Cost-effectiveness Analysis of Lercanidipine Compared to Amlodipine as an Addition to Renin-angiotensin System Blockers in Diabetic Hypertensive Patients with Albuminuria in Thailand

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ABSTRACT

Objective: Dihydropyridine calcium channel blocker (DHP-CCBs) is an appropriate add-on antihypertensive option for uncontrolled blood pressure diabetic hypertensive patients with albuminuria who are already taking renin-angiotensin system blockers (RASBs). Among DHP-CCBs, amlodipine is the first-line medication in combination with RASBs. However, new-generation DHP-CCBs like lercanidipine has demonstrated superior effectiveness and fewer side effects, although at a higher cost than amlodipine. This study aims to assess the cost-effectiveness of lercanidipine versus amlodipine when added to RASBs in diabetic hypertensive patients with albuminuria. The objective is to provide robust evidence guiding the selection of the most suitable and worthwhile treatment option in Thailand.

Materials and Methods: This study analyses the cost-effectiveness of lercanidipine versus amlodipine as an addition to RASBs in diabetic hypertensive patients with albuminuria. The analysis was conducted from a societal perspective using a Markov model.

Results: The total costs of lercanidipine and amlodipine treatments were 370,392.83 baht and 384,221.85 baht, respectively. The life years gained for lercanidipine and amlodipine treatments were 11.33 years and 10.96 years respectively. Additionally, the quality-adjusted life years (QALYs) of lercanidipine and amlodipine treatments were 8.06 years and 7.51 years respectively. The calculated ICER was negative, indicating treatment with lercanidipine as a dominant strategy.

Conclusion: Due to lercanidipine's noticeable cost-effectiveness, lower costs, and longer QALYs. Adding lercanidipine has proven to be more cost-effective than amlodipine for diabetic hypertensive patients with albuminuria who have been unable to achieve their blood pressure goals with RASBs alone. Therefore, lercanidipine should be the preferred choice as an add-on to RASBs in Thailand. These results could significantly aid policymakers in making informed decisions.

Keywords: Albuminuria; amlodipine; cost-effectiveness analysis; diabetes; hypertension; lercanidipine; renin-angiotensin system blockers (Siriraj Med J 2024; 76: 522-533)

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INTRODUCTION

Hypertension (HT) poses a significant global public health challenge due to its association with adverse health outcomes and substantial healthcare costs.[1,2] Over the last three decades, the number of adults aged 30-79 years diagnosed with hypertension has surged from 650 million to 1.28 billion, with a majority (approximately 82 percent) residing in low- and middle-income countries.[3] This overall increase in hypertensive patients is expected to expedite the progression of renal diseases, potentially leading to end-stage renal disease (ESRD).[4,5]

The coexistence of hypertension and diabetes is a common occurrence among a substantial portion of the patient population.[4,6] Individuals with both conditions often share common risk factors, including family history, ethnicity, dyslipidemia, and lifestyle choices. Previous studies have highlighted that hypertensive patients with diabetes are more prone to elevated blood pressure levels compared to those without diabetes, significantly increasing their risk of developing nephropathy, a microvascular complication.[7-9] Furthermore, this combination accelerates the progression and mortality rates associated with kidney disease.[1,2,4,9]

Prolonged, uncontrolled hypertension leads to increased intraglomerular pressure, impairing glomerular filtration. Consequently, this damages the glomeruli, causing abnormally high protein levels in the urine, a condition commonly known as albuminuria or proteinuria.[4,5] The association between hypertension and elevated urinary albumin excretion levels is well-established in both diabetic and non-diabetic patients.[10-13]

Albuminuria is a condition characterized by elevated urine albumin excretion, leading to kidney damage or a reduced glomerular filtration rate (GFR).[4] It serves as an early indicator of hypertensive renal damage. It acts as a precursor to renal insufficiency, particularly in diabetic and non-diabetic hypertensive patients with chronically uncontrolled blood pressure (BP).[4] The prevalence of albuminuria varies significantly among different studies, ranging from 10% to 40% in hypertensive patients.[14-16] This prevalence increases with age and the duration and severity of hypertension.[14-16] Effective BP control is associated with reducing urine albumin content and can delay or prevent the progression of renal degeneration. Therefore, expanding kidney replacement programs becomes crucial to prevent straining healthcare resources and ensure cost savings.[4,5]

Numerous guidelines[1,2,4,17] for hypertension management recommend the first-line use of renin-angiotensin system blockers (RASBs), such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), in patients with or without diabetes who have albuminuria. The purpose is to control blood pressure, aiming for a target of less than 130/80 mmHg or even an intensive blood pressure target (SBP 120 mmHg) if feasible.[4] If a patient cannot tolerate either class of medications or if the BP goal cannot be achieved (i.e., at least 20 mmHg above the target)[4], the alternative class should be considered. However, combinations of ACEIs and ARBs should be avoided. It is essential to note that not all antihypertensive medications have a similar effect on renal function. This factor should be taken into account when adding another antihypertensive medication, as the goal is to protect organ function.

When combined with RASBs, calcium channel blockers (CCBs) emerge as a suitable antihypertensive drug.[2,18] This combination proves especially beneficial for diabetic hypertensive patients with albuminuria, outperforming other antihypertensive classes based on current evidence, which indicates its potent antihypertensive and reno-protective benefits.[19-21] Studies have demonstrated that the combination of RASBs and a dihydropyridine (DHP) CCB is superior to a single-agent approach, reducing proteinuria and slowing down the progression of kidney degeneration in diabetic hypertensive patients with albuminuria.[19-21]

However, it is worth noting that CCBs come with common adverse effects, including peripheral edema, particularly in the lower limbs, and headaches.[22-24] The incidence of peripheral edema caused by CCBs ranges from 5% to 60%, often leading to treatment discontinuation.[24] In Thailand's National List of Essential Medicines (NLEM), amlodipine besylate is the recommended first-line DHP-CCB medication to be added to RASBs. In cases where patients cannot tolerate amlodipine's side effects, especially peripheral edema, new-generation DHP-CCBs like lercanidipine hydrochloride are suggested as a second treatment option.[17]

The effect of amlodipine, when used in combination with RASBs, is comparable to that of lercanidipine hydrochloride, a new generation DHP-CCB, in hypertensive patients with albuminuria.[25,26] However, previous randomized trials have shown that patients receiving lercanidipine in combination with RASBs experienced significant benefits, including reduced albuminuria and slowed progression of renal degeneration.[25-27] In the RED LEVEL study, which directly compared the efficacy of lercanidipine and amlodipine in combination with enalapril to protect renal function by reducing albuminuria in patients with mild-to-moderate hypertension, the findings revealed a significant decrease in albuminuria in the lercanidipine group at 3, 6, and 12 months compared to patients in

the amlodipine group.[25] Additionally, the ZAFRA study suggested that lercanidipine hydrochloride has a significantly lower rate of peripheral edema than amlodipine.[26] While lercanidipine appears to be more effective than amlodipine, it is three times more expensive when administered at equivalent dosages, according to the Drug and Medical Supply Information Center (DMSIC) and the Ministry of Public Health in Thailand.[28-30]

Amlodipine is currently considered the primary DHP-CCB to be used in conjunction with RASBs in patients with diabetic hypertension who also have albuminuria. Although lercanidipine has been demonstrated to be more effective and to have fewer side effects than amlodipine, its cost-effectiveness in Thailand and other countries has yet to be established. Therefore, this study aims to demonstrate the cost-effectiveness of lercanidipine compared to amlodipine when added to RASBs in diabetic hypertensive patients with albuminuria. The objective is to provide reliable evidence for decision-making regarding the most suitable and worthwhile treatment option in Thailand.

MATERIALS AND METHODS

Study design

The study was a cost-utility analysis (CUA) applying a Markov model analysis to simulate cost-effective treatments between amlodipine and lercanidipine as an adjunct to RASBs in diabetic hypertensive patients with albuminuria. Incremental cost-effectiveness ratio (ICER) was estimated by dividing the difference in cost in baht by the difference in quality-adjusted life years (QALYs) between treatments. Lifetime horizon was applied with a societal perspective. The study's protocol was reviewed and approved by the Human Research Ethics Committee of Silpakorn University (COE 66.0313-011).

Interventions of interest

This study compared 5 mg per day of amlodipine versus 10 mg per day of lercanidipine[28-31] in diabetic hypertensive patients with albuminuria who have been unable to achieve their blood pressure target[4] with RASBs (i.e., angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)) for at least six months.

Model structure

A five-stage Markov model was constructed based on clinical practice guidelines and previous published studies[1,4,6], see in Fig 1. The model and assumptions were validated by two nephrologists and one cardiologist for the clinical sequence to ensure its suitability for managing diabetic hypertensive patients with albuminuria. Microsoft Excel 2022 was used to perform decision analysis of a Markov model.

The model simulated patients over their lifetime, incorporating five clinical health states: normoalbuminuria, microalbuminuria, macroalbuminuria, end-stage renal disease (ESRD), and death. Chronic kidney disease (CKD) stages G1 to G4 were included as subclinical states within the normoalbuminuria, microalbuminuria, and macroalbuminuria states. Patients treated with RASBs alone initially entered the model with normoalbuminuria and blood pressure less than 150/80 mmHg, regardless of their CKD stage for hypertension treatment. During each three-month Markov cycle, patients could either stay in the same state or transition to other states if they could not achieve their blood pressure goal (i.e., at least 20 mmHg above the target or equal to or more than 150/80 mmHg[4]) despite being treated with RASBs alone for at least six months. Amlodipine or lercanidipine would be added for patients whose hypertension did not improve

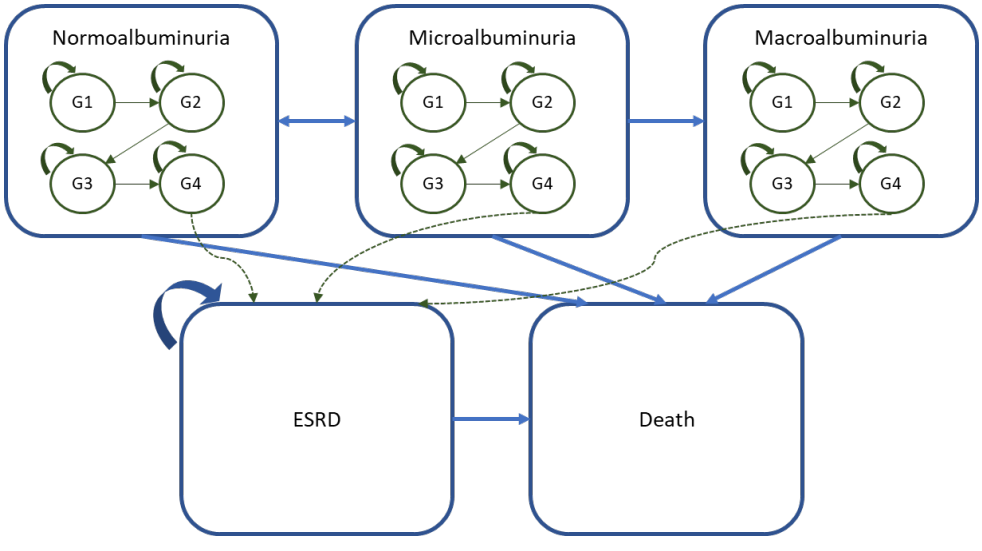

Fig 1. Markov model structure of diabetic hypertensive patients with albuminuria.

with RASBs to slow down renal degeneration. At the end of each cycle, transition probabilities for clinical status, adverse events (such as peripheral edema and headache), and mortality rates were assessed for each treatment group. Patients in the microalbuminuria state could regress to the normoalbuminuria condition. However, patients in the macroalbuminuria and ESRD states could not revert to previous states. The model continued until all patients met the criteria for the absorbing state, which was death, with an annual discount rate of 3%.

Assumptions of the model

1. The interested population in both add-on with amlodipine and lercanidipine arms is diabetic hypertensive patients who received RASBs for at least six months for hypertension and did not receive any other antihypertensive as well as other co-interventions.

2. According to a previous study in Thailand[32], the model's target population had an average age starting of 59 years and mean eGFR levels of 100 mL/min/1.73 m^2.

3. All patients used metformin as monotherapy for CKD stages G1 to G3 or eGFR ≥ 30 mL/min/1.73 m^2 or insulin for CKD stages G4/ESRD or eGFR < 30 mL/min/1.73 m^2. All had HbA1C levels between 7% and 9% and received no additional antidiabetic medications or co-interventions.

4. Patients with normoalbuminuria states have BP that is less than 150/80 mmHg and are treated with RASBs alone for hypertension.

5. Patients with microalbuminuria and macroalbuminuria states have BP that cannot be controlled or that are unable to achieve their BP goal (i.e., or more than or equal to 150/80 mmHg) while using RASBs alone for at least six months. 5 mg of amlodipine or 10 mg of lercanidipine daily would be combined to reduce BP and slow down albuminuria.

6. According to clinical practice guidelines[4], a BP of 150/80 mmHg is considered the upper limit of tolerable blood pressure, or at least 20 mmHg over the target of 130/80 mmHg. It requires the addition of other antihypertensive medications.

7. Patients with ESRD states are those who undergo continuous ambulatory peritoneal dialysis (CAPD) after being diagnosed with end-stage renal disease or increased plasma creatinine > 175 mol/L.

8. Peripheral edema and headaches were common adverse effects in all patients who added on with CCB, either amlodipine or lercanidipine.

9. Patients who experienced peripheral edema were switched from amlodipine or lercanidipine to 25 mg of hydralazine four times per day and then continued this medication to control hypertension. Patients who received hydralazine had no side effects.

10. Patients who experienced headaches were treated with paracetamol 500 mg 4 times daily.

11. Patients in microalbuminuria states of health could be transferred to normoalbuminuria conditions. Patients with macroalbuminuria and ESRD health conditions were unable to return to their previous state.

Time Horizon

A Markov model was developed to imitate the treatment of adult Thai hypertensive patients over a lifetime period from the mean age[32] of 59 until death with a life expectancy of not more than 75 years.[33,34] A three-month cycle was considered appropriate to determine the clinical efficacy of treatment in each health state from a survey of treatment in Thailand.

Probability of clinical outcomes

A systematic search for clinical parameters was conducted in Medline and Cochrane databases. The keywords were amlodipine "AND" lercanidipine". Two reviewers (KR and JL) independently reviewed abstracts and articles sequentially to select studies for data abstraction based on the study eligibility criteria. All searched literature was evaluated for the quality of studies according to the revised Cochrane risk of bias tool (RoB 2.0) for randomized trials and the STROBE statement for observational studies. All probabilities were converted into risks over three months because of the cycle length. All clinical parameters used in the Markov model were approved by the clinical experts and are shown in Table 1.

Studies were identified as eligible for inclusion if they were published as full papers in English. All transition probabilities were obtained from studies involving diabetic hypertensive patients with albuminuria who had been using RASBs for at least six months and added either amlodipine or lercanidipine to their treatments, according to the health transitions in the Markov model. The utility of health states was obtained from studies involving Thai diabetic hypertensive patients using amlodipine and lercanidipine and had the health state according to the Markov model with or without adverse effects. If search results were inconclusive, the study proceeded as follows:

(i) involving diabetic hypertensive patients with albuminuria with controlled hypertension by antihypertensive drug or BP less than 150/80 mmHg and whether they had adverse effects, or (ii) other patients who had utility

TABLE 1. All parameters used in the Markov model.

Parameters	Distribution	Mean ± SE	References
Clinical parameters:			
Transition probabilities			
Normoalbuminuria to Microalbuminuria	Beta	0.01748 ± 0.00121	39
Probability of eGFR reduction (G1 to G4)	Beta	0.00619 ± 0.00018	40
Normoalbuminuria (G4) to ESRD	Beta	0.04292 ± 0.01397	41
Microalbuminuria (G4) to ESRD	Beta	0.04292 ± 0.01397	41
Macroalbuminuria (G4) to ESRD	Beta	0.11100 ± 0.00385	42
Normoalbuminuria to Death	Beta	0.00352 ± 0.00014	43
Microalbuminuria to Death	Beta	0.00759 ± 0.00051	43
Macroalbuminuria to Death	Beta	0.01170 ± 0.00137	43
ESRD to Death	Beta	0.05190 ± 0.00665	43
Lercanidipine			
Microalbuminuria to Normoalbuminuria	Beta	0.26279 ± 0.02631	44
Microalbuminuria to Macroalbuminuria	Beta	0.00000 ± 0.00000	44
Peripheral edema	Beta	0.00473 ± 0.00222	25, 45, 46
Headache	Beta	0.01826 ± 0.00511	45, 47
Amlodipine			
Microalbuminuria to Normoalbuminuria	Beta	0.04083 ± 0.02508	48
Microalbuminuria to Macroalbuminuria	Beta	0.04083 ± 0.02508	48
Peripheral edema	Beta	0.25763 ± 0.04508	49
Headache	Beta	0.14455 ± 0.17583	49, 50
Hydralazine			
Microalbuminuria to Normoalbuminuria	Beta	0.00639 ± 0.00622	51
Microalbuminuria to Macroalbuminuria	Beta	0.06186 ± 0.01439	51
Humanistic parameters: *Utility*			
Normoalbuminuria state	Beta	0.720 ± 0.024	52
Microalbuminuria state	Beta	0.720 ± 0.024	52
Macroalbuminuria state	Beta	0.590 ± 0.041	52
ESRD state	Beta	0.550 ± 0.035	52
CKD stage G1-G2	Beta	0.85 (0.76, 0.94)	53
CKD stage G3-G4	Beta	0.72 (0.57, 0.87)	53
Reduction on utility of peripheral edema	Beta	0.033 ± 0.005	54
Reduction on utility of headache	Beta	0.115 ± 0.014	55

TABLE 1. All parameters used in the Markov model. (Continue)

Parameters	Distribution	Mean ± SE	References
Economic parameters (Baht):			
Direct medical cost			
(Normoalbuminuria, Microalbuminuria and Macroalbuminuria state)			
Medical costs			
Enalapril 20 mg (per tablet)	Gamma	0.5500 ± 0.0550	36
Lercanidipine 20 mg (per tablet)	Gamma	3.0000 ± 0.3000	36
Amlodipine 10 mg (per tablet)	Gamma	0.9000 ± 0.0900	36
Hydralazine 25 mg (per tablet)	Gamma	1.5000 ± 0.1500	36
Metformin 500 mg (per tablet)	Gamma	0.4000 ± 0.0400	36
Insulin NPH injection 100 IU/3 ml	Gamma	78.1100 ± 7.8110	36
Paracetamol 500mg (per tablet)	Gamma	0.4500 ± 0.0450	36
Laboratory costs			
Albumin test (per unit)	Gamma	33.6300 ± 3.3634	37
BUN test (per unit)	Gamma	83.4600 ± 8.3462	37
Creatinine test (per unit)	Gamma	83.4600 ± 8.3462	37
Urine protein test (per unit)	Gamma	150.7300 ± 15.0730	37
OPD treatment (per visit)	Gamma	83.4619 ± 8.3462	37
Pharmaceutical care service (per visit)	Gamma	84.6300 ± 8.4633	37
Direct medical cost *(ESRD state)*			
Erythropoietin	Gamma	2,794.84 ± 279.48	38
Palliative care (per month)	Gamma	23,454.01 ± 2345.40	38
Laboratory for ESRD (per 2 months)	Gamma	1,031.43 ± 103.14	38
Peritoneal dialysis catheter placement (per life)	Gamma	62,107.94 ± 6,210.79	38
Dialysis solution	Gamma	2,603.19 ± 260.32	38
Cleaning set	Gamma	111.79 ± 11.179	38
Direct non-medical cost			
(Normoalbuminuria, Microalbuminuria and Macroalbuminuria state)			
Travel (per visit)	Gamma	177.570 ± 17.757	37
Food (per visit)	Gamma	65.4100 ± 6.5411	37
Direct non-medical cost *(ESRD state)*			
Travel, food, and accommodation for CAPD (patients and caregivers)	Gamma	6402.84 ± 640.28	38

of health state and adverse effects, or (iii) utility was retrieved from international published studies if there was a scarcity of data in Thailand. Articles were excluded from the review if they met any of the following criteria: (i) non-full text papers, (ii) editorials and opinions, letters, research protocols, conference abstracts, duplicate reports of the same study, and notes and books.

Utility values

Utility values of clinical health states were obtained from previously published studies, see Table 1. QALYs were used as humanistic outcomes measurements in the ICER denominator. Humanistic outcomes were calculated by estimating the life years (LY) remaining of patients and weighted with utility values in different health states, ranging from 0 (death) to 1 (perfect health). Utility weights were multiplied by life expectancies to generate QALYs.

Economic values (costs)

All costs are expressed in Thai baht (as shown in Table 1) and adjusted to 2022 values using the consumer price index from the Bureau of Trade and Economic Indices, Ministry of Commerce, Thailand.[35]

Medical costs (i.e., lercanidipine, amlodipine, enalapril, hydralazine, metformin, insulin NPH injection, paracetamol) were derived from the Drug and Medical Supply Information Center (DMSIC) and the Ministry of Public Health, Thailand.[36] All direct non-medical costs (i.e., costs of travel and foods), laboratory costs, which included test for urine protein, albumin, blood urea nitrogen (BUN), creatinine, cost for OPD treatment, and pharmaceutical care service were obtained from the mean cost per unit from the standard cost lists for health technology assessment in Thailand.[37] The costs of all health states include medical costs and direct non-medical costs. Total costs include all treatment-related costs per patient from the time patient receives the treatment until death. Costs of patients in ESRD health state undergoing CAPD, including direct medical or direct non-medical costs, were derived from the previous studies in Thailand.[38]

Cost-effectiveness analysis

The ICER assessed the analysis based on a societal perspective, which was estimated by dividing the difference in cost in baht by the difference of QALYs between lercanidipine and amlodipine arms. Future costs and QALYS were discounted at 3% per year.

One-way sensitivity and Probabilistic Sensitivity Analysis (PSA)

The sensitivity analysis was performed to examine the robustness of the results using Microsoft Excel 2020. The upper and lower bounds of the 95% confidence interval (CI) around each parameter were used in a one-way and probabilistic sensitivity analysis.

For one-way sensitivity analysis, the parameter values were changed individually and regularly to the lowest and highest values. The results of one-way sensitivity analyses were presented in a tornado diagram. PSA was applied by randomly running 1,000 iterations using Random Monte Carlo Simulation to examine how parameters affected the ICER. Beta distribution was used for transition probabilities and utility values, whereas gamma distribution was used for costs. The results are presented as an ICER plane between incremental costs and incremental QALYs.

RESULTS

Cost-effectiveness analysis

The cost-effectiveness analysis results in Table 2 revealed that the total costs of lercanidipine and amlodipine treatments were 370,392.83 baht and 384,221.85 baht; LYs were 11.33 years and 10.96 years, and QALYs were 8.06 years and 7.51 years, respectively. The ICER of the lercanidipine treatment compared with the amlodipine was -25,143.67 baht/QALY gained. Because of the noticeable

TABLE 2. Cost-effectiveness results.

	Total cost (Baht)	LYs (Years)	QALYs (Years)	ICER (Baht/QALY)
Lercanidipine	370,392.83	11.33	8.06	-25,143.67
Amlodipine	384,221.85	10.96	7.51	

cost-effectiveness of lercanidipine treatment, lower costs, and longer QALYs, lercanidipine treatment was the preferred option.

Sensitivity analyses

The one-way sensitivity analysis result is shown in a tornado diagram in Fig 2. Regarding the outcomes, the variable with the most significant impact on the ICER was the probability of changes in health state in stage 4 CKD patients with normoalbuminuria to ESRD, followed by the probability of headaches of amlodipine. The probabilistic sensitivity analysis result is shown in Fig 3 as a cost-effectiveness plane between the incremental cost and the incremental QALYs of lercanidipine treatment compared with amlodipine treatment. Each variable was randomized 1,000 times in the Monte Carlo simulations. The yellow dot stands for the base-case ICER. Almost 88.6% of the ICER from randomization was dropped in quadrant 4, implying that lercanidipine had lower costs and longer QALYs.

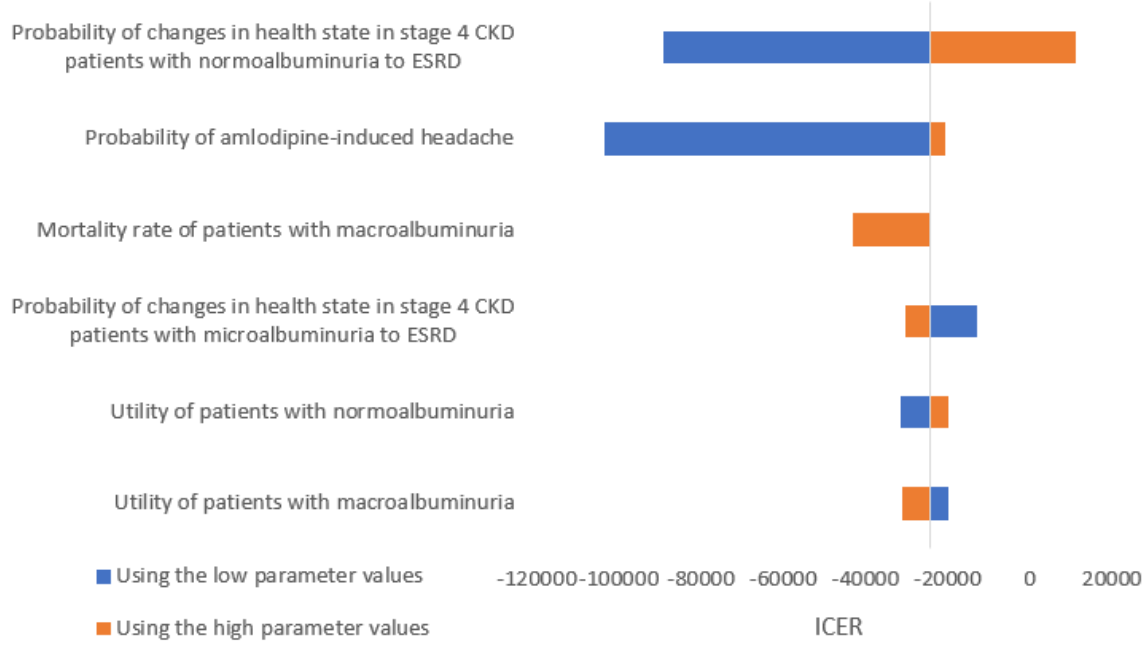

Fig 2. The tornado diagram depicts the results of a one-way sensitivity analysis.

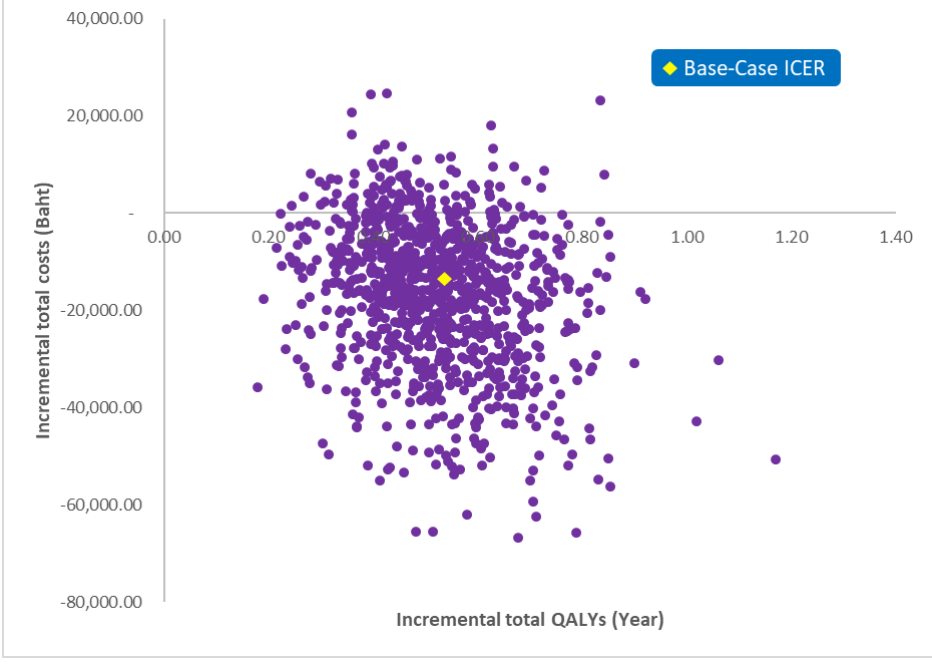

Fig 3. The cost-effectiveness plane of treatment with lercanidipine compared with amlodipine.

DISCUSSION

This is the first cost-effectiveness study to evaluate the addition of lercanidipine compared to amlodipine in diabetic hypertensive patients with albuminuria who are unable to achieve their BP target with only RASBs in Thailand. Even lercanidipine is three times more expensive compared with amlodipine. The results of this study revealed that an add-on with lercanidipine to RASBs is more cost-effective than amlodipine in the treatment of diabetic hypertensive patients with albuminuria from a societal perspective. As a result, lercanidipine has been associated with improved outcomes in terms of both LYs and QALYs gained, reducing total health expenditures. Treatments with lercanidipine demonstrate slower ESRD progression and lower adverse drug reactions, which will save on the cost of dialysis and treatments, resulting in significant cost savings. Therefore, the results indicated the ICER value is negative (i.e., -25,143.67 baht/QALY gained.), which is unquestionably lower than the GNI per capita with a ceiling threshold in Thailand of 160,000 baht per QALY. The results were also validated using one-way and probabilistic sensitivity analysis. They were consistent with the ICER-based results, which unambiguously demonstrated that adding lercanidipine was a cost-effective strategy as it reduced health expenditures for each QALY gained.

Previous clinical studies evaluating the efficacy and safety of lercanidipine and other CCBs have demonstrated its superior therapeutic efficacy in reducing albuminuria and minimizing adverse effects associated with vasodilation, particularly peripheral edema and therapy discontinuation. According to meta-analyses[31,56], lercanidipine and amlodipine (as a first-generation CCB) showed no significant differences in their long-term blood pressure-lowering effects.[31,56] However, lercanidipine was notably linked to a substantial reduction in peripheral edema and treatment discontinuation due to adverse events, in contrast to amlodipine.[31] Interestingly, lercanidipine's unique effects on renal hemodynamics, dilating both afferent and efferent glomerular arteries, contribute to preserving renal function even when used as a single medication. This is unlike amlodipine, which exhibits renal protection only when paired with RASBs.[57,58] The DIAL Study[58] demonstrated a reduction of more than 50% in microalbuminuria with lercanidipine treatment, although there was no statistically significant difference when compared to the use of RASBs alone.

Additionally, lercanidipine and RASBs have a synergic effect in reducing microalbuminuria in patients with proteinuria renal disease, which significantly reduces proteinuria by 20% to 35%.[27,45,59] Previous studies[25,44] suggested that enalapril combined with lercanidipine more reduced albuminuria than those combined with amlodipine. Lercanidipine had a higher rate of reversion to normoalbuminuria in microalbuminuria patients. In contrast, amlodipine had a greater progression from the microalbuminuria to the macroalbuminuria, the macroalbuminuria state to ESRD, and ESRD to death than lercanidipine.[44] Due to the higher likelihood of progression of renal disease and related complications, patients using amlodipine may experience higher health expenditures and less cost-effective treatment options. Our one-way sensitivity analysis revealed that the probability of changes in CKD stage 4 with normoalbuminuria to ESRD was the most sensitive parameter for the cost-effectiveness of lercanidipine versus amlodipine, indicating that the ICER values decreased when this parameter was reduced. Patients with CKD stage 4 with normoalbuminuria were less likely to develop to ESRD than those with albuminuria, according to the progression of the renal disease, which is in accordance with the previous evidence that lercanidipine can lower albuminuria to acceptable levels. Even when this parameter is raised, the ICER value increases, but the results are unchanged and remain below the Thailand ceiling threshold. These findings have substantial implications regarding optimizing the beneficial effects of controlling urinary albumin excretion to normoalbuminuria of lercanidipine.

Nevertheless, our study had several limitations due to the following factors: first, there were few studies[25,44] that directly compared the efficacy and adverse drug reactions of add-on lercanidipine and amlodipine to RASBs, and no previous studies were conducted in Thailand. Sensitivity analysis was performed utilizing ranges from all parameters to ensure the robustness of our results and reduce uncertainty influenced by confounding factors. Second, the available evidence is insufficient to distinguish macroalbuminuria from microalbuminuria in the lercanidipine arm (i.e., none would develop into macroalbuminuria), which might impact the final results of the analysis. However, we performed the worst-case scenario using the transition probability from microalbuminuria to macroalbuminuria of lercanidipine to be equal to amlodipine. The results are consistent that lercanidipine was still a dominant option (data not shown). Third, only CAPD was taken into account for the ESRD health state; we did not consider other modalities, such as hemodialysis, automated peritoneal dialysis, and kidney transplantation, which are used for kidney replacement therapy. Because CAPD was the first modality used to treat ESRD patients in Thailand, we assumed macroalbuminuria could not be

moved backward to the previous state or fully forestalled. Because albuminuria is a surrogate marker for chronic kidney disease progression.[4] Furthermore, only peripheral edema and headaches were considered adverse effects of CCB. Because these effects related to the mechanism, which were the most frequently reported from previous evidence and affect the patient's quality of life and lead to the discontinuation of treatment.[22,24,31,60]

Further economic evaluation studies require real-practice data across the country to perform a cost-effectiveness analysis for Thai diabetic hypertensive patients to provide a more accurate and reliable evaluation.

CONCLUSION

Adding lercanidipine hydrochloride, a new generation DHP-CCB, is more cost-effective than using amlodipine for diabetic hypertensive patients with albuminuria who cannot achieve their blood pressure goal with RASBs alone for at least six months. Lercanidipine not only leads to better outcomes in terms of Quality-Adjusted Life Years (QALYs) but is also more economical than amlodipine. Therefore, lercanidipine should be the preferred choice as an add-on to RASBs. This information is valuable for clinicians and policymakers as it guides future decisions regarding medical selection and reimbursement policies for diabetic hypertensive patients with albuminuria.

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Author Contributions

KR performed a systematic review, developed the model, and prepared the data for analysis. WT developed the economic methodology and conceptual framework of this study and the model and prepared the data for analysis. PU developed the model and prepared the data for analysis. JL performed a systematic review, developed the model, analyzed the cost-effectiveness result, and analyzed one-way and probabilistic sensitivity. All authors interpreted the results and participated in manuscript preparation.

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