Malaysian Journal of Pharmaceutical Sciences,
Vol. 7, No. 2, 137–152 (2009)

COST-EFFECTIVENESS OF ANTIHYPERTENSIVE TREATMENT IN MALAYSIA

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Hypertension is a prevalent chronic disease, which is strongly related to the development of cerebrovascular and cardiovascular diseases. The prevalence of hypertension in Malaysia in subjects aged 15 years and above was estimated to be 27.8%. Cost-effectiveness analysis (CEA) compares treatment options with different effectiveness and safety profiles. The utilisation of antihypertensive drugs has raised some concerns about the balance between its costs and benefits. This study was conducted to describe the healthcare costs for hypertensive subjects and to examine the cost-effectiveness of different classes of antihypertensive drugs used in Malaysia. Retrospective and prospective data analysis of a cohort of uncomplicated hypertensive patients was conducted to determine ambulatory health care costs among hypertensive patients groups. The total direct and indirect costs of controlled and uncontrolled blood pressure (BP) were described. The health care costs ($) / clinical outcome (AC/E ratio) was calculated. Mean total direct costs per patient per month was higher in uncontrolled blood pressure groups compared to the controlled blood pressure groups. The cost-effectiveness relationship was more favourable for diuretics (1.9), angiotensin converting enzyme inhibitors (ACEIs) (2.0), prazosin (2.4) and beta blockers (2.5), more than the diuretics and beta blockers combination theraphy (3.0), calcium channel blockers (CCBs) (3.4) and other combinations (6.1). Antihypertensive drugs used to treat hypertensive patients were different in their cost-effectiveness ratios. Such results will allow health care professionals and/or decision makers to make better decisions on how to select treatment options for hypertensive patients in Malaysia and how to distribute and allocate scarce health care resources. Pharmacoeconomic evaluations can help in making difficult choices rationally and allocate scarce resources efficiently.

Keywords: *Cost-effectiveness, Treatment, Hypertension*

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INTRODUCTION

Hypertension is very much prevalent and severe in Malaysia and its care is unsatisfactory. According to Rampal *et al.* (2008), the prevalence of hypertension in subjects aged 15 years and above was 27.8%. The prevalence increases with age in both genders and in all ethnic groups. Malaysian individuals with hypertension have poor blood pressure control rates and hypertension treatment is less than satisfactory. Only 32.4% of the hypertensive subjects in the study were taking antihypertensive drugs. Overall, only 8.6% of hypertensive subjects had their blood pressure controlled (Rampal *et al*. 2008).

Hypertension treatment starts with therapeutic lifestyle changes for all individuals with hypertension and prehypertension. Decisions on pharmacological treatment are based on global vascular risks and not on the level of blood pressure per se. In patients with newly diagnosed uncomplicated hypertension and no compelling indications, the choice of first line monotherapy includes angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics. Beta blockers are no longer recommended for first line monotherapy in this group of patients (Ministry of Health Malaysia 2008).

Antihypertensive drugs are developing and many drugs are available in the Malaysian market. The utilisation of antihypertensive drugs has been costly, which has raised some concerns about the balance between its costs and benefits. The choice of drug therapy is of great importance for the total treatment cost, since the cost varies significantly between different drugs. There is a large difference with regards to cost especially between the old antihypertensive drugs (primarily diuretics and beta blockers) and the newer drugs (primarily ACEIs and calcium-antagonists) (Johannesson, Borgquist and Jonsson 1991). To deal with this issue it is necessary to carry out economic evaluations (Johannesson and Jonsson 1991). Cost-effectiveness analysis (CEA) compares treatment options with different effectiveness and safety profiles. Whilst costs are calculated in monetary value, outcomes are valued in clinical terms (e.g. blood pressure, number of cases cured) (Messori 1997).

The balance between the cost of these drugs and the health benefit gained from using them has not yet been determined in this country. Conducting CEA will determine the effectiveness of these drugs and

provide results that are very much helpful to health care policy makers and clinicians. This study was conducted to determine the cost-effectiveness ratio of different antihypertensive drugs used in Malaysia.

METHODS

Study Design

A cost-effectiveness analysis was carried out with controlled blood pressure as the measure of health effects. Data obtained was designed to compare the antihypertensive efficacy of antihypertensive drugs prescribed for patients enrolled in the study. Data analyses of a cohort of hypertensive patients in different pharmacological groups was used to determine ambulatory care costs attributable to uncomplicated hypertension among hypertensive patients when blood pressure is controlled and when it is uncontrolled. Controlled blood pressure was defined as blood pressure of < 140/90 mmHg. Uncontrolled blood pressure was defined as blood pressure reading of ≥ 140/90 mmHg. Hypertensive patients were classified according to the antihypertensive class they were prescribed to and whether their blood pressure was controlled or uncontrolled by taking the average of their blood pressure readings. Because some of the data were collected retrospectively, chances of having patients who changed their drug class were low. The study was approved by the Research and Ethics Committee, Kulliyah of Medicine in International Islamic University Malaysia (IIUM).

Patients in this study were prescribed different antihypertensive drugs. Antihypertensive drugs consumed by all study subjects were classified based on the antihypertensive drug class and different combinations. These classes included diuretics, beta blockers, ACEIs, CCBs, prazosin, combination of diuretics and beta blockers, diuretics and CCBs, diuretics and ACEIs, and other combinations.

The cost-effectiveness relationship was calculated as a ratio of the monthly mean cost to the proportion of patients with controlled blood pressure, for each pharmacological group using the following formula:

$$AC/E = \frac{\text{Health care costs (\$)}}{\text{Clinical outcome (percentage of hypertensive patients with controlled BP)}}$$

Study Location, Population and Sampling Procedure

All hypertensive patients in Jaya Gading polyclinic were considered as the study population for the cost-effectiveness study. There were 2000 patients at the beginning of the study. Individuals diagnosed with hypertension only (either with controlled or uncontrolled blood pressure) with no other co-morbidities (n = 600) were selected and included based on the selection criteria after signing the informed consent. Society's perspective was used in this study.

Data Collection

Demographic data

Patients who decided to participate in the study signed the informed consent form. On the first study visit, they were interviewed for demographic data (age, sex, and race). Data on smoking, alcohol and caffeine intake habits, daily exercise and/or physical activities, and date of diagnosis of hypertension were also gathered. Body height and weight were measured. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m^2).

Clinical data

The clinical data included retrospective data (before starting the study) and new data (follow-up data). Medical charts of study subjects were reviewed to collect data on blood pressure readings that were recorded before starting this study, laboratory tests results, and antihypertensive drugs prescribed. Blood pressure was measured using standard mercury sphygmomanometer on the right arm of each participant in the sitting position after at least 5-minutes rest. Three blood pressure readings were taken during each visit; on average each patient visited the polyclinic once every month. The patients were followed up for one year. The

average blood pressure reading measurement was recorded. Any new data during the follow up process was recorded in the case record form for each patient.

Economic data

Economic data collected in this study were data related to the management of hypertensive patients. The principal source of direct health care costs, including drugs, diagnostic procedures and laboratory tests, physician's, pharmacist's and nurse's costs was the billing division in the Ministry of Health (Ministry of Health Malaysia 2007, 1982).

Data on prescriptions of antihypertensive drugs, laboratory tests: urine tests, red blood cells count, triglycerides, HDL, LDL, cholesterol, potassium, sodium, glucose, uric acid, creatinine, and ECG were collected. The duration that the physician, pharmacist, and nurse spent with the patient were estimated and collected after interviewing each health practitioner to calculate the cost of health professionals involved in treating individuals with hypertension. The average health professional time utilised by the patient was multiplied by the cost of that time. The cost of health professional time was estimated by dividing the daily allowance by number of working hours to get the cost per hour and then the cost per minute was estimated to multiply it by the time utilised by the patient. Data on transportation fare to and from Jaya Gading polyclinic was collected by interviewing the patients to estimate the direct non medical costs.

Calculation of costs

The direct medical costs were calculated through the summation of the cost produced by multiplying the quantities of each drug and other health care categories (utilisations) by its unit cost (Riewpaiboon, Pornlertwadee and Pongsawat 2007) as shown below:

$$TC_n = \sum_{J=1}^{J} QS_{nj} \times US_j + \sum_{K=1}^{K} QD_{nk} \times UD_k + \sum_{L=1}^{L} QM_{nl} \times UM_l$$

where TC_n is the total direct medical costs for patient n, QS_{nj} is the number of laboratory test j used by patient n, US_j is the unit cost of laboratory test j, QD_{nk} is the number of drug k used by patient n, UD_k is the unit cost of drug k, QM_{nl} is the number of healthcare practitioner l encountered by patient n, UM_l is the cost of the healthcare practitioner l encountered. Costs of drugs were considered as cost of drug class and not for individual drugs under one drug class and the AC/E ratio was calculated based on drug classes and not individual drug. All costs were expressed in Malaysian Ringgit (RM) (RM 3.20059 = 1 US dollar for the year 2008).

A variety of descriptive statistics such as mean, standard deviation (SD), median, and percentage were calculated to describe some parts of the results using SPSS Windows V. 13. Results were reported as mean values, SD, and median. Sensitivity analysis was performed by selecting the mean and repeating the analysis using the maximum values of direct medical cost for patients with controlled blood pressure.

RESULTS AND DISCUSSION

A total of 670 patients having hypertension without co-morbidities were considered for the study. Seventy patients were excluded for several reasons i.e. patients moved to another city or residential area (n = 42) and patient death (n = 28). Data from 600 patients were analysed. The mean age was 54.67 (± 9.75) with the median age of 55 years. Of all patients, 84.5% were ≥ 45 years old and 15.5% were < 45 years old. Majority of patients were Malay (84.3%), followed by Chinese (13.7%), Indians (1.2%), and others (0.8%). Chinese, Indians, and others races were treated as "others" in the analysis because of their small percentage in the whole sample. Females represented approximately two thirds of the patients (67.7%).

This study attempted to describe the cost of treatment and control of hypertension for patients taking antihypertensive drugs. The selection of population-based sample allows the cost-effectiveness of treatment based on drugs actually in use to be assessed. Results of such studies give different results from indirect estimates that are based upon data or information from production and sales of drugs, medical records (Alonso *et al.* 1998) or participants in randomised clinical trials (Ramsey *et al.*

1999). Each cost component was determined using direct information from the individuals under medical care for hypertension. The investigation of costs over a period of one year was employed. The expenditure on drugs represents the average monthly expenses incurred.

Our subjects were prescribed with different antihypertensive drugs. Thus, the distribution of patients (either with controlled or uncontrolled blood pressure) according to the drug class prescribed, varied significantly. The majority of patients were prescribed "other drug combinations". In addition, the majority of patients with controlled blood pressure were prescribed "other combinations" like ACEIs + diuretic, and CCBs + diuretics. Next to "other combinations" was beta blockers followed by CCBs, diuretics and beta blockers combination, diuretics and ACEIs, and prazosin, respectively. For monotherapy, beta blockers were the most frequently prescribed antihypertensive drugs in patients with controlled blood pressure. Table 1 shows the distribution of the study subjects according to the antihypertensive agents consumed. We only included and analysed the data if the drug class was consumed by at least three hypertensive patients.

Table 1: Antihypertensive agents and study subjects according to blood pressure control status.

Antihypertensive agent	**Blood pressure status**	
	Controlled [No. (%)]	**Uncontrolled [No. (%)]**
Diuretics	10 (1.66)	2 (0.33)
Beta blockers	108 (18.00)	37 (6.16)
ACEIs	8 (1.33)	4 (0.66)
CCBs	22 (3.66)	22 (3.66)
Diuretics and beta blockers	22 (3.66)	20 (3.33)
Diuretics and CCBs	–	2 (0.33)
Diuretics and ACEIs	1 (0.16)	1 (0.16)
Prazosin	3 (0.50)	1 (0.16)
Other combinations	111 (18.50)	226 (37.66)

The combination of diuretics and ACEIs group was excluded from the analysis as it was only prescribed to one hypertensive patient with controlled blood pressure and one patient with uncontrolled blood pressure. The combination of diuretics and CCBs group was also excluded from the analysis because it was only prescribed to two hypertensive patients with uncontrolled blood pressure and no patients with controlled blood pressure were on this combination.

Johannesson (1994) and Ambrosioni (2001), have shown that diuretics and beta blockers were the most effective monotherapy. However, few clinical trials have demonstrated the efficacy of ACEIs in reducing blood pressure (Neal, Macmahon and Chapman 2000; Furberg and Pitt 2001). The results of the trials were based on the analysis of selected samples of participants and did not represent the whole population of hypertensive patients. Other randomised controlled trials showed that CCBs and ACEIs have no greater benefit than diuretics and beta blockers in regards to long-term morbidity and mortality in treating hypertension (Mehta, Wilcox and Schulman 1999; Hansson *et al.* 1999a, b, 2000; Brown *et al.* 2000).

Medication costs were the primary cost driver of total costs in this study. Medication costs are frequently referred to as an important cost driver in the treatment of hypertension (Dias da Costa *et al.* 2002; American Heart Association 2008). Table 2 and Figure 1 show the monthly mean and median direct cost for treating hypertension according to drug class and "other combinations". Monthly mean direct costs of hypertensive patients with controlled blood pressure were lower for diuretics and beta blockers administered as monotherapy and for diuretics and beta blockers as a combination therapy, in comparison with other drugs or "other combinations". Mean total direct cost for all patients (with controlled and uncontrolled blood pressure) prescribed with "other combinations", beta blockers, prazosin, CCBs, diuretics, diuretics and beta blockers combination and ACEIs was found to be RM 197.70, RM 186.06, RM 183.60, RM 171.48, RM 163.84, RM 156.52, and RM 136.82, respectively. Studies in the USA have reported low costs for diuretics and beta blockers for patients with hypertension (Hilleman *et al.* 1994; Ramsey *et al.* 1999). Similarly, Xu, Moloney and Phillips (2003) reported that prescribing diuretics and beta blockers for treating uncomplicated hypertension was associated with lower costs of medications.

Table 2: Monthly mean direct costs for all patients (controlled and uncontrolled blood pressure).

Drug	Mean ± SD (median)						
	Drugs	**Labs**	**Physician**	**Pharmacist**	**Nurse**	**Travel**	**Total**
Diuretics	23.27 ± 30.47 (7.79)	1.13 ± 1.13 (0.63)	57.53 ± 20.93 (57.53)	46.15 ± 16.79 (40.96)	33.44 ± 12.17 (29.68)	2.29 ± 1.74 (1.84)	163.84 ± 60.56 (155.39)
Beta blockers	28.16 ± 138.97 (4.82)	0.99 ± 1.00 (0.72)	64.82 ± 42.84 (57.19)	52.01 ± 34.37 (45.88)	37.68 ± 24.90 (33.25)	2.39 ± 1.84 (1.88)	186.06 ± 179.70 (153.19)
ACEIs	6.74 ± 6.66 (5.07)	0.95 ± 0.64 (1.01)	53.10 ± 27.37 (46.97)	42.60 ± 21.96 (37.69)	30.87 ± 15.91 (27.31)	2.52 ± 1.74 (2.07)	136.82 ± 65.53 (128.35)
CCBs	12.67 ± 21.21 (4.29)	0.99 ± 2.41 (0.12)	65.36 ± 42.58 (53.10)	52.44 ± 34.16 (42.60)	38.00 ± 24.75 (30.87)	2.01 ± 1.30 (1.58)	171.48 ± 102.06 (133.38)
Diuretics and beta blockers	14.53 ± 26.67 (5.54)	1.17 ± 1.26 (0.79)	58.06 ± 39.34 (46.97)	46.58 ± 31.56 (37.69)	33.75 ± 22.87 (27.31)	2.40 ± 1.82 (1.78)	156.52 ± 96.78 (156.52)
Prazosin	13.46 ± 16.09 (7.30)	1.06 ± 0.36 (0.97)	70.46 ± 42.23 (65.36)	56.53 ± 33.88 (52.44)	40.96 ± 24.55 (38.00)	1.11 ± 0.95 (0.68)	183.60 ± 115.79 (165.83
Other combinations	13.37 ± 17.10 (6.27)	1.22 ± 3.30 (0.68)	75.80 ± 56.00 (57.19)	60.82 ± 44.93 (45.88)	44.07 ± 32.56 (33.25)	2.40 ± 1.81 (1.90)	197.70 ± 135.29 (159.17)

Note: Cost data are in Malaysian Ringgit (RM)

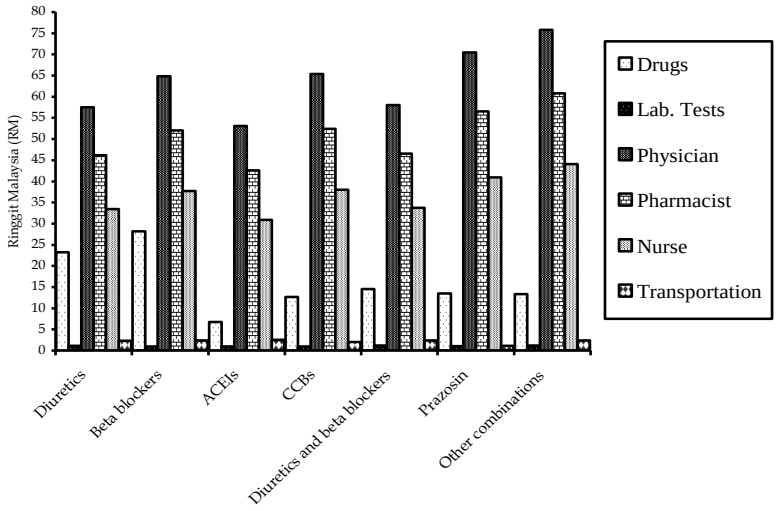

Fig. 1: Monthly mean direct cost.

The study also shows that prescribing monotherapy to control blood pressure with prazosin, ACEIs, CCBs, and "other combinations" drug classes gave the highest cost. Other studies (Hilleman *et al.* 1994; Johannesson 1994; Alonso *et al.* 1998), had shown also that monotherapy using CCBs, and ACEIs gave the highest cost. Table 3 shows the monthly mean and median direct cost for treating hypertension according to drug class, drug combination and number of patients with controlled or uncontrolled blood pressure. In patients with controlled blood pressure, the highest monthly direct costs were seen with ACEIs (180.56 ± 72.94), followed by CCBs (178.74 ± 119.69), "other combinations" (169.41 ± 117.42), prazosin (131.23 ± 60.48), beta blockers (130.85 ± 129.07), and the combination of diuretics and beta blockers (125.62 ± 90.98). The lowest direct costs were seen with diuretics (115.20 ± 50.05). There was only one hypertensive patient with uncontrolled blood pressure under the prazosin group.

Table 3: Estimated monthly direct costs (in year 2008 in RM) stratified by blood pressure control status according to drug class.

Drug	Blood pressure [Mean ± SD (Median)]	
	Controlled	**Uncontrolled**
Diuretics	115.20 ± 50.05 (110.56)	188.07 ± 80.17 (172.97)
Beta Blockers	130.85 ± 129.07 (135.34)	216.48 ± 240.72 (156.84)
ACEIs	180.56 ± 72.94 (141.56)	115.54 ± 37.78 (98.71)
CCBs	178.74 ± 119.69 (120.64)	174.00 ± 83.59 (163.33)
Diuretics and beta blockers	125.62 ± 90.98 (115.50)	176.39 ± 104.30 (155.31)
Prazosin	131.23 ± 60.48 (157.68)	340.71 ± – (-)
Other combinations	169.41 ± 117.42 (139.55)	217.32 ± 143.45 (174.36)

Note: Cost data are in Malaysian Ringgit (RM)

The control of hypertension using monotherapy was more frequently achieved in patients taking diuretics (83%), prazosin (75%) and beta blockers (74%), in comparison with those taking ACEIs (66%), combination of diuretics and beta blockers (52%), CCBs (50%) and "other combinations" (32%). Considering the cost and effective control of hypertension, the most cost-effective monotherapy was diuretics, followed by ACEIs, a result that is different with results from other studies (Pearce *et al.* 1998; Xu, Moloney and Phillips 2003). Table 4 presents the cost-effectiveness ratios (CER) of different antihypertensive drugs, drug classes and combinations. Generally, CER was more advantageous for diuretics (1.9), ACEIs (2.0), prazosin (2.4) and beta blockers (2.5), than for diuretics and beta blockers combination therapy (3.0), CCBs (3.4), and "other combinations" (6.1). Xu, Moloney and Phillips (2003) also concluded that diuretics and beta blockers are cost-effective. Pearce and colleagues (1998) found that diuretics and beta blockers can prevent cardiovascular events at a much lower cost than ACEIs, CCBs and alpha blockers.

Table 4: Cost-effectiveness of antihypertensive treatment.

Antihypertensive treatment	N=600 (%)	Monthly mean and median of cost (RM)	Patients with controlled blood pressure (%)	CER	CER (sensitivity analysis)
		Mean ± SD (median)			
Diuretics	12 (2.0)	163.84 ± 60.56 (155.39)	83	1.9	3.5
Beta blockers	145 (24.2)	186.06 ± 179.70 (153.19)	74	2.5	23.4
ACEIs	12 (2.0)	136.82 ± 65.53 (128.35)	66	2.0	3.9
CCBs	44 (7.3)	171.48 ± 102.06 (133.38)	50	3.4	10.1
Diuretics and beta blockers	42 (7.0)	156.52 ± 96.78 (156.52)	52	3.0	8.7
Prazosin	4 (0.7)	183.60 ± 115.79 (165.83)	75	2.4	4.5
Other combinations	337 (56.2)	197.70 ± 135.29 (159.17)	32	6.1	23.2

Notes: Cost data are in Malaysian Ringgit (RM)

The sensitivity analysis has shown different results compared to the first main analysis. However, diuretics (3.5) and ACEIs (3.9) remained with better CER followed by prazosin (4.5), diuretics and beta blockers combination (8.7), CCBs (10.1), other combinations (23.2) and beta blockers (23.4) respectively in sensitivity analysis. These different results might be because of the different number of subjects in each antihypertensive drug group as the mean, maximum or minimum values of direct costs may affect the analysis and the calculation of CER results accordingly.

Blood pressure control is an intermediate outcome and if some drugs showed better CER for this outcome, it does not mean that they will also have better CER for clinical outcomes. In addition, we are not entirely confident of those CER results due to the fact that some drug classes were taken by large number of patients and some were taken by small number of patients. Another factor which might affect the CER result is the reason behind different patients were put on different classes of drugs. It may be that patients using drugs with a higher CER were not adequately controlled using drugs with lower CER.

Readers should carefully interpret this study's results. The variation in proportion of patient distribution among the different drug classes may affect the results' interpretation. A large proportion of patients were prescribed with "other combinations" compared to other drug classes. Results of this cost-effectiveness analysis are limited to the treatment of uncomplicated hypertension.

The results should not be extrapolated to patients with complicated hypertension and/or patients with contraindications to diuretics and beta blockers. The study drew patients from ambulatory care clinic and excluded patients with complicated hypertension which will make the results applicable to patients with uncomplicated hypertension treated in ambulatory care clinics.

Future studies can be conducted bearing in mind the equal or even distribution of hypertensive patients according to antihypertensive drugs prescribed. Hospitalisation and death costs due to hypertension may also be included in future studies to determine the cost-effectiveness of different antihypertensive drugs in reducing hospitalisation admission or costs and even the number of deaths due to hypertension. Costs of complications due to hypertension can also be included. That will help in giving a complete picture on the cost-effectiveness of different antihypertensive drugs prescribed for individuals with hypertension in Malaysia. We hope that the knowledge and results of cost-effectiveness of different classes of drugs can be translated by health care practitioners and policy makers into providing better awareness and treatment.

CONCLUSION

This study has shown that costs of hypertension-related ambulatory care outside of hospitals are primarily reliant on the costs of antihypertensive drugs. Antihypertensive drugs used to treat uncomplicated hypertensive patients have different CER. Diuretics were the most cost-effective antihypertensive drugs followed by ACEIs, prazosin, beta blockers, combination of diuretics and beta blockers, CCBs, and "other combinations".

ACKNOWLEDGMENT

This research was funded by a research grant from the Research Management Center, International Islamic University Malaysia.

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