PHARMACOECONOMIC ANALYSIS OF UNCOMPLICATED HYPERTENSION IN AMBULATORY CARE CLINIC

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2011

PHARMACOECONOMIC ANALYSIS OF UNCOMPLICATED HYPERTENSION IN AMBULATORY CARE CLINIC

By

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

February 2011

ACKNOWLEDGMENTS

I would like to praise and thank God for blessing me with the opportunity and ability to complete this program.

Words cannot adequately express my gratitude toward my father, Mohammad Al-Efan, my mother, Raja' Bayyan, and my immediate family. Although 7652.82 kilometers separated us, my parent provided much needed emotional and mental support. My five brothers helped me to stay grounded and were ever vigilant to remind me that the little things in life are truly important. Thanks to my wife, Nosaibah, for helping me and provided me with emotional and mental support.

Thank you to Professor Mohamed Izham Mohamed Ibrahim, PhD, for giving me the chance to try, to grow and to achieve. Your guidance was thoughtful and selfless. I appreciated your support and willingness to allow me to pursue a PhD degree.

My sincere appreciation and thanks to Professor Dato' Dr. Tariq Abdul Razak, Dr. Azizi Ayub and Associate Professor Dr. Jamalludin Ab. Rahman for providing guidance during this program.

I would like to thank both nurses, Mdm. Rohani binti Hamzah and Mdm. Hamidah binti Ramis for helping me in data collection and recruiting patients for the study. A special thank you to the academic staff and graduate students I befriended while attending the Discipline of Social and Administrative Pharmacy, Universiti Sains Malaysia for your friendship and advice. I also appreciate the morale support I received from long-time friends and colleagues.

My heartiest and sincere appreciation goes to IIUM for funding my research work (grant EDW B0701-19).

Lastly, I would like to acknowledge the Malaysian Ministry of Health for allowing me to use Jaya Gading Polyclinic for data collection and patients' follow up.

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LIST OF ABBREVIATIONS

$	US Dollar
<	Less than
>	More than
≤	Less than or Equal
≥	More than or Equal
AC/E	Average Cost-Effectiveness Ratio
ACE	Angiotensin-Converting Enzyme
ACTH	Adrenocorticotropic Hormone
AMI	Acute Myocardial Infarction
ARB	Angiotensin II Receptor Blockers
BP	Blood Pressure
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CHF	Congestive Heart Failure
CMA	Cost-Minimization Analysis
COI	Cost-of-Illness
CUA	Cost-Utility Analysis
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
HDL	High Density Lipoprotein
IIUM	International Islamic University Malaysia

IQR	Interquartile range
ITL	Italian Lira
JNC 5	The Fifth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNC 6	The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
JNC 7	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
Kg	Kilogram
LDL	Low Density Lipoprotein
m^2	Meter Square
mmHg	Millimeters of Mercury
MYR	Malaysian Ringgit
N	Number
QALY	Quality Adjusted Life Years
QoL	Quality of Life
SBP	Systolic Blood Pressure
SD	Standard Deviation
TIA	Transient ischemic attack
UK	United Kingdom
US	United States

ANALISIS FARMAKOEKONOMI KE ATAS KES-KES HIPERTENSI YANG TAK RUMIT DI KLINIK RAWATAN AMBULATORI

ABSTRAK

Peningkatan ketidaknormalan tekanan darah dikaitkan dengan penyakit-penyakit kardiovaskular dan ginjal. Hipertensi merupakan masalah utama kesihatan yang dihadapi di serata dunia, berdasarkan frekuensinya yang tinggi. Di Malaysia, prevalens hipertensi di kalangan umur penduduk ≥ 15 tahun adalah 27.8%. Kos langsung dan kos tidak langsung yang tinggi telah dikaitkan dengan hipertensi. Farmakoekonomi mengaplikasikan etika dan metodologi ekonomi kesihatan dalam bidang farmaseutikal dan polisi farmaseutikal. Kajian ini dijalankan untuk: 1) menganggarkan kos bagi merawat hipertensi tanpa komplikasi; 2) menganggarkan impak tekanan darah yang tidak terkawal terhadap sumber penjagaan ambulatori; dan 3) menilai keberkesanan kos bagi jenis ubat antihipertensi yang berbeza.

Data telah dicatat secara prospektif pada sekumpulan pesakit hipertensi selama satu tahun dan data dianalisis secara retrospektif telah dibuat untuk menentukan kos (langsung dan tidak langsung) yang berkaitan dengan pengendalian pesakit hipertensi yang tak rumit. Nisbah kos keberkesanan kelas-kelas ubat hipertensi yang berbeza telah dikira dan dibuat perbandingan. Ujian tak parametrik (Kruskal Wallis dan Mann-Whitney) telah digunakan untuk menentukan perbezaan signifikan antara kos dan nilai $p < 0.05$ dianggap sebagai perbezaan yang signifikan.

Kos-kos langsung berkaitan pengendalian hipertensi pelbagai fasa adalah signifikan (prehipertensi (MYR 12.19), fasa 1 (MYR 11. 86) dan fasa 2 (MYR 14.05)).

Kehilangan produktiviti akibat hipertensi antara ketiga-tiga fasa di atas adalah tidak signifikan (prehipertensi (MYR 10.48), fasa 1 (MYR 8.91) dan fasa 2 (9.43)). Kos-kos langsung berkaitan dengan hipertensi tak terkawal adalah lebih tinggi daripada kos-kos langsung berkaitan dengan kumpulan hipertensi terkawal pada ketiga-tiga kumpulan fasa hipertensi dalam kajian (prehipertensi (MYR 16.79 berbanding MYR 12.19); fasa 1 (MYR 22.31 berbanding MYR 11.86) dan pada fasa 2 (MYR 17.96 berbanding MYR 14.05)). Kos tak langsung bulanan berkaitan hipertensi tak terkawal adalah lebih tinggi berbanding dengan kos-kos tak langsung yang berkaitan dengan kumpulan hipertensi terkawal pada fasa 1 dan fasa 2 dan sebaliknya berlaku fasa prehipertensi (MYR 9.71 berbanding MYR 10.48), pada fasa 1 (MYR 11.18 berbanding MYR 8.91) dan pada fasa 2 (MYR 11.02 berbanding MYR 9.79)). Nisbah kos keberkesanan adalah lebih baik untuk kumpulan-kumpulan diuretik (MYR 2364.86), perencat ACE (MYR 2456.63) dan penghalang beta (MYR 2615.08) daripada penghalang alpha (MYR 2689.26), daripada kumpulan-kumpulan diuretik berserta penghalang beta (MYR 3209.34), penghalang saluran kalsium (MYR 3369.60) dan campuran-campuran lain (MYR 6546.06).

Rumusannya adalah pengurangan kos langsung boleh dicapai dengan kawalan hipertensi. Sumber kos rawatan ambulatori adalah lebih tinggi jika hipertensi tidak terkawal. Ini dapat dilihat pada hipertensi tak rumit tidak kira di fasa apa pun dan ia boleh meningkatkan kos penyelenggaraan kesihatan Negara Malaysia keseluruhannya. Oleh itu, strategi rawatan adalah untuk mengawal hipertensi, tidak kira pada fasa atau peringkat apa pun. Kajian ini juga menunjukkan bahawa rawatan dengan diuretik adalah

paling berkesan kos dalam rawatan hipertensi tak rumit. Akhir kata, analisis farmakoekonomi adalah satu cara yang utama yang dapat membantu polisi penyelenggaraan kesihatan oleh yang berwajib dengan data yang diperolehi.

PHARMACOECONOMIC ANALYSIS OF UNCOMPLICATED HYPERTENSION IN AMBULATORY CARE CLINIC

ABSTRACT

Abnormal elevation in BP is associated with cardiovascular and renal diseases. Prevalence of hypertension in subjects aged ≥ 15 years is 27.8% in Malaysia. Studies have reported high direct and indirect costs are attributable to hypertension. Pharmacoeconomics implements and applies methodologies of health economics to the field of pharmaceuticals and pharmaceutical policy. Malaysia lacks data on how much it cost to treat hypertension and what is the size of the economic burden of hypertension. This study was done to: 1) estimate the cost of treating uncomplicated hypertension, 2) estimate the impact of uncontrolled BP on ambulatory care resources, and 3) evaluate the cost-effectiveness of different antihypertensive drug classes.

Prospective data collection of a cohort of hypertensive patients who had signed the informed consent sheet and followed up for one year were analyzed retrospectively to determine the costs (direct and indirect) attributable to uncomplicated hypertension. Cost-effectiveness ratios of different antihypertensive drug classes were calculated and compared. Nonparametric tests (i.e., Kruskal Wallis and Mann-Whitney) were used to determine the statistically significant differences in costs and a p value of < 0.05 was defined as statistically significant.

Direct costs attributable to hypertension stages were significantly different (prehypertension (MYR 12.19), Stage 1 (MYR 11.86) and Stage 2 (MYR 14.05)).

Productivity lost due to hypertension between the three stages were not significantly different (prehypertension (MYR 10.48), Stage 1 (MYR 8.91) and Stage 2 (MYR 9.43)). Direct costs associated with uncontrolled hypertension groups were significantly higher than direct costs associated with controlled hypertension groups in all stages of hypertension (in prehypertension (MYR 16.79 vs. MYR 12.19), in Stage 1 (MYR 22.31 vs. MYR 11.86) and in Stage 2 (MYR 17.96 vs. MYR 14.05), respectively. Monthly indirect costs associated with uncontrolled hypertension groups were higher than indirect costs associated with the controlled hypertension groups in stage 1 and stage 2 and the opposite was noticed in prehypertension stage (in prehypertension (MYR 9.71 vs. MYR 10.48), in Stage 1 (MYR 11.18 vs. MYR 8.91) and in Stage 2 (MYR 11.02 vs. MYR 9.79). Cost-effectiveness ratio was better for diuretics (MYR 2364.86), ACE inhibitors (MYR 2456.63), and beta-blockers (MYR 2615.08) than for alpha-blockers (MYR 2689.26), the diuretics and beta-blockers combination therapy (MYR 3209.34), calcium channel blockers (MYR 3369.60), and other combinations (MYR 6546.06), respectively.

In conclusion, avoidance of extra direct costs can be accomplished by controlling hypertension. Higher ambulatory care resources costs are associated with poorly controlled hypertensive individuals. Moreover, uncomplicated hypertension, regardless of its stage or severity, may increase the total Malaysian national health costs, and thus, treatment strategies for uncomplicated hypertension should target all hypertensive patients irrespective of their stage. Additionally, this study indicates that diuretics are the most cost effective drug class in managing uncomplicated hypertensive patients.

Finally, pharmacoeconomic analysis is an important method of informing health care policy makers by providing them with supportive information.

CHAPTER ONE

GENERAL INTRODUCTION

1.1 Background

1.1.1 Overview

Abnormal elevation in blood pressure is associated with cardiovascular and renal diseases. Clinicians believe that identifying and treating large number of patients with hypertension is on the top of their list of priorities. Most of the patients diagnosed with hypertension have no particular cause. The deleterious effects of high blood pressure are seen with the normal range of blood pressure and continue with rising blood pressure. There is no sharp distinction between normal and pathologic blood pressure level. However, an agreement as to what levels blood pressure is tolerable and what levels represent hypertension has been described in clinical practice guidelines. Hypertension treatment is still the main goal to reduce cardiovascular and kidney diseases as well as stroke morbidity and mortality (Brent, 2004).

Hypertension is a common disease and is defined as steadily elevated blood pressure. Blood pressure increases with age and hypertension is very common in the elderly. In most cases, there is unknown path physiology for hypertension particularly in the case of essential or primary hypertension. There is no cure for essential or primary hypertension. However, the blood pressure can be controlled. The majority (90 %) of

hypertensive patients has essential hypertension; less than 10% have secondary hypertension (Dipiro, 2008). Secondary hypertension results from a co-morbid disease or drug (Table 1.1). The most common cause of secondary hypertension is severe chronic kidney disease (Dipiro, 2008). Drugs can directly or indirectly cause hypertension or increase blood pressure (Dipiro, 2008).

Table 1.1 Secondary Causes of Hypertension

Disease	Drugs associated with hypertension
Chronic kidney disease Coarctation of the aorta Obstructive sleep apnea Parathyroid disease Pheochromocytoma Primary aldosteronism Renovascular disease Thyroid disease	**Prescription drugs** Corticosteroids, ACTH Estrogens" (usually oral contraceptives with high estrogenic activity) Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors Phenylpropanolamine and analogues Cyclosporine and tacrolimus Erythropoetin Sibutramine Antidepressants (especially venlafaxine), bromocriptine, buspirone, carbamazepine, clozapine, desfulrane, ketamine, metoclopramide Clonidine/ β-blocker combination Pheochromocytoma: β-blocker without α-blocker first **Street Drugs and Other Natural Products** Cocaine and cocaine withdrawal Ma huang, "herbal ecstasy," other phenylpropanolamine analogues Nicotine and nicotine withdrawal, anabolic steroids, narcotic withdrawal, methylphenidate, phencyclidine, ketamine, ergotamine and other ergot-containing herbal products, St. John's wort **Food Substances** Sodium, Ethanol, Licorice, Tyramine-containing foods if taking a monoamine oxidase inhibitor **Chemical Elements and Other Industrial Chemicals** Lead, mercury, thallium and other heavy metals, lithium

Source: Dipiro, J.T., 2008.

Hypertension is a major risk factor for cardiovascular diseases. Coronary heart disease is the most common and lethal complication of hypertension and this due to the low efficacy of antihypertensive drugs against coronary heart disease (Giuseppe, 2002).

1.1.2 Definition and Classification of Hypertension

Arterial hypertension is defined as systolic arterial pressure ≥ 140 mmHg and diastolic arterial pressure ≥ 90 mmHg. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) classified blood pressure in adults (age ≥ 18 years) based on the average of two or more accurately measured blood pressure readings from two or more clinical encounters (Chobanian et al., 2003). Normal blood pressure values considered a systolic blood pressure (SBP) of less than 120 mmHg and a diastolic blood pressure (DBP) of less than 80 mmHg, prehypertension stage (SBP of 120-139 or DBP of 80-89) Stage 1 (SBP of 140-159 or DBP of 90-99) and Stage 2 (SBP ≥ 160 or DBP ≥ 100) (Chobanian et al., 2003). The following table provides a classification of blood pressure for adults at 18 years of age and older.

Table 1.2 Classification of Blood Pressure

Classification	**Systolic Blood Pressure (mmHg)**		**Diastolic Blood Pressure (mmHg)**
Normal	Less than 120	and	Less than 80
Prehypertension	120-139	or	80-89
Stage 1	140-159	or	90-99
Stage 2	Greater than or equal to 160	or	Greater than or equal to 100

Source: Chobanian et al., (2003b)

Hypertensive crises are clinical circumstances where blood pressure values are greater than 180/120 mmHg. They are labeled as a hypertensive emergency. This category of hypertension is characterized by a great elevation in blood pressure that comes with acute or progressing target-organ damage, like encephalopathy, intracranial hemorrhage, acute left ventricular failure with pulmonary edema, dissecting aortic aneurysm, unstable angina, and eclampsia or severe hypertension during pregnancy (Chobanian et al., 2003).

1.1.3 Hypertension Epidemiology

Systolic blood pressure increases as age increases. Diastolic blood pressure increases just until 50 years of age; after that, it becomes steady or decreases to some extent. Increasing age will lead to a swing from diastolic pressure to systolic pressure and finally to pulse pressures as the chief predictor of cardiovascular disease risk (Franklin et al., 2001). At the age of below 50 years, diastolic pressure is the strongest predictor for cardiovascular diseases risk. The transition period when all three blood pressure signs are similar predictors, starts at the age of 50-59. From the age of 60 onwards, diastolic pressure is negatively related to the risk of cardiovascular diseases, and pulse pressure becomes a superior predictor to systolic pressure (Franklin et al., 2001).

Staessen, et al. (2000) found that in middle-aged and older individuals with hypertension, cardiovascular diseases risk worsened with raised pulse pressure; it is

consistent in men and women. Furthermore, the risk increases in treated and untreated hypertensive individuals, and in hypertensive patients with a history of myocardial infarction (Mitchel et al., 1997) or renal failure (Safar et al., 2002). In addition, in older systolic hypertensive patients, ambulatory pulse pressure is a stronger predictor of cardiovascular diseases risk than the pulse pressure measured by conventional sphygmomanometer, while mean pressure regardless of the type of blood pressure measurement, is not predictive (Staessen et al., 2002a).

Hypertension is the most commonly cited reason for a physician's office visit. In a study based in the United States of America in 2000, over 10 million office visits were attributable to high blood pressure (Cherry and Woodwell, 2000). Furthermore, poor control or uncontrolled high blood pressure can increase the severity of hypertension, and thus, healthcare expenditure, through the number of physician visits or even the time interval between the visits to seek health care (Berlowitz et al., 1998; Paramore et al., 2001).

Hypertension is an important public-health challenge in the world due to its high frequency and associated risks of cardiovascular and kidney diseases (Whelton, 1994; He and Whelton, 1997). It has been identified as the primary risk factor for death, and is the third cause of disability-adjusted life-years (Ezzati et al., 2002). Its prevalence in different areas of the world has been extensively reported (Gupta, 1999; Halberstein, 1999; Hernandez et al., 2000; Singh et al., 2000; Ueshima et al., 2000; Wolf-Maier et al., 2003).

Kearney et al. (2005) collected data from different areas of the world to estimate the prevalence and burden of hypertension in 2000, and to estimate the global burden in 2025. Using MEDLINE, supplemented by searching the bibliographies of retrieved articles manually, they have searched the published literature from Jan 1, 1980, to Dec 31, 2002. They included sex age-specific prevalence of hypertension studies in representative population samples. According to Kearney et al. (2005), 26.4 % of the world's male adult population in 2000 and 26.1 % of women suffered from hypertension. By 2025, 29.2 % of the adult population was predicted to have hypertension, and of these, 29 % was predicted in men and 29.5 % in women. However, the study did not mention the reasons behind this difference. World regions with the highest prevalence of hypertension had a rate, which is about twice the rate of areas with the lowest prevalence of hypertension. In men, the highest prevalence was in Latin America and the Caribbean areas, whereas for women the highest prevalence was in the former socialist economies. The lowest prevalence of hypertension for both men and women was in the area called "other Asia and islands" (Figure 1.1) (Kearney et al., 2005).

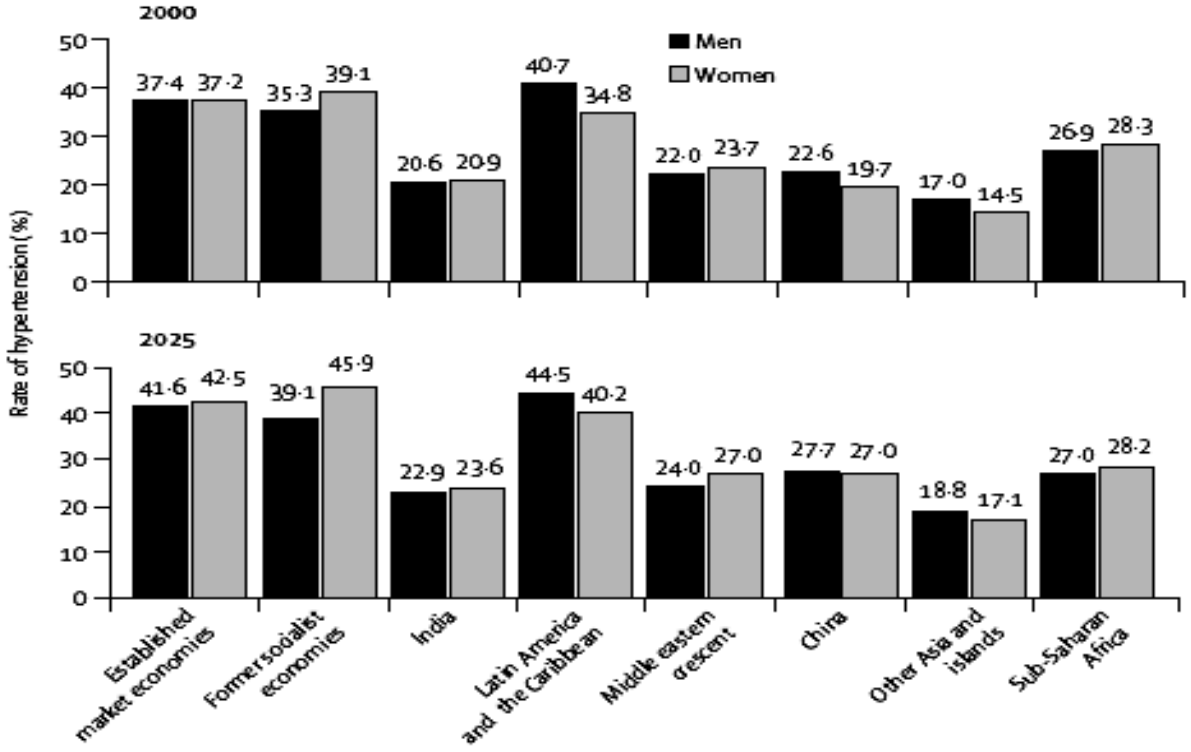

Figure 1.1 Estimated Prevalence of Hypertension in People Aged 20 Years and Older for 2000 and 2025 (Kearney et al., 2005).

Whereas:

Established market economies: USA, Canada, Spain, England, Germany, Greece, Italy, Sweden, Australia and Japan
Former socialist economies: Slovakia
Latin America and the Caribbean: Mexico, Paraguay and Venezuela
Middle Eastern crescent: Egypt and Turkey
Other Asia and islands: Korea, Thailand and Taiwan
Sub-Saharan Africa: South Africa, Cameroon, Tanzania and Zimbabwe

Because of the expected changes in the age of the population between 2000 and 2025, the worldwide prevalence of hypertension was predicted to increase by 9 % in men and 13 % in women (Kearney et al., 2005). The relation between gender and the prevalence

of hypertension according to world geographical area is as in the following: four areas had higher prevalence in men and four had higher prevalence in women. At young ages, prevalence of hypertension is higher in men than in women, while in older people they are higher in women than in men. Figure 1.2 shows approximation of the absolute number of hypertensive individuals in different world areas (Kearney et al., 2005).

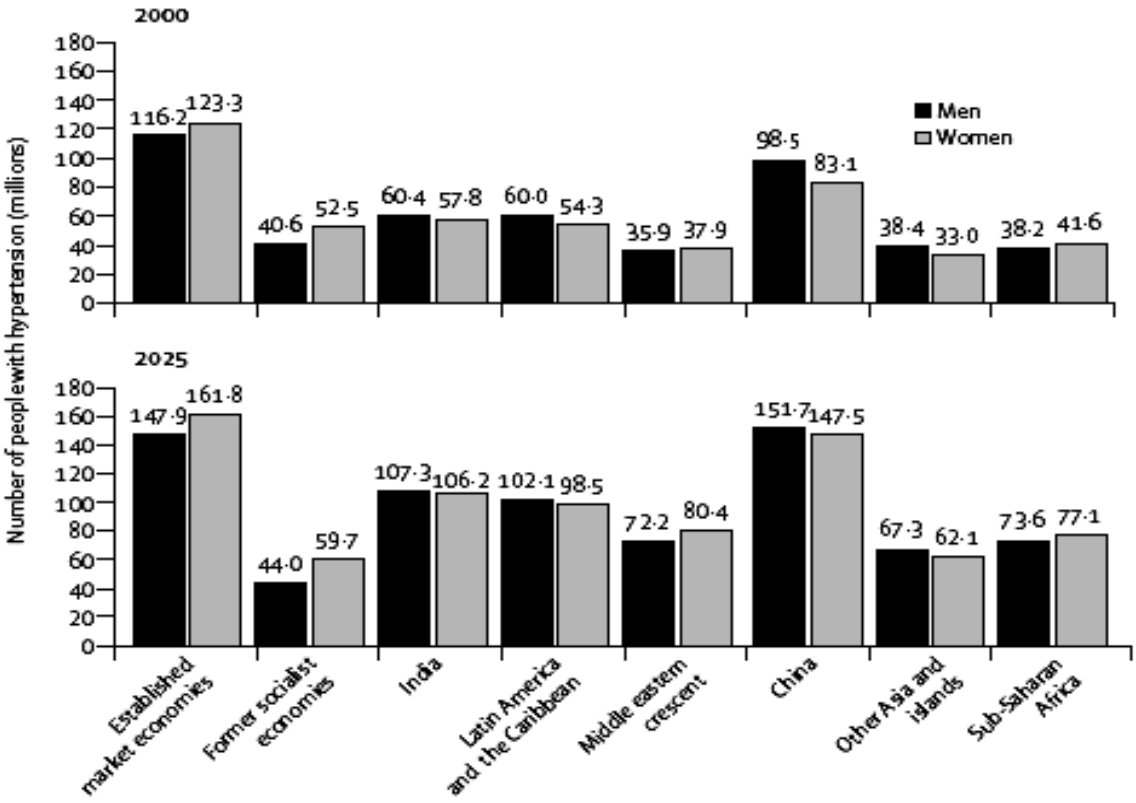

Figure 1.2 Number of Hypertensive Individuals in Different World Areas (Kearney et al., 2005).

The estimated total number of people with hypertension in 2000 was around 972 million; about 333 million were in economically developed countries, and around 639 million in economically developing countries (Kearney et al., 2005). The greatest number of hypertensive individuals was found to be in the established market economies. Nevertheless, both economically developed and developing areas had many individuals with hypertension, and about two-thirds of these hypertensive individuals were in developing areas. In 2025, the number of adult individuals with hypertension is expected to increase by 60 % to 1.56 billion. Although the number of individuals with hypertension in economically developed countries was expected to increase by 24 % from 333 million to 413 million, a rise of 80 % was expected for economically developing countries from 639 million to 1.15 billion. Almost three-quarters of the world's hypertensive population will be in the economically developing countries by 2025 (Kearney et al., 2005).

1.1.4 Hypertension Prevalence in Malaysia

About 30 % (around 2.6 million) of Malaysian adults at the age of 30 years or older have hypertension (Lim et al., 2004). Women have a higher prevalence of hypertension than men do. Malay women and women of other indigenous groups have the highest age-adjusted prevalence of hypertension, whereas Chinese and Indian women have the lowest prevalence. Malay women have a higher prevalence of hypertension than all other sex-ethnic groups (Lim et al., 2004).

According to Lim, et al. (2004), Malay women and women from other indigenous groups have the highest mean systolic blood pressure, Chinese and Indian men had the highest diastolic blood pressure, whereas Chinese and Indian women have the lowest diastolic blood pressure as well as systolic blood pressure. The mean systolic blood pressure rises with growing age, and diastolic blood pressure is likely to decline beyond the age of 50-55 years in all groups. Young women have lower systolic blood pressure than men do. Young Malay women and those from other indigenous groups (aged 35-40) have higher mean systolic blood pressure than the young women do in the Chinese and Indian groups for the whole age range.

In all groups, normotensive men have higher mean systolic blood pressure and diastolic blood pressure than women. Nevertheless, among individuals with hypertension who are treated and untreated, the women have higher mean systolic blood pressure than men, except in the Indian population. Mean diastolic blood pressure in individuals with hypertension who are treated and untreated is higher for men than for women. There is no difference in mean systolic blood pressure and diastolic blood pressure between treated and untreated individuals with hypertension in all groups. A difference in mean blood pressure between treated and untreated hypertensives is found in other indigenous ethnic group (Lim et al., 2004).

According to Lim and colleagues (2004), about one third of people with hypertension are aware of their hypertension status, 31 % had never been treated and only 23% are on antihypertensive drugs. Barely, 6 % of people with hypertension have controlled blood pressure (less than 140/90). In all ethnic-age groups, women are more aware of their

hypertension status than men are. Women are also more likely to be treated and to remain on treatment with antihypertensive drugs. Among people with hypertension being treated, only 26 % achieved blood pressure control. Men tend to have better blood pressure control than women do. Blood pressure control deteriorates with increasing age except for Indians and other indigenous men. However, another most recent study on the prevalence of hypertension in Malaysia reported that the mean systolic blood pressure in men was significantly higher than that in women. Likewise, the mean diastolic blood pressure in men was significantly higher than that in women (Rampal et al., 2008).

In the most recent Malaysian study by Rampal, et al. (2008) (Table 1.4), the prevalence of hypertension in subjects aged ≥ 15 years was 27.8 % and it increased with age in both genders. Hypertension was more prevalent in males than females in subjects aged between 15 to 39 years. Generally, mean systolic blood pressure was 122 mmHg and mean diastolic blood pressure was 79 mmHg. Both means (systolic 124 mmHg and diastolic 80 mmHg) for males were significantly higher than those for females (systolic 121 mmHg and diastolic 78 mmHg).

The prevalence of hypertension increased with age in all ethnic groups. For subjects aged ≥ 15 years, the Chinese had the highest prevalence (30.6 %), followed by the Malays (26.7 %) and the Indians (25.1 %) (Table 1.5). The indigenous people from the state of Sarawak, 'the Sarawak Bumiputra', had a higher prevalence of hypertension (31.1 %) than other ethnic groups (Rampal et al., 2008). Rasool et al., (2000) reported that the Malays might have higher beta-adrenergic receptor sensitivity than the Chinese

and Indians, an observation that could explain the observed difference in hypertension prevalence between the ethnic groups in both studies.

Only 34.6 % were aware of their hypertension. Females were more aware of their hypertensive status (40.6 %) than males (29.4 %) (Table 1.6). Only 32.4 % of the hypertensive subjects in the study were taking antihypertensive drugs and of these, only 26.6 % had a controlled blood pressure (≤ 140/90 mmHg). Overall, 8.6 % of hypertensive subjects had their blood pressure controlled (Rampal et al., 2008).

Previous research conducted by the Malaysian Ministry of Health in 2006 reported that the prevalence of hypertension was 42.6 % amongst subjects aged ≥ 30 years. Additionally, about 36% of hypertensive subjects were aware that they had hypertension and about 87.7% of them were receiving treatment. However, only 26% of those subjects who are on treatment were able to achieve the target blood pressure (Ministry of Health, 2006). The prevalence of hypertension remained high but may be slightly decreased since 2006. In 2009, it is estimated that there are about 4.8 million Malaysians with hypertension.

1.1.5 Management of Hypertension

The main goal of antihypertensive treatment (i.e. pharmacological and non-pharmacological therapy) is to not only reduce blood pressure, but also to prevent cardiovascular and other complications related to elevated blood pressure, to prolong existence, and to improve the quality of life. In the meanwhile, drug approval agencies have approved many new drugs for antihypertensive treatment on the basis that treatment will decrease blood pressure as an intermediate endpoint. As far as controlling blood pressure is concerned, policies call for decreasing both systolic and diastolic blood pressure because of the evidence of the risk of isolated systolic hypertension in old people (Staessen et al., 2000).

Hypertension is associated with cardiovascular and renal diseases. Collins and MacMahon (1994) and Staessen et al. (2001; and 2002b) provided a thorough account of the outcome trials in hypertension and the effects of treatments on primary and secondary endpoints. Additionally, most of the evidences on the effects of blood pressure on the risks of cardiovascular disease derived from prospective observational studies of the associations between blood pressure and the incidence of stroke and coronary heart disease, and from randomized trials of antihypertensive drug therapy (Collins and MacMahon, 1994; Chobanian et al., 2003a; Lawes et al., 2008). The evidence from observational studies is more applicable to the eventual effects of prolonged blood pressure differences on stroke and coronary heart disease risk. The worldwide burden of diseases attributable to hypertension is about 7.6 million premature deaths and 92 million disability-adjusted life years. Additionally, half of

strokes and ischemic heart disease worldwide were attributable to hypertension (Lawes et al., 2008). On the other hand, the evidence from randomized trials is more relevant to assessing how rapidly, and to what degree, the epidemiologically expected reductions in stroke or in coronary heart disease are produced by lowering blood pressure in middle and old age (Collins and MacMahon, 1994).

Ambulatory measurement of blood pressure plays an important role in the management of hypertension. Staessen et al. (2001) investigated whether ambulatory measurement of pulse pressure and mean pressure can refine risk stratification. Their study enrolled 808 older patients with high isolated systolic hypertension. Patients aged ≥ 60 years were randomized to nitrendipine 10-40 mg/day with the possible addition of enalapril 5-20 mg/day or hydrochlorothiazide 12.5-25 mg/day or to matching placebos. Pulse pressure and mean pressure were determined from six conventional blood pressure readings and from 24 hours ambulatory recordings. Later, they computed the relative hazard rates associated with 10-mmHg increase in pulse pressure or mean pressure. As a result, they found that in older patients with isolated systolic hypertension higher pulse pressure estimated by 24 hour ambulatory monitoring was a better predictor of undesirable outcomes than conventional pulse pressure, whereas conventional and ambulatory mean pressures were not correlated with a worse outcome (Staessen et al., 2001).

1.1.5.1 Lifestyle Intervention

Sodium restriction is an effective nutritional therapy in patients with hypertension (Whelton et al., 1997; Hermansen, 2000; Chobanian et al., 2003a). In the Dietary Approaches to Stop Hypertension (DASH) trial, study subjects were given meals with different salt levels for more than 4 weeks. The study diet was rich in fresh fruits, vegetables, and low-fat dairy products. As a result, for both the DASH and traditional diets, the lower the salt intake, the lower was the blood pressure (Sacks et al., 2001). Likewise, calcium food supplementation may also help to reduce blood pressure (Griffith et al., 1999; Zemel, 2001).

In addition, physical activity can lower blood pressure. Regular aerobic exercise for at least half an hour a day for at least 4 days per week is ideal for most hypertensive patients (Fagard, 2001). Patients with target-organ disease should consult their physicians before starting an exercise programme to see whether they are fit to do that specific program or not. Additionally, cigarette smoking is a major independent risk factor for cardiovascular disease and stopping smoking can help in diminishing blood pressure (Mikkelsen et al., 1997). Because of this fact, hypertensive patients, who smoke, should be counseled and encouraged to stop smoking. Figure 1.3 demonstrates the hypertension treatment approach.

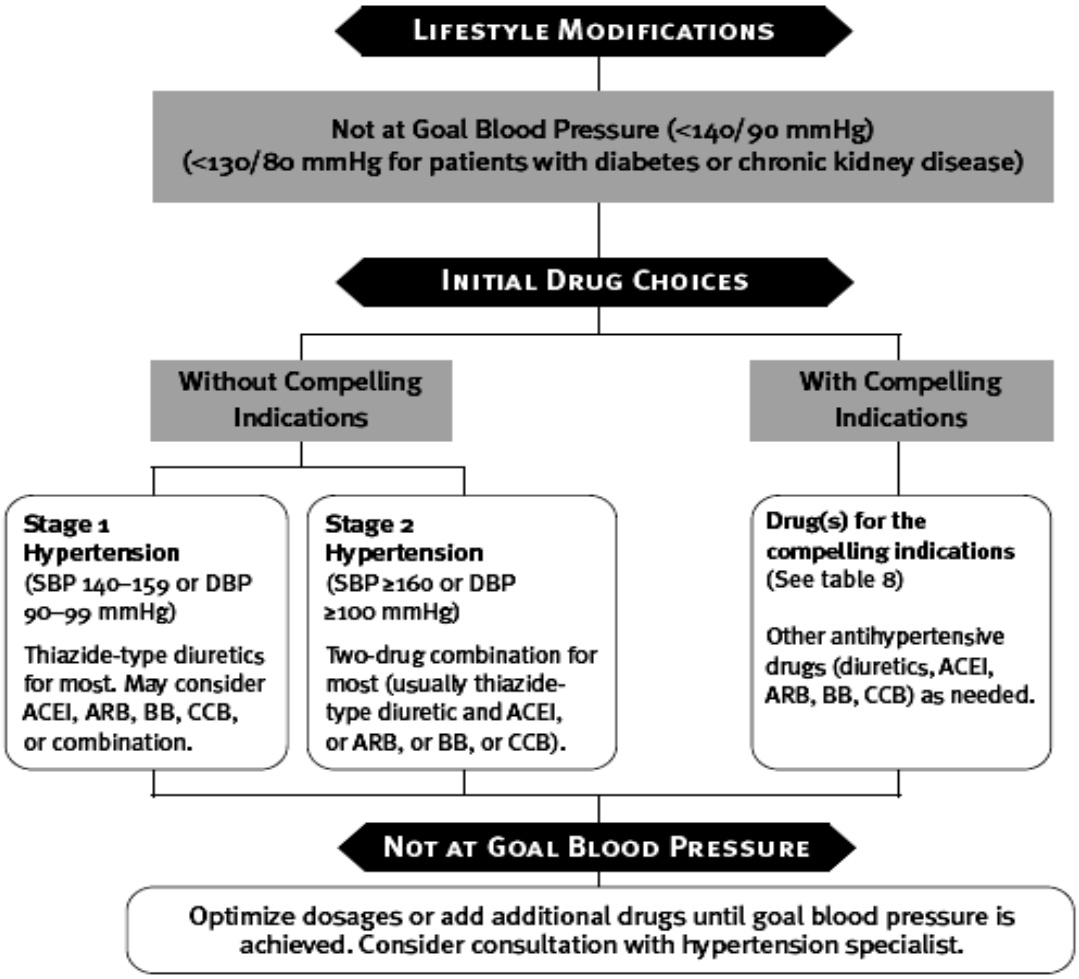

Figure 1.3 Hypertension Treatment Algorithm (Chobanian et al., 2003b).

1.1.5.2 Pharmacological Treatment

The most important indication for antihypertensive drugs is hypertension (Appendix D), and new drugs are being introduced and promoted in the health care market (Woodwell and Cherry, 2004). Although the choices of the antihypertensive drug affect the

effectiveness of the therapy, these choices are sometimes taken based on promotional activities, which might be biased (Blumenthal, 2004).

The use of antihypertensive drugs with appropriate lifestyle modifications and self blood pressure monitoring can control the blood pressure in most of hypertensive patients (Singer et al., 2004; Canzanello et al., 2005). However, poor control of blood pressure has been shown in different samples of population from different countries in the world (Wolf-Maier et al., 2004). Wolf-Maier et al. (2004) estimated the relative impact of hypertension treatment strategies in Germany, Sweden, England, Spain, Italy, Canada, and the United States. Their study found that 66 % of 35 to 64 years aged hypertensive persons in the United States had controlled blood pressure at 160/95 mmHg, compared with 49 % in Canada and 23 % to 38 % in Europe. Around 29% of hypertensives in the United States, 17 % in Canada, and ≤ 10% in European countries had their blood pressure controlled at the 140/90 mmHg threshold. Two thirds to three quarters of the hypertensives in Canada and Europe were untreated compared with slightly less than half in the United States at the 140/90 mmHg cut-point. In addition to the higher prevalence of hypertension, low treatment and control rates in Europe might contribute to a higher burden of cardiovascular disease risk attributable to hypertension. Hypertension treatment and control status vary between Europe and North America.

Clinical practice guidelines to manage hypertension have been developed to help health care practitioners to decide on proper health care options for hypertensive patients rationally. When implemented successfully, they must improve quality of care (Audet et al., 1990; Chassin, 1990). Although the guidelines are widely spread among health care

practitioners, their effect on changing physician behavior in managing the disease is limited (Woolf, 1993; Hayward, 1997).

The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) was designed to help clinicians to manage hypertension (Chobanian et al., 2003a). The guidelines recommended diuretics as first-line therapy for uncomplicated hypertension. This recommendation was based on published controlled clinical trials data that showed reduced morbidity and mortality with the use of diuretics. Additionally, the guidelines state that thiazide-type diuretics must be used in most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. However, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers are used in hypertensive patients who are with certain high-risk conditions (Chobanian et al., 2003a). Likewise, the latest Malaysian clinical practice guidelines recommended diuretics, ACE inhibitors, ARBs and CCBs as the choice of first-line treatment in the form of monotherapy for patients with uncomplicated hypertension with no compelling indications (Malaysian Clinical Practice Guidelines on the Management of Hypertension, 2008). The recommendation was based on studies that have compared thiazides with beta-blockers and found that rates of withdrawal because of adverse effects were lower with thiazides than beta-blockers and that thiazides were associated with lower incidence of cardiovascular events. Moreover, studies demonstrated that thiazides lowered systolic blood pressure more than beta-blockers and calcium channel blockers (Medical Research Council, 1992; Veterans Administration Cooperative Study