBs (phenylalkylamines, dihydropyridines and benzothiazepines), which have different pharmacological characteristics and all are effective in lowering BP (Malaysian Index of Medical Specialties, 2007). With only a few exceptions, they have no undesirable metabolic effects, and their side effect profile in the management of hypertension is good. Dihydropyridines are particularly effective in reducing isolated systolic hypertension (Chobanian et al., 2003). They are also effective in reducing cerebrovascular events by 10% compared with other active therapies (Zhang et al., 2006).

A study by Julius et al. (2004) revealed the potentially harmful effects of short-acting calcium channel blockers, especially of the dihydropyridine type, in patients with coronary heart disease. Some have argued that long-acting calcium channel blockers are safer.

The use of sublingual nifedipine is also discouraged. Its adverse effects include initial tachycardia, headache, flushing, constipation and ankle edema. Unlike other CCBs, verapamil may reduce the heart rate of the patient and care should be taken when used in combination with beta-blockers (Zhang et al., 2006).

Table 2.3: CCBs commonly used for the treatment of hypertension in Malaysia

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

Source: Malaysian Index of Medical Specialties (2007)

Angiotensin-converting enzyme inhibitors (ACEIs)

Angiotensin II is a very potent chemical that causes the muscles surrounding blood vessels to contract, thereby narrowing the vessels. The narrowing of the vessels increases the pressure within the vessels causing high blood pressure (hypertension). Angiotensin II is formed from angiotensin I in the blood by the enzyme angiotensin converting enzyme (ACE). ACE inhibitors are medications that slow (inhibit) the activity of the enzyme ACE, which decreases the production of angiotensin II. As a result, the blood vessels enlarge or dilate, and blood pressure is reduced. This lower blood pressure makes it easier for the heart to pump blood and can improve the function of a failing heart.

ACEIs are generally well-tolerated and do not have adverse effects on the metabolism of lipid and glucose. Their safety profile is good. ACEIs have been shown to reduce

mortality and morbidity in patients with congestive heart failure and in patients who have suffered a myocardial infarction with reduced left ventricular ejection fraction (Malaysian Index of Medical Specialties, 2007).

In the patient with diabetes, ACEIs have been shown to reduce the moratlity rate due to cardiovascular complications (Jafar et al., 2003). In addition, they have been shown to prevent the onset of microalbuminuria, reduce proteinuria and delay the progression of renal disease (Heeg et al., 1989). ACEIs have also been shown to reduce proteinuria and delay the progression of non-diabetic renal disease (Klahr et al., 1994).

In patients with established vascular disease but with normal left ventricular function, ACEIs reduce mortality, myocardial infarction, stroke and new onset congestive heart failure (Malaysian Index of Medical Specialties, 2007). These benefits are independent of their effects on left ventricular function and blood pressure.

The adverse effects of ACEIs include cough and, rarely, angioedema. In patients with renovascular disease or renal impairment, a deterioration in renal function may occur. Serum creatinine should be checked before the initiation of ACEI therapy and repeated within one to two weeks after initiation. Any increase in creatinine should be confirmed immediately and monitored. If there is a rise of serum creatinine of more than 30% from the baseline level within two months, the ACEI should be stopped (Jafar et al., 2003). ACEIs may increase fetal and neonatal mortality and, therefore, are contraindicated in pregnancy and in those planning pregnancy.

Table 2.4: ACEIs commonly used for the treatment of hypertension in Malaysia

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

Source: Malaysian Index of Medical Specialties (2007)

Angiotensin receptor blockers (ARBs)

ARBs are receptor antagonists that block type 1 angiotensin II (AT1) receptors on bloods vessels and other tissues such as the heart. These receptors are coupled to the Gq-protein and IP3 signal transduction pathway that stimulates vascular smooth muscle contraction.

Unlike ACEIs, the side effect of a persistently dry cough is less of a problem as the lung-specific ACE is not inhibited as well. As such, ARBs are recommended in patients who are intolerant to ACEI treatment. However, as with ACEIs, they are contraindicated in pregnancy and patients who have bilateral renal artery stenosis to avoid increasing the risk of acute renal failure due to renal artery contraction. ARBs are effective in preventing the progression of diabetic nephropathy (Brenner et al., 2001) and may reduce the incidence of major cardiac events in patients with heart failure (McMurray et al., 2003), hypertensive left ventricular hypertrophy (LVH; Dahlof et al., 2002), and heart failure (Yusuf et al., 2003).

Table 2.5: ARBs commonly used for the treatment of hypertension in Malaysia

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

Source: Malaysian Index of Medical Specialties (2007)

Miscellaneous drugs

(i) The a-blockers and the combined a- b blockers

a-blockers lower BP by mediating a reduction in peripheral vascular resistance. They also reduce prostatic and urethral smooth muscle tone and provide symptomatic relief for patients with early benign prostatic hypertrophy (BPH). They are the logical choice for the treatment of hypertensive patients with BPH. The use of non-specific a-blockers, such as phentolamine and phenoxybenzamine, has been restricted to the treatment of pheochromocytoma.

a-blockers have favorable effects on lipid metabolism. However, postural hypotension is a well-described side effect; especially at the initiation of therapy (Gillenwater et al., 1995).

Table 2.6: a- blockers commonly used for the treatment of hypertension

a- blockers	Starting dose	Maximum daily dose
Doxazosin	1 mg od	16 mg od
Prazosin	0.5 mg bd	10 mg bd
Terazosin	1 mg od	5 mg od

Source: Malaysian Index of Medical Specialties (2007)

Alpha-beta blockers belong to a larger class of medicines called adrenergic inhibitors. They combine the effects of two types of medicines. They behave like alpha blocker medicines when they affect special receptor cells in the smooth muscles of blood vessels. This action stops cells from receiving chemicals called catecholamines. These chemicals narrow arteries. This makes blood pressure go up. When these chemicals are blocked, blood vessels can relax. This in turn allows blood to flow more easily, resulting in lower blood pressure.

Combined a-b blockers that are commonly used for the treatment of hypertension in Malaysia include labetalol and carvedilol. Labetalol has been in use for over 20 years and is known to be safe for use during pregnancy. The intravenous formulation is also useful in hypertensive emergencies, including pre-eclampsia and eclampsia (Vigil et al., 2006).

Carvedilol has been shown to be effective in the control of primary hypertension and also improves the mortality and morbidity rates of patients with heart failure (Bakris et al., 2004). In addition, it has no adverse effects on insulin resistance and lipid metabolism (Balenis et al., 2004). However, its safety in pregnancy has not been established.

Table 2.7: a , b -blockers commonly used for the treatment of hypertension

a , b - blockers	Starting dose	Maximum daily dose
Labetalol*	100 mg bd	800 mg tds
Carvedilol	12.5 mg od	50 mg od

* In the elderly, start with 50 mg bd
Source: Malaysian Index of Medical Specialties (2007)