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Cost-utility analysis of empagliflozin on chronic kidney disease progression in Thailand

Piyameth Dilokthornsakul[a], Paweena Susantitaphong[b,c], Bancha Satirapoj[d], Wanchana Singhan[a], and Vuddhidej Ophascharoensuk[e]

[a]Center for Medical and Health Technology Assessment (CM-HTA), Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [b]Division of Nephrology, Department of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand; [c]Center of Excellence for Metabolic Bone Disease in CKD patients, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [d]Division of Nephrology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand; [e]Division of Nephrology, Department of Internal Medicine, Chiang Mai University Hospital, Chiang Mai, Thailand

ABSTRACT

Objective: The prevalence of chronic kidney disease (CKD) in Thailand is high and kidney disease progression remains a problem. Empagliflozin has been known to be used to slow CKD progression, but its accessibility remains limited. This study aimed to assess the cost-utility of empagliflozin for CKD progression in Thailand.

Methods: A state-transition model was developed consisting of eight health states: five eGFR health states (G2, G3a, G3b, G4, and G5), dialysis, kidney transplantation, and death. Empagliflozin 10 mg was assessed as an add-on treatment to standard of care (SoC). The efficacy of empagliflozin was derived from the EMPA-KIDNEY trial, while other inputs were obtained from a comprehensive literature review. The incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) was calculated. A probabilistic sensitivity analysis (PSA) was performed to explore uncertainties.

Results: Empagliflozin could improve QALYs by 0.62 and 0.71 for patients with CKD without and with diabetes mellitus (DM) compared with SoC, respectively. However, it required higher total lifetime costs of 77,966 Thai baht (THB) and 59,454 THB for patients with CKD without and with DM, respectively. The ICER for CKD without DM was 126,201 THB/QALY, while the ICER for CKD with DM was 83,473 THB/QALY. The PSA indicated that empagliflozin had a 64.00% probability of being cost-effective for CKD without DM and an 89.18% probability for CKD with DM.

Limitations: An important limitation was that the treatment effects of empagliflozin were derived from the EMPA-KIDNEY and assumed to be the same in patients with and without DM because of the limited evidence.

Conclusion: At the current willingness-to-pay threshold of 160,000 THB/QALY, empagliflozin was cost-effective for treating patients with CKD without or with DM.

PLAIN LANGUAGE SUMMARY

Chronic kidney disease (CKD) is a major health issue in Thailand, and finding effective treatments to slow its progression is important. Empagliflozin, a medication known to help with CKD, is not widely available. This study looked at whether using empagliflozin along with standard treatment is worth the cost in Thailand.

Researchers created a model to track how CKD progresses in patients. They used clinical trial data and other research to estimate the benefits and costs of adding empagliflozin to standard care.

The study found that empagliflozin helped patients live longer with a better quality-of-life, adding about 0.6–0.7 extra years of good health. However, it also increased lifetime medical costs by around 60,000 to 78,000 Thai baht. When comparing the extra cost to the health benefits, the analysis showed that empagliflozin is likely a cost-effective treatment, especially for people with diabetes.

Overall, regarding Thailand's standard for determining if a treatment is worth the cost, empagliflozin is considered a good investment for CKD patients, whether they have diabetes or not.

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CONTACT Piyameth Dilokthornsakul piyameth.dilok@cmu.ac.th Center for Medical and Health Technology Assessment (CM-HTA), 239 Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Mueang, Chiang Mai, Thailand 50200

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Introduction

Chronic kidney disease (CKD) is a significant global health problem. The estimated number of CKD cases was 697.3 million, with 19.0 million new cases in 2019, more than twice that in 1990. The number of deaths from CKD has risen from 0.6 million in 1990 to 1.4 million in 2019, making it the 11th leading cause of death[1]. Additionally, CKD can substantially decrease patients' quality-of-life. The estimated global disability-adjusted life-years (DALYs) doubled from 21.5 million in 1990 to 41.5 million in 2019. In Thailand, the prevalence of CKD varied from 8.9–26.8%[2–4]. The mortality rate among patients with CKD in Thailand is relatively high. According to the Thailand Renal Replacement Therapy, mortality is high among patients with advanced CKD on hemodialysis, with a 5-year survival rate at 41.2%[5].

Current standard treatments for CKD primarily focus on controlling blood pressure, managing diabetes and reducing proteinuria to slow disease progression[6]. Despite these interventions, many patients continue to experience a decline in renal function, highlighting the need for additional therapeutic options. Sodium-glucose co-transporter 2 inhibitors (SGLT-2i) are promising medications for managing CKD[7–9]. An expert consensus statement from the Asia-Pacific countries shows that SGLT-2i is effective in reducing the risks of cardiovascular and renal events among both patients without and with type 2 diabetes mellitus (DM). However, the use of SGLT-2i has been unexpectedly low in many countries, a trend that is much more noticeable in low-resource settings[10]. Empagliflozin is one of the SGLT-2i that has been studied to slow kidney disease progression among patients without and with DM. The efficacy and safety of empagliflozin among patients with CKD were evaluated in the EMPA-KIDNEY study[9]. This shows that empagliflozin could significantly prevent end-stage kidney disease (ESKD) or death from cardiovascular causes by 28% compared with placebo. In addition, there has been significant improvement in hospitalization for any causes and progression of kidney disease with a safety profile. A recent report from the EMPA-KIDNEY study also revealed that empagliflozin could also slow kidney disease progression in each stage of progression from the estimated glomerular filtration rate (eGFR) stage G2 to G4[11].

Given the promising clinical benefits of empagliflozin and the high burden of CKD in Thailand, where the incidence of CKD stage G5 or the need for chronic dialysis was 16.4 per 1,000 person-years[12], evaluating the cost-utility of empagliflozin among patients with CKD in the Thai healthcare context is necessary. Understanding the economic implications of adding empagliflozin to the SoC could provide valuable insights for healthcare providers and policymakers, facilitating informed decision-making and optimal resource allocation. Even though a recent cost-utility study showed that empagliflozin was cost-saving, the study adopted a model framework based on a global model from a healthcare payer perspective, which might not directly align with clinical practices in Thailand[13]. In addition, the study employed the patient-level micro-simulation technique using risk-equations based on data from US or European populations[14], which might not reflect data on patients with CKD in Thailand. Another Thai CUA study reported similar findings, indicating that empagliflozin was cost-effective at its current price of $44.9 per day. However, the study focused on CKD patients with DM, leaving a gap in evidence regarding the cost-effectiveness of empagliflozin in CKD patients without DM[15]. Therefore, a Thailand-specific cost-utility analysis encompassing both CKD patients with and without DM is necessary to bolster evidence supporting empagliflozin's role in slowing CKD progression. This study aims to evaluate the cost-utility of empagliflozin as an add-on treatment to the standard of care (SoC) for slowing CKD progression in Thailand. Given the significant impact of DM as a comorbidity, which influences both treatment efficacy and disease progression, we conducted separate cost-utility assessments based on DM status, examining empagliflozin's effects in patients with and without DM.

Methods

Overall study design

A cost-utility analysis with a lifetime horizon from a societal perspective was conducted. A state-transition Markov model was developed with a 1-year cycle length using Microsoft Excel® 365. Patients with CKD stages G2, G3a, G3b, G4, and G5, according to the KDIGO guidelines[6] with the average age of 45 years old were simulated. Patients with CKD were classified depending on diabetes status as patients with CKD without and with DM.

Interventions and comparator

Empagliflozin 10 mg once daily was assessed as an add-on medication to SoC. The SoC in this study was a stable, optimized dose of either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Patients receiving empagliflozin used ACEIs or ARBs similar to those receiving SoC.

Model structure and assumptions

A hypothetical cohort of 100,000 patients with CKD was simulated. The state-transition Markov model was developed based on eGFR and ESKD in a total of eight health states as follows: (1) eGFR >60 ml/min/1.73 m^2 (stage G2), (2) eGFR $45-59$ ml/min/1.73 m^2 (stage G3a), (3) eGFR $30-44$ ml/min/1.73 m^2 (stage G3b), (4) eGFR $15-29$ ml/min/1.73 m^2 (stage G4), (5) eGFR <15 ml/min/1.73 m^2 (stage G5), (6) kidney transplantation (KT), (7) dialysis, and (8) death (Figure 1).

Patients entered the model based on the proportion of patients in different eGFR stages based on the patients in a related Thai study, representing the distribution of patients with CKD in Thailand[16]. The patients would only progress to worse health states or death. CKD disease regression was not considered because only a few patients with CKD could regress to better health states. Patients aged 65 years or more were assumed to be ineligible for KT based on the minimal rate of KT in such a population in Thailand. Heart

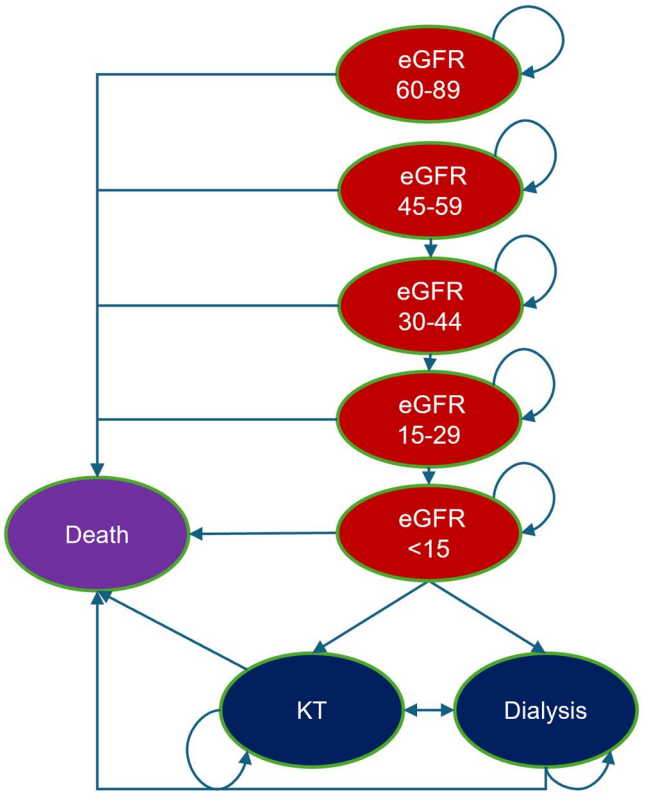

Figure 1. A Markov model mimicking the chronic kidney disease progression.

failure hospitalization (HHF) was incorporated in each eGFR health state according to a related study[17]. Adverse events of empagliflozin, including severe hypoglycemia, serious dehydration, serious urinary tract infection, serious hypokalemia and serious acute kidney injury, were considered in the model.

Model inputs

Treatment effects of empagliflozin on clinical outcomes

The EMPA-KIDNEY trial[9] was selected to derive the treatment effect of empagliflozin on kidney disease progression. No treatment effect of empagliflozin concerning the changes among eGFR stages was reported; however, the changes in eGFR in each stage were reported. Thus, we performed four steps of Monte Carlo simulations to estimate the relative effects of empagliflozin on eGFR stage progression compared with placebo. First, 1,000 random patients were generated with the mean and standard deviation for each eGFR stage from the EMPA-KIDNEY trial[9,11]. Second, the 1-year chronic slopes of eGFR changes were used to estimate the proportion of patients changing among eGFR stages for both empagliflozin and placebo. Third, the relative risks (RR) of the changes among eGFR stages were calculated. Fourth, another 1,000 iterations of the RRs were simulated to determine the average RRs and their corresponding 95% credible intervals. The treatment effects were assumed to be equal among patients with and without DM. RRs for ESKD including KT and dialysis, all-cause death and adverse events were directly retrieved from the EMPA-KIDNEY[9]. Details for the inputs are presented in Table 1.

Health state transition, mortality, and health utility

A comprehensive literature review was performed to determine inputs for the model. Studies conducted on Thai patients with suitable data were first selected to inform the model; however, when Thai studies were unavailable, studies from Asian or landmark trials were further considered, hierarchically.

According to our approach, the health state transitions among eGFR stages G2 – G5 were derived from a recent Thai epidemiologic study[9], while the health state transitions from eGFR stage 5 to KT or dialysis were derived from another Thai study[18]. Age-specific mortality of the general Thai population was used to add to the all-cause death rate among patients with CKD. The all-cause mortality rates among patients with CKD were derived according to eGFR and albuminuria categories[16]. Health utilities for eGFR health states were retrieved from a related cost-effectiveness analysis among patients with CKD stage G3 – G4 in Thailand[36], while health utilities of dialysis and KT were from different studies[19,37]. All clinical inputs are reported in Table 1.

Costs

The Thai health technology assessment guidelines explicitly recommend excluding the productivity loss (indirect cost) of patients for cost-utility analysis from a societal perspective to avoid double-counting[38]. Thus, this study derived only direct medical and direct nonmedical costs.

The price of empagliflozin 10 mg was approximately 40.45 THB (1.16 US Dollars; USD) per tablet based on the median reference price[25]. The costs of CKD treatment in each eGFR stage were determined from a CKDNET Thai study[26], while the cost of peritoneal dialysis, hemodialysis and KT were from a cost-effectiveness study[28]. All costs were adjusted to the year 2023 value using the Consumer Price Index[39] and converted from THB to USD using the average exchange rate in 2023 of 34.9649 THB per USD[40]. All clinical inputs are reported in Table 1.

Model validation

Three nephrologists and one nephrology pharmacist clinically validated this model and inputs during four expert meetings. A health economist verified the model codes.

Analysis

The quality-adjusted life-years (QALYs) and total lifetime costs were estimated. They were presented as QALY and total cost per patient. The discount rate of 3% was applied for both QALYs and costs. The incremental cost-effectiveness ratio (ICER) was calculated using the following equation:

$$\text{ICER} = \frac{\text{Total discounted cost of empagliflozin} - \text{Total discounted cost of SoC}}{\text{Discounted QALY of empagliflozin} - \text{Discounted QALY of SoC}}.$$

Two scenario analyses were conducted to explore the effect of different contexts on the findings. First, we varied the starting age of the cohort from 45 years to 50, 55, 60,

Table 1. Inputs.

Input	Value (range)	Distribution	References
Clinical input for patients with CKD without DM			
Transitional probability from G2 to G3a	0.0483 (± 20%)	Beta	16
Transitional probability from G3a to G3b	0.0611 (± 20%)	Beta	16
Transitional probability from G3b to G4	0.0490 (± 20%)	Beta	16
Transitional probability from G4 to G5	0.0473 (± 20%)	Beta	16
Transitional probability from G5 to Dialysis (age 45–49)	0.3070 (± 20%)	Beta	18
Transitional probability from G5 to Dialysis (age 50–54)	0.2770 (± 20%)	Beta	18
Transitional probability from G5 to Dialysis (age 55–59)	0.2290 (± 20%)	Beta	18
Transitional probability from G5 to Dialysis (age 60–64)	0.1830 (± 20%)	Beta	18
Transitional probability from G5 to Dialysis (age 65+)	0.1370 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 45–49)	0.0130 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 50–54)	0.0050 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 55–59)	0.0040 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 60–64)	0.0020 (± 20%)	Beta	18
Transitional probability from dialysis to kidney transplantation	0.1800 (0.0996 – 0.2604)	Beta	19
Kidney transplantation loss in the first year	0.0400 (0.0322 – 0.0478)	Beta	19
Kidney transplantation loss in the subsequent year	0.0100 (0.0080 – 0.0120)	Beta	19
Proportion of patients with G2 at baseline	0.0890 (0.0743 – 0.1037)	Dirichlet	16
Proportion of patients with G3a at baseline	0.3925 (0.3805 – 0.4045)	Dirichlet	16
Proportion of patients with G3b at baseline	0.2767 (0.2636 – 0.2898)	Dirichlet	16
Proportion of patients with G4 at baseline	0.1706 (0.1566 – 0.1846)	Dirichlet	16
Proportion of patients with G5 at baseline	0.0712 (0.0564 – 0.0861)	Dirichlet	16
All-cause death in patients with G2A1	0.0469 (± 20%)	Beta	16
All-cause death in patients with G2A2	0.0450 (± 20%)	Beta	16
All-cause death in patients with G2A3	0.0469 (± 20%)	Beta	16
All-cause death in patients with G3aA1	0.0478 (± 20%)	Beta	16
All-cause death in patients with G3aA2	0.0516 (± 20%)	Beta	16
All-cause death in patients with G3aA3	0.0582 (± 20%)	Beta	16
All-cause death in patients with G3bA1	0.0648 (± 20%)	Beta	16
All-cause death in patients with G3bA2	0.0657 (± 20%)	Beta	16
All-cause death in patients with G3bA3	0.0732 (± 20%)	Beta	16
All-cause death in patients with G4A1	0.0648 (± 20%)	Beta	16
All-cause death in patients with G4A2	0.0924 (± 20%)	Beta	16
All-cause death in patients with G4A3	0.1051 (± 20%)	Beta	16
All-cause death in patients with G5A1	0.1864 (± 20%)	Beta	16
All-cause death in patients with G5A2	0.1862 (± 20%)	Beta	16
All-cause death in patients with G5A3	0.2220 (± 20%)	Beta	16
Proportion of peritoneal dialysis compared to hemodialysis	0.2202 (0.2147 – 0.2257)	Beta	20
All-cause death in patients with hemodialysis	0.0650 (0.0630 – 0.0670)	Beta	5
All-cause death in patients with peritoneal dialysis	0.2115 (0.1692 – 0.2538)	Beta	21
All-cause death in patients with kidney transplantation	0.0280 (0.0143 – 0.0417)	Beta	22
Proportion of patients with UACR stage 1	0.7973 (0.7770 – 0.8175)	Dirichlet	23
Proportion of patients with UACR stage 2	0.1159 (0.0736 – 0.1581)	Dirichlet	23
Proportion of patients with UACR stage 3	0.0869 (0.0439 – 0.1299)	Dirichlet	23
Heart failure hospitalization rate among patients with G2	0.0310 (0.0250 – 0.0370)	Beta	17
Heart failure hospitalization rate among patients with G3a	0.0310 (0.0250 – 0.0370)	Beta	17
Heart failure hospitalization rate among patients with G3b	0.0740 (0.0620 – 0.0860)	Beta	17
Heart failure hospitalization rate among patients with G4	0.1030 (0.0840 – 0.1220)	Beta	17
Heart failure hospitalization rate among patients with G5	0.1030 (0.0840 – 0.1220)	Beta	17
Clinical input for among patients with CKD and DM			
Transitional probability from G2 to G3a	0.1074 (± 20%)	Beta	16
Transitional probability from G3a to G3b	0.1319 (± 20%)	Beta	16
Transitional probability from G3b to G4	0.1042 (± 20%)	Beta	16
Transitional probability from G4 to G5	0.0741 (± 20%)	Beta	16
Transitional probability from G5 to dialysis (age 45–49)	0.3070 (± 20%)	Beta	18
Transitional probability from G5 to dialysis (age 50–54)	0.2770 (± 20%)	Beta	18
Transitional probability from G5 to dialysis (age 55–59)	0.2290 (± 20%)	Beta	18
Transitional probability from G5 to dialysis (age 60–64)	0.1830 (± 20%)	Beta	18
Transitional probability from G5 to dialysis (age 65+)	0.1370 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 45–49)	0.0130 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 50–54)	0.0050 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 55–59)	0.0040 (± 20%)	Beta	18
Transitional probability from G5 to kidney transplantation (age 60–64)	0.0020 (± 20%)	Beta	18
Transitional probability from dialysis to kidney transplantation	0.1800 (0.0996 – 0.2604)	Beta	19
Kidney transplantation loss in the first year	0.0400 (0.0322 – 0.0478)	Beta	19
Kidney transplantation loss in the subsequent year	0.0100 (0.0080 – 0.0120)	Beta	19
Proportion of patients with G2 at baseline	0.0741 (0.0584 – 0.0898)	Dirichlet	16
Proportion of patients with G3a at baseline	0.4851 (0.04734 – 0.4968)	Dirichlet	16
Proportion of patients with G3b at baseline	0.2877 (0.2739 – 0.3015)	Dirichlet	16
Proportion of patients with G4 at baseline	0.1265 (0.1112 – 0.1417)	Dirichlet	16
Proportion of patients with G5 at baseline	0.0266 (0.0105 – 0.0427)	Dirichlet	16
All-cause death in patients with G2A1	0.0411 (± 20%)	Beta	16
All-cause death in patients with G2A2	0.0363 (± 20%)	Beta	16
All-cause death in patients with G2A3	0.0620 (± 20%)	Beta	16

(*continued*)

Table 1. Continued.

Input	Value (range)	Distribution	References
All-cause death in patients with G3aA1	0.0334 (± 20%)	Beta	16
All-cause death in patients with G3aA2	0.0469 (± 20%)	Beta	16
All-cause death in patients with G3aA3	0.0620 (± 20%)	Beta	16
All-cause death in patients with G3bA1	0.0469 (± 20%)	Beta	16
All-cause death in patients with G3bA2	0.0620 (± 20%)	Beta	16
All-cause death in patients with G3bA3	0.0888 (± 20%)	Beta	16
All-cause death in patients with G4A1	0.0806 (± 20%)	Beta	16
All-cause death in patients with G4A2	0.0943 (± 20%)	Beta	16
All-cause death in patients with G4A3	0.1393 (± 20%)	Beta	16
All-cause death in patients with G5A1	0.2570 (± 20%)	Beta	16
All-cause death in patients with G5A2	0.2599 (± 20%)	Beta	16
All-cause death in patients with G5A3	0.3617 (± 20%)	Beta	16
Proportion of peritoneal dialysis compared to hemodialysis	0.2202 (0.2147 – 0.2257)	Beta	20
All-cause death among patients with hemodialysis	0.0650 (0.0630 – 0.0670)	Beta	5
All-cause death among patients with peritoneal dialysis	0.2115 (0.1692 – 0.2538)	Beta	21
All-cause death among patients with kidney transplantation	0.0280 (0.0143 – 0.0417)	Beta	22
Proportion of patients with A1	0.5973 (0.5772 – 0.6173)	Dirichlet	23
Proportion of patients with A2	0.1995 (0.1713 – 0.2278)	Dirichlet	23
Proportion of patients with A3	0.2032 (0.1750 – 0.2314)	Dirichlet	23
Heart failure hospitalization rate among patients with G2	0.0310 (0.0250 – 0.0370)	Beta	17
Heart failure hospitalization rate among patients with G3a	0.0310 (0.0250 – 0.0370)	Beta	17
Heart failure hospitalization rate among patients with G3b	0.0740 (0.0620 – 0.0860)	Beta	17
Heart failure hospitalization rate among patients with G4	0.1030 (0.0840 – 0.1220)	Beta	17
Heart failure hospitalization rate among patients with G5	0.1030 (0.0840 – 0.1220)	Beta	17
Treatment effects of empagliflozin 10 mg			
Relative risk of G2 to G3a	0.6499 (0.5096 – 0.8040)	Lognormal	11
Relative risk of G3a to G3b	0.6521 (0.5000 – 0.8155)	Lognormal	11
Relative risk of G3b to G4	0.7106 (0.6059 – 0.8224)	Lognormal	11
Relative risk of G4 to G5	0.7275 (0.5490 – 0.9452)	Lognormal	11
Relative risk of G5 to ESRD	0.7029 (0.5496 – 0.8991)	Lognormal	9
Relative risk of heart failure hospitalization	0.78 (0.59 – 1.05)	Lognormal	9
Relative risk of all-cause mortality	0.87 (0.70 – 1.08)	Lognormal	9
Adverse events			
Baseline risk of severe hypoglycemia	0.0120 (0.0096 – 0.0115)	Gamma	9
Baseline risk of serious dehydration	0.0037 (0.0030 – 0.0035)	Gamma	9
Baseline risk of serious urinary tract infection	0.0084 (0.0067 – 0.0080)	Gamma	9
Baseline risk of serious hyperkalemia	0.0171 (0.0136 – 0.0164)	Gamma	9
Baseline risk of acute kidney injury for nonDM	0.0171 (0.0136 – 0.0164)	Gamma	9
Baseline risk of acute kidney injury for DM	0.0266 (0.0213 – 0.0256)	Gamma	9
Hazard ratio of severe hypoglycemia	1.00 (0.73 – 1.37)	Lognormal	9
Hazard ratio of serious dehydration	1.25 (0.73 – 2.14)	Lognormal	9
Hazard ratio of serious urinary tract infection	0.94 (0.64 – 1.37)	Lognormal	9
Hazard ratio of serious hyperkalemia	0.83 (0.63 – 1.09)	Lognormal	9
Relative risk of acute kidney injury for non-DM	0.63 (0.41 – 0.97)	Lognormal	24
Relative risk of acute kidney injury for DM	0.88 (0.64 – 1.20)	Lognormal	24
Costs			
Empagliflozin (THB/tablet)	40.45 (± 20%)	Fixed	25
Cost of CKD treatment for G2 (outpatient)	2,932 (2,346 – 3,519)	Gamma	26
Cost of CKD treatment for G3a (outpatient)	17,060 (13,648 – 20,473)	Gamma	26
Cost of CKD treatment for G3b (outpatient)	17,060 (13,648 – 20,473)	Gamma	26
Cost of CKD treatment for G4 (outpatient)	18,724 (14,980 – 22,469)	Gamma	26
Cost of CKD treatment for G5 (outpatient)	28,657 (22,926 – 34,388)	Gamma	26
Cost of CKD treatment for G2 (admission)	6,451 (5,161 – 7,742)	Gamma	26
Cost of CKD treatment for G3a (admission)	14,124 (11,299 – 16,949)	Gamma	26
Cost of CKD treatment for G3b (admission)	14,124 (11,299 – 16,949)	Gamma	26
Cost of CKD treatment for G4 (admission)	15,530 (12,424 – 18,636)	Gamma	26
Cost of CKD treatment for G5 (admission)	15,649 (12,519 – 17,778)	Gamma	26
Rate of admission for G2	0.1626 (0.0974 – 0.2278)	Beta	27
Rate of admission for G3a	0.1626 (0.0974 – 0.2278)	Beta	27
Rate of admission for G3b	0.1791 (0.0874 – 0.2709)	Beta	27
Rate of admission for G4	0.4091 (0.2036 – 0.6145)	Beta	27
Rate of admission for G5	0.4091 (0.2036 – 0.6145)	Beta	27
Cost of peritoneal dialysis (first year)	497,009 (397,607 – 596,410)	Gamma	28
Cost of peritoneal dialysis (following year)	440,788 (352,630 – 528,945)	Gamma	28
Cost of hemodialysis (first year)	488,358 (390,686 – 586,029)	Gamma	28
Cost of hemodialysis (following year)	462,457 (369,965 – 554,948)	Gamma	28
Cost of kidney transplantation (first year)	1,002,380 (801,904 – 1,202,856)	Gamma	28
Cost of kidney transplantation (following year)	463,644 (370,915 – 556,373)	Gamma	28
Cost of severe hypoglycemia (per event)	31,077 (18,872 – 43,282)	Gamma	29
Cost of serious dehydration (per event)	23,602 (21,442 – 25,763)	Gamma	30
Cost of serious urinary tract infection (per event)	55,811 (44,649 – 66,973)	Gamma	31
Cost of serious hyperkalemia (per event)	28,580 (27,635 – 29,525)	Gamma	32
Cost of serious acute kidney injury (per event)	120,161 (96,129 – 144,193)	Gamma	33
Food and travel cost for nondialysis state	1,086 (925 – 1,246)	Gamma	30

(*continued*)

Table 1. Continued.

Input	Value (range)	Distribution	References
Food and travel cost for dialysis state	8,734 (6,612 – 10,855)	Gamma	30
Cost of heart failure hospitalization (per event)	130,846 (107,036 – 160,554)	Gamma	34
Utility			
eGFR stage 2	0.85 (0.70 – 0.90)	Beta	35
eGFR stage 3a	0.72 (0.57 – 0.87)	Beta	36
eGFR stage 3b	0.72 (0.57 – 0.87)	Beta	36
eGFR stage 4	0.72 (0.57 – 0.87)	Beta	36
eGFR stage 5	0.70 (0.63 – 0.77)	Beta	36
Dialysis	0.55 (0.50 – 0.60)	Beta	37
Kidney transplantation	0.89 (0.63 – 1.00)	Beta	19

Abbreviations. A, albuminuria category; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; G, estimated glomerular filtration rate stage.

and 65 years old. Second, we varied the proportion of the starting cohort by different eGFR stages to a starting cohort of only eGFR stage 2, 3a or 3b to explore which eGFR stage empagliflozin should be initiated when healthcare resources are limited, and decision-making must be made for some subpopulation.

One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) with 10,000 iterations were simulated. The 95% confidence interval (CI) of each input was used to represent uncertainties around the inputs, while the 20% variation was applied when the 95% CI was unavailable. A cost-effectiveness acceptability curve (CEAC) was also generated, while the willingness-to-pay (WTP) of 160,000 THB/QALY (4,576 USD/QALY) was used as the cost-effectiveness threshold.

Results

Base-case analysis

We found that empagliflozin could improve patients' life-years (LYs) and QALYs by 0.84 LYs and 0.62 QALYs for patients without DM and 0.97 LYs and 0.71 QALYs for patients with DM. However, empagliflozin requires additional total lifetime costs of 77,966 THB (2,231 USD) and 59,454 THB (1,700 USD) for patients without DM and with DM, respectively. The ICERs for patients without DM and with DM were 126,201 THB/QALY (3,609 USD/QALY) and 83,473 THB/QALY (2,387 USD/QALY), respectively (Table 2).

Scenario analysis

Our scenario analysis showed the robustness of the base-case results. All scenario analyses indicated that empagliflozin could improve LYs and QALYs compared with SoC and required additional lifetime costs. All analyses showed that empagliflozin was cost-effective at the current WTP threshold, except when hypothesizing its use for patients without DM at eGFR stage G3a. However, the ICER of this analysis was 175,708 THB/QALY (5,025 USD/QALY), slightly higher than the current WTP threshold (Table 3).

Sensitivity analysis

One-way sensitivity analysis indicated that the top three most influential factors on ICERs for patients with CKD without DM were the relative risk of the treatment effect of empagliflozin from eGFR stage G5 to ESKD, the discount rate for outcomes and the price of empagliflozin. For patients with CKD and DM, the top three most influential factors on ICERs were the relative risk of empagliflozin on all-cause mortality, the relative risk of the treatment effect of empagliflozin from eGFR stage G4 to eGFR stage G5 and the relative risk of the treatment effect of empagliflozin from eGFR stage G5 to ESKD (Supplementary Figure S1).

Probabilistic sensitivity analyses revealed that most iterations fell in the upper right quadrant for both patients with CKD without DM and those with DM (Supplementary Figure S2). The percentage of iterations in the upper right quadrant for patients without DM was 82.64%, while patients with DM totaled 81.13%. This indicated the robustness of the base-case findings that empagliflozin could improve QALY but requires additional lifetime costs. The CEACs demonstrated that empagliflozin had a notable 64.00% probability of being cost-effective at the current WTP threshold for patients without DM. In comparison, it had a notable 89.18% probability of being cost-effective for patients with DM (Figure 2).

Discussion

This study evaluated the cost-utility of empagliflozin 10 mg as an add-on treatment to SoC among patients with CKD without and with DM. We found that empagliflozin, in addition to SoC, could improve LYs and QALYs compared with SoC alone. However, it required additional lifetime costs. Considering both clinical benefits and costs, empagliflozin at the current price is cost-effective for both patients with CKD without and with DM in Thailand.

Our findings are consistent with previous related studies[13,41–43], also showing better clinical benefits over the costs of empagliflozin in preventing CKD progression in general patients with CKD. Evidence from the UK, the Netherlands, and Malaysia indicated that empagliflozin could improve QALYs and save total healthcare costs compared with SoC, while evidence from Vietnam showed that empagliflozin could improve QALYs but required higher total healthcare costs.

Specific to the Thai context, the findings from Varghese et al.[13] and our findings are similar in terms of clinical benefits. Both studies indicated that empagliflozin could improve LYs and QALYs. However, the study by Varghese et al. showed that empagliflozin could save total cost. Conversely, our findings showed that empagliflozin required additional

Table 2. Base-case analysis results.

Stage	Empagliflozin			Standard of care			Incremental cost (THB)	Incremental LY	Incremental QALY	ICER/QALY gained (THB)
	Cost (THB)	LY	QALY	Cost (THB)	LY	QALY				
Patients with CKD without DM										
G2	17,089	0.66	0.56	7,190	0.54	0.46	9,900	0.12	0.10	–
G3a	116,782	2.82	2.03	66,227	2.30	1.66	50,556	0.52	0.37	–
G3b	118,136	2.57	1.85	82,359	2.38	1.71	35,777	0.19	0.14	–
G4	89,136	1.65	1.19	69,029	1.57	1.13	20,658	0.08	0.05	–
G5	16,439	0.26	0.18	12,046	0.22	0.16	4,393	0.03	0.02	–
Dialysis	110,188	0.22	0.12	129,456	0.27	0.15	−19,268	−0.05	−0.03	–
Kidney transplantation	185,931	0.35	0.31	209,950	0.39	0.35	−24,019	−0.05	−0.05	–
Total	654,255	8.52	6.24	576,259	7.68	5.62	77,966	0.84	0.62	126,201 (3,609 USD)
Patients with CKD and DM										
G2	11,290	0.42	0.35	4,247	0.31	0.26	7,043	0.11	0.09	–
G3a	113,275	2.66	1.92	57,166	1.96	1.41	56,109	0.70	0.50	–
G3b	137,696	2.92	2.10	90,783	2.60	1.87	46,913	0.33	0.23	–
G4	98,795	1.78	1.28	78,492	1.77	1.28	20,303	0.00	0.00	–
G5	15,968	0.24	0.17	13,747	0.25	0.18	2,222	−0.01	−0.01	–
Dialysis	84,334	0.17	0.09	114,447	0.24	0.13	−30,113	−0.07	−0.04	–
Kidney transplantation	123,192	0.23	0.20	166,215	0.31	0.27	−43,023	−0.08	−0.07	–
Total	584,550	8.42	6.12	525,096	7.44	5.41	59,454	0.97	0.71	83,473 (2,387 USD)

Abbreviations. G, estimated glomerular filtration rate stage; LY, life-year; QALY, quality-adjusted life-year; THB, Thai baht; USD, US dollar.
Note: Willingness-to-pay (WTP) of 160,000 THB/QALY (4,576 USD/QALY) was used as the cost-effectiveness threshold.

Table 3. Scenario analysis results.

Scenario	Empagliflozin			Standard of care			Incremental cost (THB)	Incremental LY	Incremental QALY	ICER/QALY gained (THB)
	Cost (THB)	LY	QALY	Cost (THB)	LY	QALY				
Patients with CKD without DM										
Starting age: 50 years	571,387	7.89	5.76	493,834	7.10	5.18	77,553	0.78	0.58	134,229
Starting age: 55 years	480,901	7.13	5.20	405,285	6.41	4.67	75,616	0.72	0.53	142,420
Starting age: 60 years	383,981	6.21	4.52	311,616	5.56	4.03	72,365	0.65	0.48	150,186
Starting age: 65 years	296,376	5.21	3.78	228,643	4.63	3.35	67,732	0.58	0.43	157,219
All start with G2	290,740	9.67	7.92	171,165	8.77	7.10	119,576	0.89	0.82	146,098
All start with G3a	410,803	9.25	6.66	292,230	8.31	5.98	118,573	0.94	0.67	175,708
All start with G3b	467,351	8.23	5.92	395,816	7.38	5.31	71,536	0.84	0.61	118,208
Patients with CKD and DM										
Starting age: 50 years	508,904	7.83	5.68	441,051	6.92	5.02	67,853	0.91	0.67	101,937
Starting age: 55 years	430,889	7.11	5.16	356,643	6.29	4.55	74,247	0.82	0.61	121,936
Starting age: 60 years	351,953	6.23	4.51	276,179	5.50	3.97	75,775	0.73	0.54	139,301
Starting age: 65 years	280,990	5.26	3.81	210,457	4.62	3.34	70,533	0.64	0.47	149,550
All start with G2	352,108	9.72	7.72	247,161	8.69	6.79	104,947	1.03	0.93	113,119
All start with G3a	475,565	9.24	6.64	385,279	8.13	5.85	90,286	1.11	0.80	112,913
All start with G3b	553,503	7.91	5.70	514,724	6.98	5.03	38,778	0.93	0.67	58,070

Abbreviations. G, estimated glomerular filtration rate stage; LY, life-year; QALY, quality-adjusted life-year; THB, Thai Baht.
Note: Willingness-to-pay (WTP) of 160,000 THB/QALY (4,576 USD/QALY) was used as the cost-effectiveness threshold.

totaled costs. The difference might be due to several reasons. First, our study was conducted from a societal perspective, while the previous study was conducted from a healthcare payer perspective. Our study estimated both direct medical and direct nonmedical costs, while the related study estimated only direct medical costs according to their perspectives. Second, different CKD complications and adverse events were incorporated into the model. Our study considered HHF and serious adverse events reported in the EMPA-KIDNEY[9]. In contrast, the related study incorporated myocardial infarction, unstable angina, chronic heart failure, stroke, anemia, acute kidney injury and lower-limb amputation. The differences in the perspectives and adverse events considered might affect the total treatment costs and the overall effects of empagliflozin on LYs and QALYs.

The recent CUA study conducted in Thailand demonstrated that empagliflozin 10 mg once daily was cost-effective for CKD patients with DM at the WTP threshold[15]. Our findings align with those of the previous study and further confirm that empagliflozin is cost-effective at its current market price for CKD patients with DM. However, our ICER of 2,387 USD/QALY was slightly lower than the 3,386 USD/QALY reported in the earlier study. This discrepancy likely stems from differences in the clinical benefits included in the respective models. The previous study did not account for the benefit of empagliflozin in reducing the risk of HHF, which represents a significant limitation. In contrast, our study incorporated HHF reduction as an additional clinical benefit, making our analysis more comprehensive in evaluating the overall benefits of empagliflozin for CKD patients with DM. Furthermore, our study uniquely assessed and demonstrated the cost-effectiveness of empagliflozin among CKD patients without DM, an area not explored in the earlier analysis. This expanded scope highlights the broader economic value of empagliflozin in slowing CKD progression across diverse patient populations.

Because no relative effect of empagliflozin on CKD progression of each eGFR health state is available, we used a

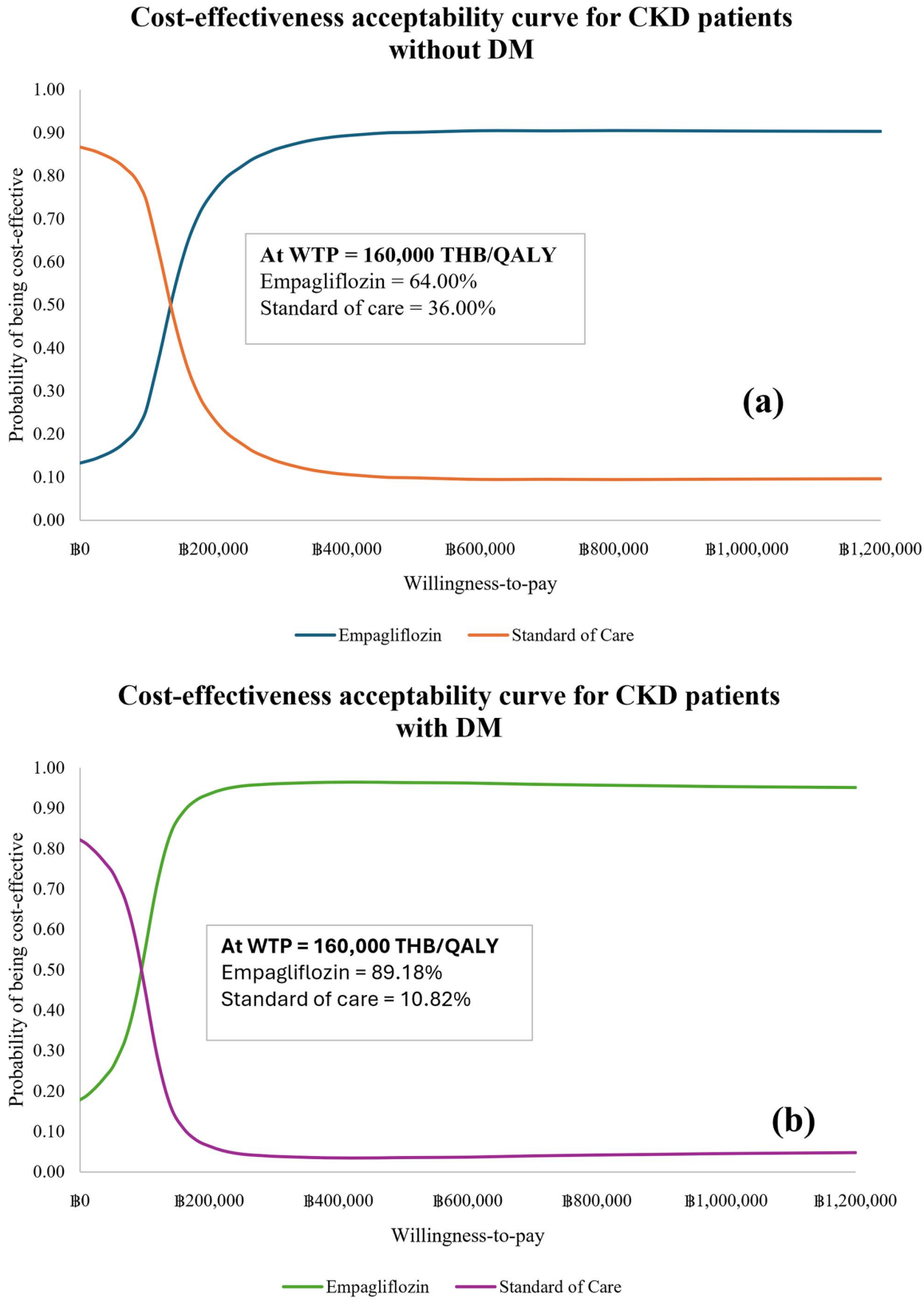

Figure 2. Cost-effectiveness acceptability curves (a) patients with CKD without DM, (b) patients with CKD and DM.

Monte Carlo simulation technique using the annual absolute changes in eGFR to estimate the relative effects. This technique was also used in related studies[44,45] when the relative effects were unavailable; however, this could raise the uncertainties of the findings. Thus, we performed one-way sensitivity analyses to explore uncertainties around the inputs. We found that a change in the relative effects of empagliflozin on each eGFR stage might not change the

cost-effectiveness conclusion among patients with CKD and DM. Still, it might affect the cost-effectiveness conclusion among patients with CKD without DM. Thus, further studies on the relative effects of empagliflozin on the CKD progression of each eGFR stage are warranted.

Our analysis showed that LYs and QALYs gained were mostly from the pre-renal replacement health states (Table 2), while they were lower in the renal replacement health states (dialysis or KT). This observation would imply that empagliflozin could slow CKD disease progression to renal replacement health states and provide better LYs and QALYs at the pre-renal replacement health states. In addition, we also observed that, because empagliflozin could slow CKD progression, the number of patients receiving add-on empagliflozin progressing to renal replacement health state was lower than that of those receiving only SoC, resulting in a lower total lifetime cost at the renal replacement health states.

Our scenario analyses by varying starting ages from 45- to 50-, 55-, 60-, and 65-year-olds showed that the ICERs were lower than the current WTP for both patients with CKD with and without DM, showing the robustness of our findings in terms of starting empagliflozin at difference ages. In addition, we observed that adding empagliflozin at earlier ages seems to have better clinical benefits over the increased cost. For instance, the QALY gained at the starting age of 65 was 0.43 for patients without DM, while the QALY gained at the starting age of 45 was 0.62, resulting in a difference of 0.19 QALY gained. However, the incremental lifetime cost for patients at the starting age of 65 was 67,732 THB (1,937 USD) and that for patients at the starting age of 45 was 77,966 THB (2,230 USD), resulting in a difference of 10,234 THB (293 USD) (Table 3). Thus, adding empagliflozin at an earlier age seems to add more clinical and economic benefits than later.

Another scenario analysis by varying the starting empagliflozin in different eGFR stages based on the current distribution of eGFR stages to starting empagliflozin at eGFR stage G2, G3a, and G3b showed similar results that ICERs were lower than the current WTP threshold. This also revealed the robustness of our findings that empagliflozin is cost-effective for CKD progression among both patients without and with DM. In addition, we also observed that starting empagliflozin at an earlier eGFR stage could provide better QALY with a small increase in total lifetime costs. For instance, starting empagliflozin at G2 for patients without DM gained 0.82 QALYs with an additional lifetime cost of 119,576 THB (3,420 USD) compared with SoC, while starting it at G3a gained only 0.67 QALY with an additional lifetime cost of 118,573 THB (3,391 USD). The difference in QALY gained was 0.15, and the difference in total lifetime cost was 1,003 THB (29 USD) (Table 3). Thus, adding empagliflozin at the lower eGFR stage seems to add more clinical and economic benefits than the higher eGFR stage.

Our study encountered several strengths. First, this study used local-specific data from both clinical and economic inputs that reflect real-world clinical practice in Thailand and increase the generalizability of our findings. Second, the study included HHF as a treatment outcome of empagliflozin. The HHF is an important clinical outcome for treating patients with CKD. Thus, our findings could better reflect the clinical benefits of empagliflozin in addition to the slow progression of CKD. Third, we separately evaluated the cost-utility of empagliflozin among patients with CKD without and with DM. Our study could provide better information for healthcare policymakers to decide which patients receiving empagliflozin should be covered if only some patients could be covered.

Several assumptions were made and are worthy of discussion. First, because of the limited evidence, we assumed the same treatment effects of empagliflozin on CKD progression of each eGFR stage for both patients with and without DM. According to the hazard ratios of CKD progression to ESKD from the EMPA-KIDNEY trial[9,23], relative treatment effect for patients with DM might be slightly higher than that of patients without DM. The findings might slightly differ if data on the treatment effects in such subpopulations are separately available. Second, we assumed that patients could not regress to a better eGFR stage. By considering real-world practice, there might be some patients using SGLT-2i that could regress to a better health state, but the number of patients could be minimal. This assumption might not affect the findings. Third, the CKD progression considered in this study was based only on eGFR, and albuminuria progression/regression was excluded. Including albuminuria status in the model could better reflect the overall real-world CKD progression. However, because of the limited local data on albuminuria progression/regression, we were unable to incorporate albuminuria progression/regression in the model. Fourth, our analyses were based only on the DM status of patients with CKD. Other clinical co-morbidities, such as hypertension, that might also affect CKD progression were not included in the model. Last, we used disease progression data from a local observation study[16], in which the cohort was less severe than those from the EMPA-KIDNEY trial[9]. This might have influenced the treatment effect of empagliflozin on CKD progression. However, because of the limited data on CKD progression in Thailand, we believe that data from the observational study was appropriate.

Conclusion

At Thailand's current willingness-to-pay threshold of 160,000 THB per QALY, empagliflozin was found to be cost-effective for treating patients with CKD, both without and with DM. For CKD patients without DM, the ICER was approximately 130,000 THB/QALY, while for those with DM, the ICER was approximately 80,000 THB/QALY – both well below the threshold – demonstrating its economic value in slowing CKD progression across these patient subgroups.

Transparency

Declaration of funding

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Boehringer Ingelheim was given the opportunity to review the model and manuscript for medical and scientific accuracy as well as intellectual property considerations.

Declaration of interests

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Authors' contribution

The author(s) meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

Study concept and design: PD, PS, BS, WS, VO

Data acquisition and verification: PD, PS, BS, WS, VO

Data analysis: PD

Manuscript drafting: PD

Manuscript review for important intellectual content: PD, PS, BS, WS, VO

Final approval of the manuscript: PD, PS, BS, WS, VO

Agree to be accountable for all aspects of the work: PD, PS, BS, WS, VO

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This study used Grammarly for English editor and grammar checking to improve the readability and language of the work.

Data availability statement

The datasets generated during or analyzed during the current study are available from the corresponding author (PD) upon reasonable request.

Code availability

Models used in the current study are available from the corresponding author upon reasonable request.

ORCID

Piyameth Dilokthornsakul http://orcid.org/0000-0002-6981-1771

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