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Cost-effectiveness analysis of manidipine versus amlodipine as an add-on to renin-angiotensin system blockers in hypertensive patients with diabetes mellitus and proteinuria

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ABSTRACT

Objectives: Diabetes and hypertension are the most common causes of chronic kidney disease. Calcium channel blockers are beneficial in blood pressure reduction while also stall kidney degeneration. The aim of this study was to compare the cost-effectiveness of manidipine to amlodipine as an add-on to renin-angiotensin system blockers (RASBs) to slow down kidney degeneration in hypertensive patients with diabetes mellitus and proteinuria. **Methods:** A lifetime Markov decision model was used to evaluate total costs and quality-adjusted life-years (QALYs) from published data on clinical outcomes and Thai data on cost and humanistic outcomes. This study adopted a societal perspective. **Results:** The results demonstrated that the total cost of the treatment with manidipine was 69,892.28 baht compared to 458,508.22 baht for amlodipine, and the QALYs were 9.15 and 6.84 years, respectively. **Conclusions:** Manidipine was more cost-effective than amlodipine in the treatment of Thai hypertensive patients with diabetes mellitus and proteinuria, and it was associated with better clinical outcomes in terms of QALYs and lower costs than amlodipine. Manidipine should be used as the first choice as an add-on to RASBs. The results of this study could contribute to appropriate decision making by policymakers.

Keywords: Cost-effectiveness analysis, amlodipine, manidipine, diabetes mellitus, hypertension, proteinuria

INTRODUCTION

Diabetes, primarily type 2 diabetes mellitus, has long been a growing global epidemic.[1] In 2017, it had been estimated that as many as 425 million people worldwide or 8.8% of adults 20–79 years of age have diabetes. This prevalence is expected to increase to 629 million people by 2045, with over 79% being from low and middle-income countries. This overall increase in the number of diabetes' patients, will eventually lead to an increase in the occurrences of complications associated with diabetes, including the development of kidney disease, commonly known as diabetic nephropathy.[2]

Diabetic nephropathy, a microvascular complication of diabetes, is defined by elevated urine albumin excretion or reduced glomerular filtration rate or both. Approximately 20–40% of all patients with diabetes develop nephropathy. Data from the Thailand Diabetes Registry Project indicated that prevalence of diabetic nephropathy in Thai diabetes patients was 42.9% (microalbuminuria 19.7% and macroalbuminuria 23.2%).[3] Diabetic nephropathy is a significant cause of chronic kidney disease and is largely the leading cause of the end-stage renal disease (ESRD) globally.[1,2,4] Almost half of ESRD in the world in 2017 was caused by diabetes (44%), followed by hypertension (29%).[5] In Thailand, the Thai SEEK study showed that chronic kidney disease prevalence

was 17.5% in the Thai population. Moreover, the study suggested that diabetic nephropathy was the primary cause of ESRD, accounting for 38.57% of ESRD cases followed in 2015 by 30.71% from hypertension nephropathy.[6] Diabetes, hypertension, or a combination of both are directly associated with decreased renal function. Uncontrolled blood sugar and/or blood pressure (BP) in patients can promote the progression of chronic kidney disease and ESRD.[4] Consequently, preventing or reducing the incidence of promoting conditions in patients with chronic kidney disease will slow down kidney degeneration. As a result, the kidney replacement program will need to be prolonged, thus, preventing a drain on health resources and reducing expenditures.

Both the American Diabetes Association and the Joint National Committee, as well as the American College of Cardiology's/American Heart Association's annual guidelines, updated the recommendation for the use of Renin-angiotensin System Blockers (RASBs), including Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs), as first-line agents in the treatment of confirmed hypertension in people with diabetes and albuminuria. If either class is not tolerated or hypertension remains uncontrolled, the other should be added; otherwise, combinations of ACEIs and ARBs should be avoided.[4,7,8] In line with these recommendations, Thai Hypertension Guidelines recommend that ACEIs or ARBs should be started at the appropriate initial dose in people with hypertension with diabetes nephropathy, followed by Calcium Channel Blockers (CCBs) if they are unable to achieve the BP goal.[9]

CCBs appear to be an optimal antihypertensive drug in combination with ACEIs or ARBs. It is more appropriate for patients with hypertensive and diabetes nephropathy than other antihypertensive classes because current evidence indicates that it has both potent antihypertensive and renoprotective effects. The combination of an ACEIs/or an ARBs and a dihydropyridine (DHP) CCB exhibited a superior effect in the reduction of proteinuria associated with nephropathy in patients with diabetes mellitus and delayed the progression of kidney degeneration compared to a single agent.[10-13] However, common side effects of CCBs, including peripheral edema and headaches, have been detected. In addition, they are associated with a considerable risk of peripheral edema which often leads to the discontinuation of treatment.[14,15] The National List of Essential Medicines of Thailand (NLED) described the indication of CCBs, including amlodipine, manidipine, and lercanidipine, for the treatment of hypertension. Amlodipine besilate is the first-recommended DHP-CCB drug while manidipine hydrochloride and lercanidipine hydrochloride, and the new generation DHP-CCBs, are substitutes for patients who cannot tolerate the side effects of amlodipine, especially peripheral edema.[16]

The effectiveness of amlodipine in reducing BP, especially systolic BP, is comparable to that of new generation DHP-CCBs. However, beneficial effects on reducing proteinuria and slowing down the progression of kidney degeneration are greater among new DHP-CCBs. Furthermore, the new generation DHP-CCBs are associated with a significantly lower incidence of peripheral edema than amlodipine.[17-19] Although the new generation DHP-CCBs is more effective than amlodipine, they are twice as expensive.[20]

From literature reviews, manidipine is the only new DHP-CCBs with a reported effect on slowing down the progression of kidney degeneration in populations with both hypertension and diabetes nephropathy.[19,21,22] Earlier research on lercanidipine focused on people with hypertensive nephropathy without diabetes.[19,21,22] Consequently, manidipine also appears to be more suitable for hypertensive patients with diabetes nephropathy than lercanidipine among new DHP-CCBs on the NLED.

At present, amlodipine is considered the first DHP CCB as an add on to ACEIs or ARBs in hypertensive patients with diabetes mellitus and proteinuria.[7,9] Even though manidipine has been shown to be more effective and has fewer side effects than amlodipine, the cost-effectiveness has not been established in Thailand or international countries. The major aim of this study was to demonstrate the cost-effectiveness of manidipine compared with amlodipine as an add-on to RASBs to slow down kidney degeneration in hypertensive patients with diabetes mellitus and proteinuria. This study is the first cost-effectiveness study of manidipine in international literature.

MATERIALS AND METHODS

Study Design

The study was a model-based economic evaluation in health technology assessment. A Markov model was developed to compare the cost-effectiveness of manidipine to amlodipine as an add-on to RASBs. The perspective of this study was societal.

Treatments

A meta-analysis of head-to-head randomized controlled trials (RCT) showed 10 mg of amlodipine and 20 mg of manidipine have statistically equivalent efficacy in the reduction of diastolic and systolic BP.[18] Consequently, this study compared 10 mg/day of amlodipine and 20 mg/day of manidipine in hypertensive patients with diabetes mellitus and proteinuria that were unable to achieve the BP goal with RASBs (e.g., ACEIs or ARBs) for at least 6 months. Patients with peripheral edema from amlodipine or manidipine were switched to 100 mg/day of hydralazine.

Decision Model

The model was developed based on KDIGO 2012[23] and previously published studies[19] of antihypertensive drugs used in the treatment of hypertensive patients with diabetes mellitus and proteinuria. A Markov model was used to perform decision analysis by Microsoft Excel 2013.[24] The model and assumption (in the model) were validated for the disease sequence to ensure its appropriateness for hypertensive patients with diabetes mellitus and proteinuria treatment in Thailand by two cardiologists and one cardiology residency pharmacist, as demonstrated in Figure 1.

Assumptions of the Model

1. Patients who enter the model would remain on their antihypertensive medications as well as the add-on CCB or hydralazine until the end of their Markov cycle.

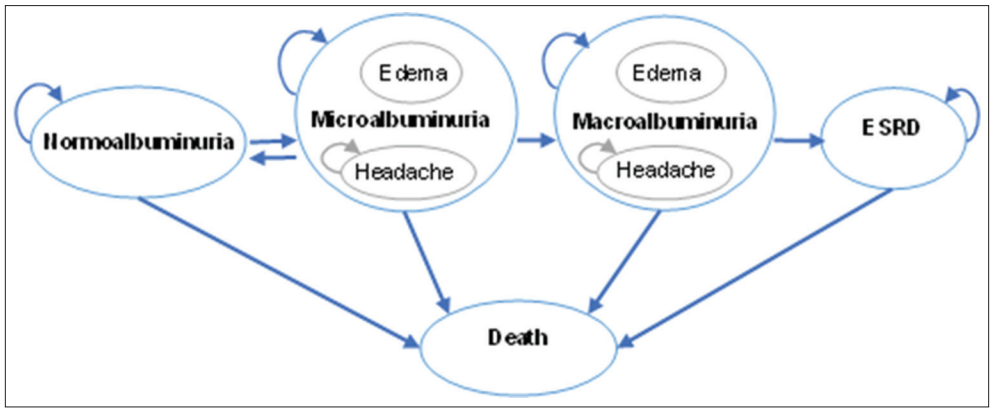

Figure 1: Markov model structure of hypertension with diabetes mellitus and proteinuria

2. Patients in the "normoalbuminuria" health states are those who have BP <150/90 mmHg are only used RASBs for treatment of hypertension.
3. Patients in the "microalbuminuria" and "macroalbuminuria" health states are those whose BP is not controllable or ≥150/90 mmHg when treated with RASBs alone. In addition, 10 mg of amlodipine or 20 mg of manidipine would be added on for patients whose conditions are not showing signs of improvement for hypertension. BP is 150/90 mmHg or greater, as a maximum acceptable BP levels in clinical practice, which must be add-on other antihypertensive drugs for controlling BP and proteinuria in patients who are not controllable BP when treated with RASBs alone.
4. Patients in "ESRD" health states are defined as those who have ESRD or elevated plasma creatinine >175 μmol/L followed by continuous ambulatory peritoneal dialysis (CAPD).
5. Patients in "ESRD" health states did not experience any side effects from the add-on CCB because the study by Handler *et al*. shows that the incidence of side effects from CCB is not found after 6 months.[25]
6. All patients had levels of HbA1C between 7% and 9% and used metformin as monotherapy.
7. All patients treated with either amlodipine or manidipine would experience only peripheral edema and/or headache as the side effects of the drugs.
8. Peripheral edema that has side effects from amlodipine or manidipine is defined as patients who have swelling of the ankle, feet, or other extremities from fluid accumulation. Patients with peripheral edema were required to switch from amlodipine or manidipine to 25 mg of hydralazine 4 times daily and then continue to take this medication for controlling BP. Patients had no side effects from hydralazine.
9. Headache was assumed to be reversible when treated with paracetamol 500 mg 4 times/day.
10. Patients in microalbuminuria health states could be moved to normoalbuminuria health states. Conversely, patients in macroalbuminuria and ESRD health states could not return to a previous state.
11. Patients whose diabetic condition did not improve were moved from macroalbuminuria to ESRD health states and all of those whose conditions did not improve moved to death state.
12. Patients in both amlodipine and manidipine arms did not receive any other antihypertensive and antidiabetic drugs, as well as other co-interventions.
13. Model structure and assumptions were approved by experts during the expert consultation meeting.

Time Horizon

The previous study showed that the median age of populations was 55.8–56.9 years old;[19] therefore, a Markov model was developed to follow the treatment of hypertension and diabetes nephropathy patients from 55 years old until death (with life expectancy being 75 years old[26]). A cycle length of 3 months was properly considered to evaluate the clinical treatment and health states and complications from albuminuria, ESRD as well as the side effects of amlodipine/or manidipine.[27]

Probability of Clinical Outcomes

A systematic search was conducted in PubMed, Cochrane Library, and Scopus. The keywords were Diabetes mellitus "AND" Proteinuria. Two reviewers independently reviewed titles, abstracts, and articles sequentially to select studies for data abstraction based on the study eligibility criteria.

Study Eligibility Criteria

Studies were identified as eligible for inclusion if they were published as full papers and in the English language. All transition probabilities were obtained from the study (i) involving hypertensive patients with diabetes mellitus and proteinuria who have used RASBs for at least 6 months. (ii) If a searching was not found, the studies involving patients with diabetes mellitus and proteinuria with controlled hypertension by antihypertensive drug or BP <150/90 mmHg were included in the study. The utility of health states was obtained from the study involving Thai hypertension patients with diabetes mellitus and proteinuria, who used RASBs for at least 6 months and had side effects. If search results were inconclusive, the study proceeded as follows: (i) Involving diabetes mellitus and proteinuria with controlled hypertension by antihypertensive drug or BP <150/90 mmHg and whether they had side effects, or (ii) other patients who had utility of health state and side effects, or (iii) utility was retrieved from international published studies due to the limited data in Thailand.

Articles were excluded from the review if they met any of the following criteria: (i) Injectable antihypertensive drug, (ii) pregnancy and lactation, (iii) non-English language, (iv) non-full text papers, and (v) editorials and opinions, letters, research protocols, conference abstracts, duplicate reports of the same study, and notes and books.

Study appraisal and synthesis

The quality of included studies was assessed according to "JADAD scale" for RCT and "STROBE Statement" for observational studies. Included studies were classified into 2 levels of evidence as follows: Level 1, RCT or systematic review or meta-analysis and level 2, observational study. All probabilities were converted into risks over 3 months because of the cycle length. Meta-analysis was used only when this was meaningful (i.e., if participants, treatment, and the underlying clinical question were similar enough for pooling to make sense).

A total of 5 published studies were selected for final inclusion. Three studies were conducted from RCT, while two used observational studies. Two randomized studies were of good quality (scores more than 3 out of 5) based on the JADAD score, but another was of a poor quality (score <3). Two observational studies were of good quality. Meta-analysis was not performed. Included studies are shown in Table 1.

All parameters used in the Markov model were approved by the experts during the expert consultation meeting and shown in Table 2.

Costs

All costs were expressed in Thai baht and are shown in Table 1. Costs of enalapril 20 mg, amlodipine 10 mg, manidipine 20 mg, hydralazine 25 mg, and paracetamol 500 mg were derived from the Drug and Medical Supply Information Center and the Ministry of Public Health, Thailand.[20] All direct non-medical costs, laboratory costs, which included tests for albumin, blood urea nitrogen, creatinine, and the urine protein test, and costs of travel and foods were obtained from the mean cost per unit from the standard cost lists for health technology assessment in Thailand.[28] Costs of ESRD patients with CAPD were derived from previous studies in Thailand.[29] All costs were adjusted to 2017 values using the consumer price index from the Bureau of Trade and Economic indices, The Ministry of Commerce, Thailand.

Table 1: Included studies

Included studies	Level of evidence	Quality of studies
Pérez-Maraver (2008)[34]	Level 1; Randomized controlled trial	Good
Adler (2003)[35]	Level 1; Randomized controlled trial	Good
Martinez-Martin (2008)[19]	Level 1; Randomized controlled trial	Poor (JADAD score=2)
Korsah (2010)[36]	Level 2; Observational study	Good
Berhane (2011)[37]	Level 2; Observational study	Good

Utility Values

Quality-adjusted life-years (QALYs) were used for outcomes measurement. The humanistic outcomes were measured in utility weights for different health states and side effects, ranging from 0 (death) to 1 (perfect health). Utility weights were multiplied by life-expectancies to generate QALYs.

Utility values of health states were obtained from international published studies[30,31] and Thai studies.[32] All utility values are shown in Table 2.

Analysis

Cost-effectiveness analysis

The analysis was assessed by the incremental cost-effectiveness ratio (ICER). Future costs and QALYS were discounted at 3%/year.[33]

One-way sensitivity and probabilistic sensitivity analysis (PSA)

Parameter uncertainties were identified using a one-way and PSA method and were presented by a tornado diagram and a cost-effectiveness plane, respectively.

To test the uncertainty of the parameters, one-way sensitivity and PSA were performed by Microsoft Excel 2013 parameters. The effect of this uncertainty was assessed by varying the parameter values and computing the model results with these new inputs

In a one-way sensitivity analysis, parameter values are changed one by one, usually to a low and a high value. Model results are presented on a tornado diagram to demonstrate how a change in the value of one parameter impacts the model results shown as the ICER values. The vertical line indicated the change in ICER from the base case values. Tornado diagram is shown in Figure 2.

In addition to the PSA, random Monte Carlo simulations were run 1000 times to generate the probability distribution and the ICER estimation. Probability and utility were varied based on the range of 95% confidence interval (95% CI). Costs were assumed to be varied by 10% from their mean value. The results are shown as a cost-effectiveness plane by the vertical axis representing incremental cost and the horizontal axis representing incremental QALYs, and a cost-effectiveness acceptability curve between probabilities of manidipine and amlodipine and willingness to pay. The results are shown in Figure 3.

RESULTS

Cost-effectiveness Analysis

The results in Table 3 demonstrated that the total costs of the treatment with manidipine were 69,892.28 baht compared to 458,508,22 baht for amlodipine, and the QALYs were 9.15 and 6.84 years, respectively. Therefore, the study showed that manidipine was a dominant option due to its lower cost and higher effectiveness. The ICER showed a negative value, according to the ICER calculation based on formula as followed.

$$ICER = \frac{Cost\ Manidipine - Cost\ Amlodipine}{QALY\ Manidipine - QALY\ Amlodipine}$$

Table 2: All parameters used in the Markov model

Parameters	Distribution	Mean	95% CI	References
Probabilities				
Transition probabilities				
Amlodipine				
Normoalbuminuria to Microalbuminuria	Beta	0.0175	0.0151–0.0198	[36]
Microalbuminuria to Normoalbuminuria	Beta	0.0408	−0.0083–0.0900	[19]
Microalbuminuria to Macroalbuminuria	Beta	0.0408	−0.0083–0.0900	[19]
Macroalbuminuria to ESRD	Beta	0.0154	0.0129–0.0179	[37]
Normoalbuminuria to Death	Beta	0.0035	0.0033–0.0038	[35]
Microalbuminuria to Death	Beta	0.0076	0.0066–0.0086	[35]
Macroalbuminuria to Death	Beta	0.0117	0.0091–0.0146	[35]
ESRD to Death	Beta	0.0519	0.0370–0.0675	[35]
Manidipine				
Normoalbuminuria to Microalbuminuria	Beta	0.0175	0.0151–0.0198	[36]
Microalbuminuria to Normoalbuminuria	Beta	0.2145	0.1525–0.2765	[19]
Microalbuminuria to Macroalbuminuria	Beta	0.0000	0.0000	[19]
Macroalbuminuria to ESRD	Beta	0.0154	0.0129–0.0179	[37]
Normoalbuminuria to Death	Beta	0.0035	0.0033–0.0038	[35]
Microalbuminuria to Death	Beta	0.0076	0.0066–0.0086	[35]
Macroalbuminuria to Death	Beta	0.0117	0.0091–0.0146	[35]
ESRD to Death	Beta	0.0519	0.0370–0.0675	[35]
Hydralazine				
Normoalbuminuria to Microalbuminuria	Beta	0.0175	0.0151–0.0198	[36]
Microalbuminuria to Normoalbuminuria	Beta	0.0064	−0.0058–0.0186	[34]
Microalbuminuria to Macroalbuminuria	Beta	0.0619	0.0336–0.0900	[34]
Macroalbuminuria to ESRD	Beta	0.0154	0.0129–0.0179	[37]
Normoalbuminuria to Death	Beta	0.0035	0.0033–0.0038	[35]
Microalbuminuria to Death	Beta	0.0076	0.0066–0.0086	[35]
Macroalbuminuria to Death	Beta	0.0117	0.0091–0.0146	[35]
ESRD to Death	Beta	0.0519	0.0370–0.0675	[35]
Probabilities of side effects				
Amlodipine				
Edema	Beta	0.0513	−0.0031–0.1057	[19]
Headache	Beta	0.0168	−0.0156–0.0492	[19]
Manidipine				
Edema	Beta	0.0082	−0.0078–0.0242	[19]
Headache	Beta	0.0333	0.0020–0.0647	[19]
Costs (baht)				
Medicine costs				
Enalapril 20 mg (per tablet)	Gamma	0.42	0.378–0.462	[20]
Amlodipine 10 mg (per tablet)	Gamma	1.41	1.269–1.551	[20]
Manidipine 20 mg (per tablet)	Gamma	2.79	2.511–3.069	[20]
Hydralazine 25 mg (per tablet)	Gamma	1.402	1.2618–1.5422	[20]
Paracetamol 500 mg (per tablet)	Gamma	0.206	0.1854–0.2266	[20]
Direct medical costs				
Normoalbuminuria, Microalbuminuria and Macroalbuminuria state				

(*Contd*...)

Table 2: (*Continued*)

Parameters	Distribution	Mean	95% CI	References
Laboratory costs				
Albumin test (per unit)	Gamma	29.0165	26.1148–31.9181	[28]
Blood urea nitrogen test (per unit)	Gamma	72.0038	64.8034–79.2041	[28]
Creatinine test (per unit)	Gamma	72.0038	64.8034–79.2041	[28]
Urine protein test (per unit)	Gamma	130.0367	117.0330–143.0404	[28]
OPD treatment (per visit)	Gamma	72.0038	64.8034–79.2042	[28]
Pharmaceutical care service (per visit)	Gamma	73.014	65.7126–80.3154	[28]
Direct non-medical costs				
Travel (per visit)	Gamma	148.3319	133.4987–163.1650	[28]
Foods (per visit)	Gamma	71.3739	64.2365–78.5113	[28]
Indirect costs				
Income loss from sick leave of patients (per visit)	Gamma	89.0640	80.1576–97.9705	[28]
ESRD state				
Direct medical costs				
Palliative care (per month)	Gamma	19,269.8993	17,342.9093–21,196.8891	[29]
Laboratory for ESRD (per 2 months)	Gamma	847.4251	762.6826–932.1676	[29]
Peritoneal dialysis catheter placement (per life)	Gamma	51,028.1103	45,925.2993–56,130.9214	[29]
Dialysis solution	Gamma	2,138.7915	1,924.9124–2,352.6707	[29]
Cleaning set	Gamma	91.8499	82.6649–101.0349	[29]
Erythropoietin	Gamma	2,296.2486	2,066.6237–2,525.8734	[29]
Direct non-medical costs				
Travel, food, and accommodation of patients and caregivers for CAPD	Gamma	6,205.8547	5,585.2692–6,826.4402	[29]
Utility				
Health state				
Normoalbuminuria	Beta	0.72	0.6734–0.7666	[32]
Microalbuminuria	Beta	0.72	0.6731–0.7670	[32]
Macroalbuminuria	Beta	0.59	0.5104–0.6696	[32]
ESRD	Beta	0.55	0.4816–0.6184	[32]
Side effects				
Edema	Beta	−0.033	−0.0428–−0.0232	[31]
Headache	Beta	−0.115	−0.087–−0.144	[30]

Table 3: Results

Results	Total costs (baht)	QALYs (Year)
Manidipine	69,892.28	9.15
Amlodipine	458,508.22	6.84

Sensitivity Analyses

The one-way sensitivity analysis in Figure 2 was presented in a tornado diagram. Each line shows how setting the parameter to its lowest and highest value impacts ICER. Green color bar represented the ICER changing when using the highest parameter values, while pink color bar represented the ICER changing when using the lowest parameter values.

The results demonstrate that utility of patients with normoalbuminuria has the greatest impact on the ICER, followed by the transition probability of ESRD to death in patients who switch from CCBs to hydralazine. As a result of reducing the first two parameters, the ICER values decreased. Conversely, a decrease in the utility of patients with macroalbuminuria showed an increase in the ICER values. However, the transition probability from microalbuminuria to macroalbuminuria of manidipine is 0.0000. It might be effective to overestimate the results of manidipine. The sensitivity analysis was repeated using the transition probability from microalbuminuria to macroalbuminuria of manidipine was found to be equal to amlodipine is 0.0408. Nonetheless, the results of this sensitivity analysis are consistent with those

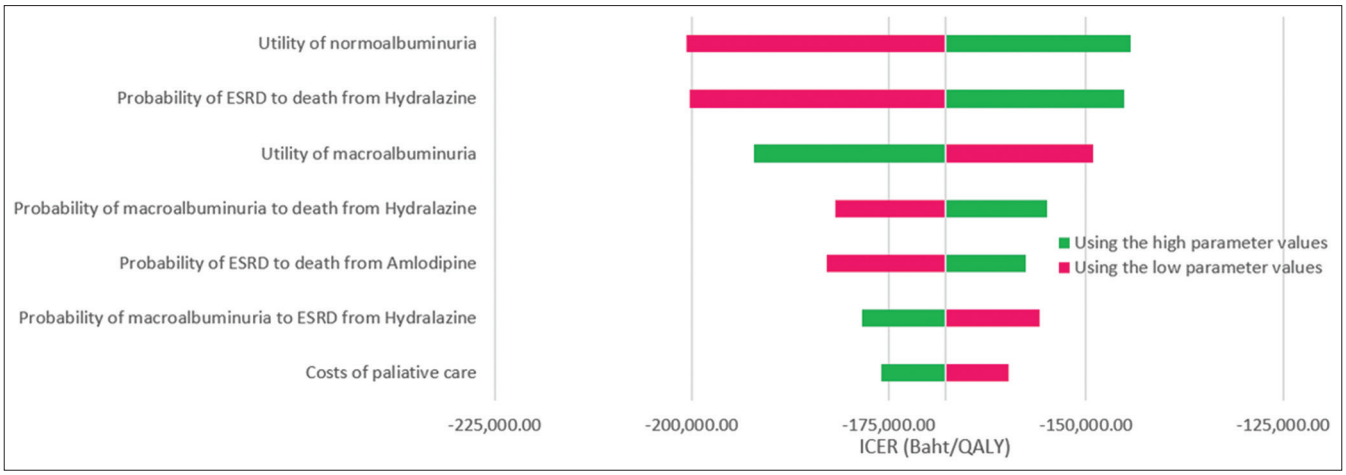

Figure 2: Tornado diagram

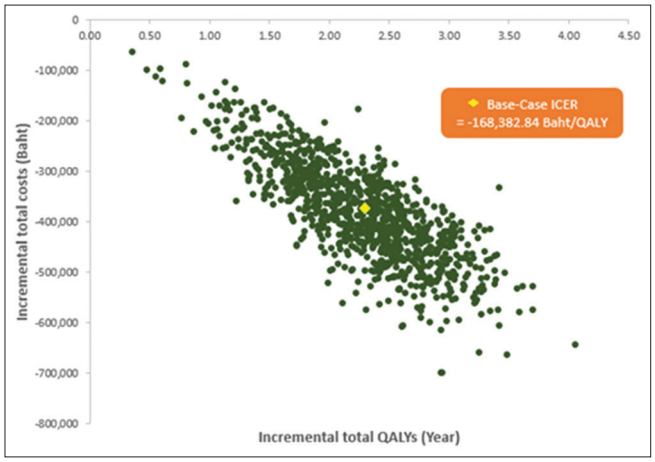

Figure 3: The cost-effectiveness plane between manidipine and amlodipine

of the primary analysis and manidipine was still a dominant option (data not shown).

The PSA in Figure 3 presents the incremental costs and QALYs for manidipine compared with amlodipine as a cost-effectiveness plane. After randomizing each variable 1000 times in the Monte Carlo simulations and evaluating the simultaneous uncertainties regarding each parameter which might influence the base-case ICER. The ICER value was located on the lower right-hand quadrant of the plane indicated extended QALYs with lower costs. This revealed a probability of 100% that manidipine was more cost-effective compared to amlodipine. Obviously, manidipine was significantly more cost-effective than amlodipine as an add-on treatment to renin-angiotensin system blockers in hypertensive patients with diabetes mellitus and proteinuria.

DISCUSSION

This is the first study of economic evaluation to assess third-generation DHP CCB, especially manidipine, and to compare them with amlodipine as an add on to RASBs in hypertensive patients and those with diabetic nephropathy. The results of this study were that manidipine is more cost-effective than amlodipine in the treatment of hypertensive patients with diabetes mellitus and proteinuria. Manidipine was associated with better clinical outcomes in terms of QALYs than amlodipine by 2.31 in 1 year. Furthermore, manidipine reduced expenditures by 388,615.94 baht. Therefore, the results of the analysis cannot show the ICER value (−168,382.84 baht per QALY; negative number of value), which is certainly below the GNI per capita and the selection criterion of 160,000 baht per QALY. Manidipine decreased expenditure for each QALY gained.

The above findings on clinical and safety outcomes are in line with previous studies that manidipine has been associated with improved therapeutic outcomes such as a reduction in albuminuria and side effects, especially peripheral edema. The MAISH study[38] found that both manidipine and amlodipine have been shown to be equally effective in reducing BP in elderly people with isolated systolic hypertension. However, the incidence of peripheral edema in the manidipine group was significantly smaller than in the amlodipine group. In addition, the MARIMBA study[39] showed that the BP of hypertensive patients with metabolic syndrome was reduced by a similar extent from both manidipine and amlodipine. Furthermore, manidipine had a significant beneficial effect on albuminuria and insulin resistance, while amlodipine did not. The meta-analysis of head-to-head RCT[18] indicated that 10 mg of amlodipine and 20 mg of manidipine have statistically equivalent efficacy in the reduction of diastolic and systolic BP, while the overall safety (i.e., adverse event, ankle edema) of manidipine was significantly superior to amlodipine.

Above all, the AMANDHA study[19] (JADAD score = 2) was the only study that indicated beneficial effects on reducing urinary albumin excretion in diabetes patients with microalbuminuria and uncontrolled hypertension on RAAS monotherapy. The addition of manidipine resulted in a better reversion rate to normoalbuminuria than amlodipine. Moreover, the progression from the microalbuminuria state to the macroalbuminuria state and the macroalbuminuria state to ESRD and ESRD to death in amlodipine is higher than manidipine. Therefore, patients receiving amlodipine over manidipine are associated with increased expenditures due to the higher rate of renal disease progression and its

complications. However, when the sensitivity analysis was repeated using the transition probability from microalbuminuria to macroalbuminuria of manidipine, it was found to be equal to amlodipine as a worst-case scenario. Nonetheless, the results of this sensitivity analysis are consistent with those of – the primary analysis that manidipine was still the dominant option (data not shown). Future studies should take this outcome into account as they could elaborate on the cost-effectiveness model of this drug class.

There is some limitation regarding the availability of data. There have been few studies that have compared the efficacy, side effects, and utility of manidipine with amlodipine, and there have not been any studies conducted in Thailand. The probability of transition health states, probability of side effects, and utility values used in this study were derived from international resources.

This study did not receive any specific grant from funding agencies in the public or commercial domains.

CONCLUSIONS

Manidipine is more cost-effective than amlodipine in the treatment of Thai hypertensive patients with diabetes mellitus and proteinuria, and it was associated with better clinical outcomes in terms of QALYs and lower costs than amlodipine. Manidipine should be used as the first choice as an add-on to RASBs. The results of this study could contribute to appropriate decision making by policymakers.

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