Original article

Cost-effectiveness of annual microalbuminuria screening in Thai diabetics

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Background: Diabetes is a leading cause of end stage renal disease (ESRD), which impacts on treatment costs and patients' quality of life. Microalbuminuria screening in patients with diabetes as an early intervention is beneficial in slowing the progression of diabetic nephropathy.
Objectives: We aimed to assess the cost-effectiveness of annual microalbuminuria screening in type 2 diabetic patients.
Methods: We compared screening by urine dipsticks with a "do nothing" scenario. To replicate the natural history of diabetic nephropathy, a Markov model based on a simulated cohort of 10,000 45-year-old normotensive diabetic patients was utilized. We calculated the cost and quality of life gathered from a cross-sectional survey. The costs of dialysis were derived from The National Health Security Office (NHSO). We also calculated the incremental cost-effectiveness ratio (ICER) for lifetime with a future discount rate of 3%.
Results: The ICER was 3,035 THB per quality-adjusted life year (QALY) gained. One-way and probabilistic sensitivity analyses showed that all ICERs were less than the Thai Gross Domestic Product (GDP) per capita (150,000 THB in 2011) based on World Health Organization's suggested criteria.
Conclusions: Annual microalbuminuria screening using urine dipsticks in type 2 diabetic patients is very cost-effective in Thailand based on World Health Organization's recommendations. This finding has corroborated the benefit of this screening in the public health benefit package.

Keywords: Cost-effectiveness, diabetes, healthcare system, microalbuminuria, screening

The prevalence of diabetes mellitus is increasing worldwide and is high in developing countries. Diabetic nephropathy is a devastating complication as one-third of patients will progress to end stage renal disease (ESRD). Approximately 10% of ESRD is found in patients who have recently been diagnosed with type 2 diabetes [1]. Such patients may face later complicated and costly renal replacement therapy. Screening for microalbuminuria allows for recognition and early treatment with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB). This has been proven to slow the progression of ESRD and improve patient quality of life (QoL) [2-4]. Therefore, it is recommended microalbuminuria screening in type 2 diabetics be done

routinely [5]. Annual screening for microalbuminuria is recommended in Thai clinical practice guidelines for diabetes, under the Thai Universal Health Coverage Scheme. Treatment with renoprotective drugs at an early stage of microalbuminuria has been shown to be effective. In diabetic patients with hypertension, ACEI are recommended as the first line drug to control blood pressure and prevent progressive nephropathy. For diabetic patients that are normotensive, studies of cost-effective treatment are limited and remain controversial [5-6]. Costs for microalbuminuria screening remain relatively high and are not covered by the Thai Universal Health Coverage Scheme. Currently, urine dipstick screening; a semi-quantitative method, is a simple and suitable method used in healthcare centers including in remote areas. As such, we assessed cost and effectiveness of microalbuminuria screening in normotensive type 2 diabetic patients, using urine dipsticks compared with no screening.

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Materials and methods

A cost-effectiveness study of microalbuminuria screening, using the Markov model, was conducted. We collected data on empirical costs and patients' quality of life status at different stages of nephropathy using a cross-sectional survey in Thai hospital settings, from January to August 2011. A cohort of diabetic patients with normo-, micro-, macroalbuminuria, and ESRD were recruited from community, general, and regional hospitals. We collected direct nonmedical costs (food and travel), opportunity cost, and quality of life data of 196 type 2 diabetic patients and in 140 patients with hemodialysis or peritoneal dialysis. Opportunity cost (lost income) was calculated on the basis of time loss multiplied by patient's income. QoL at each stage was collected by using a Thai EuroQol five-dimensional (EQ-5D) questionnaire. We used urine dipsticks (Micral test; Roche Diagnostics) to detect microalbuminuria in diabetic patients.

This study was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health and The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand. All 336 participating patients gave their written informed consent to participate in this study.

Formulation

We used a Markov model to simulate the natural history of diabetic nephropathy based on Adler et al. [7]. The states of elevated serum creatinine and ESRD were separated to represent better the natural course of nephropathy. All stages of diabetic nephropathy in the model were mutually exclusive, consisting of normo-, micro-, macroalbuminuria, elevated serum creatinine, ESRD, and death (**Figure 1**).

We compared both costs and outcomes of microalbuminuria screening using the urine dipstick with a "do nothing" scenario. The numbers of patients with positive screening results were based on positive predictive value (PPV) of the test, which was 72.7% when the prevalence of microalbuminuria in diabetes in Thailand was approximately 30% [8]. Sensitivity and specificity of urine dipsticks were 95.2% and 84.7% respectively [9]. A cohort of 10,000 45-year-old diabetic patients with normotension was simulated to screen at community hospital settings in our model.

Patients with negative result were screened annually for 30 years until the age of 75, which is the average life expectancy for Thais [10]. Those who had positive results received ACEI 10 mg a day and were moved into the Markov model until death. We discounted costs and outcomes at 3% and the lifetime time horizon was used from the age of 45 years to 75 years. The model was developed with Microsoft Office Excel 2007.
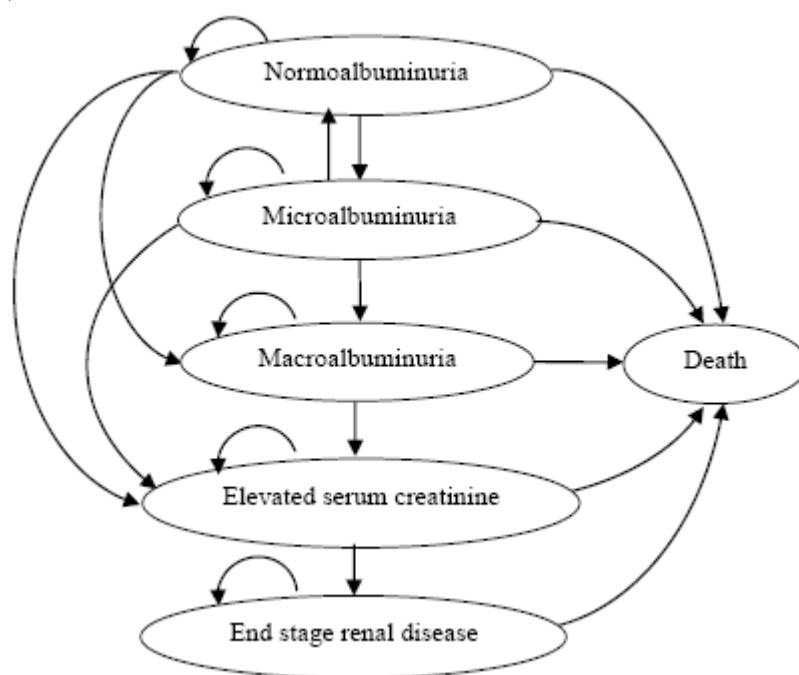

Figure 1. State transition diagram of diabetic nephropathy in diabetes

The following were the assumptions of this model:

1) In the "do nothing" scenario, patients received ACEI at discovery of macroalbuminuria and ESRD.

2) QoL in normo- and microalbuminuria stages were measured together because the presence or absence of nephropathy was not different. Similarly, costs and QoL of macroalbuminuria stage were also assumed for the stage when elevated serum creatinine appeared.

3) We considered only dialysis (hemodialysis and peritoneal dialysis) in the state of ESRD because of the low incidence of kidney transplantations (only 1.5% of patients, who needed renal replacement therapy, actually received kidney transplantations in 2011) [11].

4) We measured QoL among patients with ESRD in diabetics and nondiabetics together because there was no difference in QoL in both groups [12].

Transition probabilities

Markov model in this study used a cycle length of one year. Thus, annual transition probabilities (tp) for the progression from one state to another during diabetic nephropathy are presented in **Table 1**. The progression transition from the state of elevated serum creatinine to ESRD was calculated from data from Remuzzi et al. [13]. Cumulative incidence of ESRD in type 2 diabetic patients with macroalbuminuria in the high serum creatinine group was 45.3% within 4 years. Microalbuminuria had regressed to the normoalbuminuria stage in 30% within 10 years [14]. For overall probabilities over a period of time, we performed yearly progression probability using the following formula [15]:

$$tp_1 = 1 - (1 - tp_t)^{1/t}$$

where tp_1 is the yearly progression probability and tp_t are the overall probabilities over a period of time t. Therefore, 1-year progression probability from elevated serum creatinine to ESRD and micro- to normoalbumonuria were 0.140 and 0.035, respectively. Relative risk (RR) was used to present the effectiveness of ACEI in type 2 diabetic patients [3, 16] (**Table 1**). Age-specific mortality of the Thai population was calculated based on Thai mortality statistics [17] for the transition probabilities of death. Furthermore, relative to the state of normoalbuminuria, we multiplied these transition probabilities by the hazard ratio of dying in the state of micro-, macroalbuminuria, elevated serum creatinine, and ESRD that were 2.80, 5.90, 6.85, and 13.90, respectively [18-19].

Table 1. Annual transition probabilities of diabetic nephropathy

Annual transition probabilities	Value	Reference
Diabetic nephropathy progression		
Normo- to microalbuminuria	0.020	[7]
Normo- to macroalbuminuria	0.001	[7]
Normoalbuminuria to elevated S_{Cr}	0.001	[7]
Micro- to normoalbuminuria	0.030	Calculated from McIntosh et al., [14]
Micro- to Macroalbuminuria	0.028	[7]
Microalbuminuria to elevated S_{Cr}	0.003	[7]
Macroalbuminuria to elevated S_{Cr}	0.023	[7]
Elevated S_{Cr} to ESRD	0.140	Calculated from Remuzzi et al., [13]
Relative risk for progression with ACEI		
Normo- to microalbuminuria	0.32	[16]
Micro- to macroalbuminuria	0.45	[3]
Micro- to normoalbuminuria	3.06	[3]
Death	Age-specific mortality	[17-19]

ACEI = angiotensin converting enzyme inhibitor, ESRD = end stage renal disease, S_{Cr} = serum creatinine

Data analyses
Cost calculation

All costs were calculated in Thai Baht (THB). Total costs per year consisted of direct medical costs; 3 urine dipsticks for screening test (150 THB), drugs, and dialysis, direct nonmedical costs (food and travel), and opportunity cost (income forgone). The screening cost was calculated using 3 urine dipsticks a year. The cost of a single urine dipstick is 50 THB. Thus, it amounts to 150 THB per person per year. ACEI was calculated at enalapril 10 mg per day (Enaril; Biolab). This drug is listed on the National List of Essential Medicines of Thailand, which was 91 THB per year. Treatment cost of dialysis (hemodialysis and peritoneal dialysis) included complications that were collected by the Thai National Health Security Office (NHSO), was approximately 200,000 THB per patient per year.

Utilities

We used quality-adjusted life-years (QALYs) for outcomes measurement in our study. They are composed of length of life and QoL. EuroQol five-dimensional questionnaire was used to measure QoL. It contains five dimensions of health, which are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of three levels of severity: no problems, some/moderate problems, and extreme problems [20]. Then, we translated the QoL into utility scores using Thai preference scores for EQ-5D health states [21]. The utility scores for perfect health and finally the death were 1 and 0 respectively.

Incremental cost-effectiveness ratio (ICER)

We calculated the ICER using the following formula:

$$ICER = \frac{Cost_{screening} - Cost_{no\ screening}}{QALYs_{screening} - QALYs_{no\ screening}}$$

According to World Health Organization (WHO)'s recommendations, an ICER of approximately 1–3 times of GDP per capita is considered cost-effective. In addition, an ICER that is less than GDP per capita is very cost-effective [22]. The GDP per capita in Thailand was approximately 150,000 THB in 2011 [23].

Sensitivity analyses

We obtained one-way and probabilistic sensitivity analyses to evaluate the uncertainty of our model. Each variable in the one-way sensitivity analysis affecting the results was adjusted to evaluate the robustness of model. Additionally, the input parameters for the probabilistic sensitivity analysis were changed simultaneously for 1,000 iterations using Microsoft Office Excel 2007.

Results
Baseline

Baseline data are shown in **Table 2**. The mean serum creatinine was 0.91, 1.12, and 1.64 mg/dL in the normo-, micro-, and macroalbuminuria groups, respectively. Creatinine clearance was calculated using Cockcroft-Gault formula. We also computed estimated glomerular filtration rate (eGFR) using Chinese Modification of Diet in Renal Disease (MDRD) equation [24], which was higher than creatinine clearance at each stage. The mean utility scores of dialysis patients from EQ-5D was 0.55. The visual analog scale (VAS) was higher than EQ-5D. The highest utility scores of hemodialysis in Thai patients from a previous study was 0.69 [25]. However, we used the utility scores from EQ-5D, which was 0.55 in our model based on the comparability with a previously published systematic review and meta-analysis [26].

Cost and outcomes

From the microalbuminuria screening model for the cohort of 10,000 type 2 diabetic patients at age 45 years, we found that the incremental cost was 12.98×10^6 THB. Screening increased the life years and QALYs which were 8.60×10^3 and 4.27×10^3, respectively. Thus, the ICERs of screening cost were 1.51×10^3 THB per life year gained, and 3.03×10^3 THB per QALY gained (**Table 3**).

Sensitivity analyses

All sensitivity analyses of microalbuminuria screening results showed that the cost per QALY gained was less than Thai GDP per capita. A Tornado diagram showed that ICERs per QALY gained decreased when the positive predictive value of urine dipstick increased and cost of test decreased (**Figure 2**).

The cost-effectiveness acceptability curve is shown in **Figure 3**. The probability of microalbuminuria screening cost-effectiveness in diabetes using urine dipsticks was 88%.

Table 2. Baseline characteristics, costs and utilities of participants

Variables	Normoalbuminuria (n = 78)	Microalbuminuria (n = 77)	Macroalbuminuria (n = 41)	ESRD	
				Hemodialysis (n = 56)	Peritoneal dialysis (n = 84)
Baseline					
Age (y)	62.40 (10.34)	62.74 (9.76)	61.43 (9.20)	58.66 (12.19)	60.28 (11.87)
Weight (kg)	67.26 (26.38)	66.21 (13.53)	67.83 (12.36)	61.08 (13.30)	61.24 (13.33)
Serum creatinine (mg/dL)	0.91 (0.28)	1.12 (0.61)	1.64 (1.76)	8.98 (2.42)	9.67 (2.62)
Creatinine clearance (mL/min)	77.52 (48.40)	70.46 (42.00)	62.47 (33.46)	-	-
eGFR* (mL/min/1.73 m^2)	85.98 (24.52)	78.86 (38.73)	66.10 (36.14)	-	-
Cost (THB)					
Food and travel cost	966.60 (727.26)	1294.23 (979.86)	1956.95 (3926.31)	9,035.00 (17,526.59)	4,100.00 (4,088.39)
Opportunity cost	672.78 (1106.82)	1267.81 (3283.84)	891.12 (3150.00)	19,014 (32,519.06)	16,066 (29,809.43)
Utility					
EQ-5D	0.72 (0.21)		0.59 (0.26)	0.55 (0.38)	0.55 (0.32)
VAS	0.76 (0.17)		0.71 (0.19)	0.68 (0.19)	0.73 (0.19)

Data was shown with mean (SD), THB = Thai Baht, VAS = visual analog scale, *Estimated glomerular filtration rate was calculated from Modification of Diet in Renal Disease (MDRD) using the Chinese equation; eGFR $= 175 \times Cr_{(Jaffe)}^{-1.234} \times Age^{-0.179} \times 0.79$ (if female).

Table 3. Cost, outcomes and cost-effectiveness for a simulated 10,000 diabetic patient cohort

	Microalbuinuria	
	Do nothing	**Screening using urine dipsticks**
Life-long cost ($\times 10^6$ THB)	126.45	139.43
Life years ($\times 10^3$ years)	56.22	64.82
QALYs $\times 10^3$	36.60	40.87
Incremental cost ($\times 10^6$ THB)	–	12.98
Incremental life years ($\times 10^3$ years)	–	8.60
Incremental QALYs $\times 10^3$	–	4.27
ICER (THB per LY gained)	–	1,510
ICER (THB per QALY gained)	–	3,035

ICER = incremental cost-effectiveness ratio, LY = life year, QALY = quality adjusted life year, THB = Thai Baht
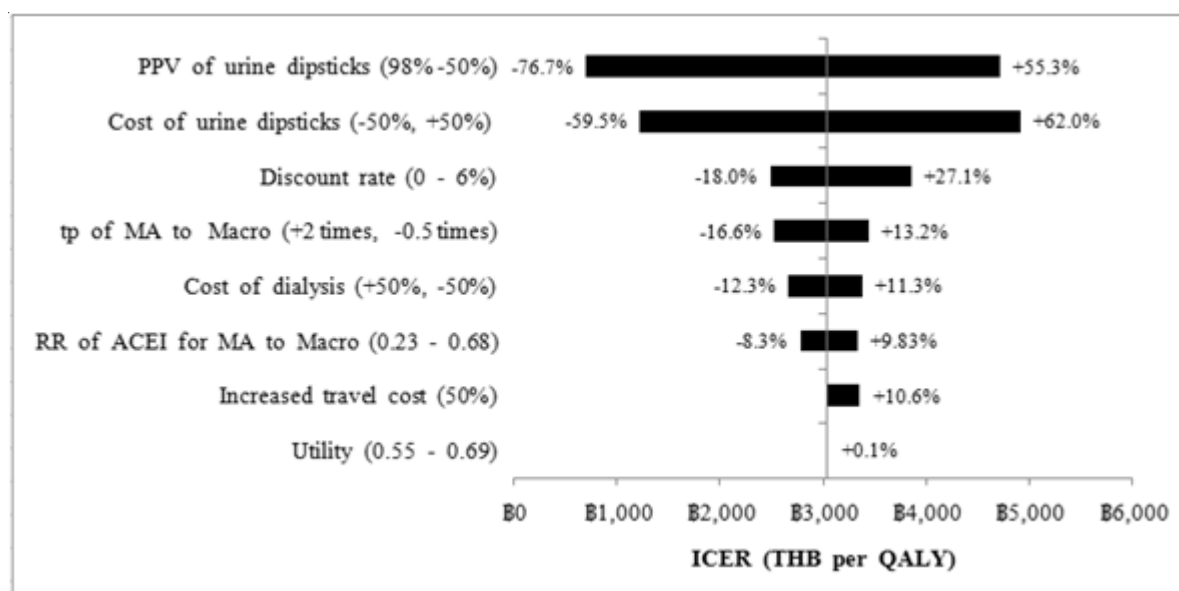

ACEI = angiotensin converting enzyme inhibitor, ICER = incremental cost-effectiveness ratio, MA = microalbuminuria, Macro = macroalbuminuria, QALY = quality adjusted life year, RR = relative risk, THB = Thai Baht, tp = transition probability

Figure 2. Tornado diagram of microalbuminuria screening using urine dipsticks

Discussions

Microalbuminuria screening by urine dipsticks in diabetic patients as an early intervention is highly cost-effective from a socioeconomic perspective, according to WHO's suggestion criterion of being less than GDP per capita [22]. A previous study assessing the threshold for health investment in Thailand reported that the willingness to pay per QALY was approximately at GDP per capita for treatment and 0.5 GDP per capita for disease prevention [27]. These ceilings were not a national guideline for economic evaluations; however, our study nevertheless confirms that the screening for microalbuminuria using urine dipsticks in normotensive type 2 diabetes was highly cost-effective, although the threshold value was changed to half of GDP per capita. Thus, these findings demonstrated the assumption that annual microalbuminuria screening in diabetic patients with normotension and on treatment with ACEI was able to improve patient QoL, as measured by the EQ-5D survey, at acceptable costs. Furthermore, patients in remote areas may save travel cost by this type of screening done at their communities instead of travelling long distances to general hospitals.
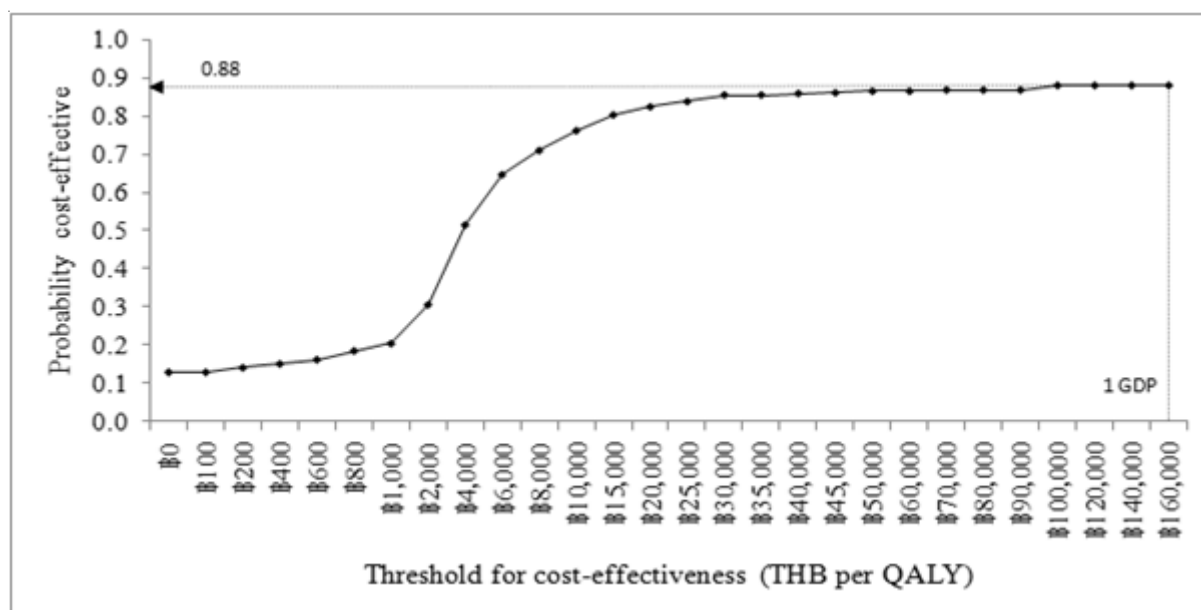
QALY = quality adjusted life year, THB = Thai Baht, GDP = Gross Domestic Product

Figure 3. Acceptability curve of microalbuminuria screening using urine dipsticks

Our study was consistent with previous studies of microalbuminuria screening. A study from Switzerland by Kessler et al., [28] reported that annual screening versus no screening was cost-effective because the QALY was lower than GDP per capita. Moreover, biannual screening of diabetics was more cost-effective. The study in type 1 diabetes showed the benefit of screening and treatment with ACEI if screening cost was affordable [29]. Nevertheless, our results differed from other studies. The cost-effectiveness was found only in high-risk groups with hypertension and proteinuria [30]. Palmer et al. reported that screening for microalbuminuria and overt nephropathy in diabetic patients with hypertension and use of renoprotective agents was cost-effective in the USA and France [31-32]. Proteinuria screening in subjects without diabetes or hypertension for early treatment with ACEI to delay progression of nephropathy was not cost-effective, except in high-risk groups such as the elderly, hypertensives, and diabetic patients [33-34]. Furthermore, a study by Kiberd et al. found that Pima Indians with type 2 diabetes routinely treated with ACEI lived longer and the treatment cost was lower when compared with microalbuminuria screening before receiving ACEI [35]. Whereas treating all type 2 diabetics with ACEI was more expensive with higher QALYs than screening for microalbuminuria [36].

According to the uncertainty of variables, the one-way and probabilistic sensitivity analyses in our study always demonstrated efficiency of microalbuminuria screening. Two sensitive input parameters in one-way sensitivity analysis showed positive predictive value and the cost of tests. Results different from those of Palmer et al. in that sensitivity analysis showed benefits of cost and outcomes of the screening in type 2 diabetes with hypertension; especially in patients at the age of 40 years [31-32]. On the other hand, Kiberd et al. [35] reported that annual costs of ESRD were moderately sensitive to the model, whereas screening and drug cost had little effect.

We used the positive predictive value of the test to identify the number of patients with microalbuminuria. Results showed that most were detected in the first year of screening (high prevalence). Therefore, compared with the "do nothing" scenario, the ICER of screenings and treatment was lowest in the first screening. When screening was done annually, a small number of patients were found and the positive predictive value decreased. Thus, we had to select the appropriate screening test to be consistent with the study of Kiberd et al. [30].

There were some limitations to this study. First, transition probabilities for changing among states of nephropathy were derived from literature reviews

because of a lack of data from the Thai population. Second, we focused on the effectiveness of ACEI and drug side effects were ignored in our model. Third, cost of dialysis from the Thai NHSO might be lower than that paid by the hospitals. Thus, the cost per QALY gained for microalbuminuria screening in our findings may be lower than reality. These limitations may lead to overestimate of the benefit of microalbuminuria screening compared with the "do nothing" scenario in diabetic patients. However, sensitivity analyses showed that this screening was always cost-effective.

Conclusions

Annual microalbuminuria screening using urine dipsticks in normotensive type 2 diabetic patients from a societal perspective proved to be cost-effective in Thailand. Thus, policy makers should support such screening as part of the universal coverage policy programs and approve this as part of the Thai healthcare program. Microalbuminuria screening should be an essential part of our preventive medicine efforts. It will be more cost-effective if the expense of the test can be reduced over time.

Acknowledgments

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