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ORIGINAL RESEARCH

Cost–Utility of Liraglutide Plus Standard of Care Versus Standard of Care in People with Type 2 Diabetes and Cardiovascular Risk in Thailand

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ABSTRACT

Introduction: Liraglutide has demonstrated a significant reduction in the primary major composite cardiovascular (CV) outcome (CV death, non-fatal myocardial infarction, non-fatal stroke). This study aimed to determine the cost–utility of adding liraglutide to the standard of care (SoC) for treating type 2 diabetes (T2D) in Thailand for three cohorts: people with atherosclerotic cardiovascular disease (ASCVD), with no ASCVD, and all people with T2D.

Methods: A Markov model was developed to capture the long-term costs and outcomes under the perspective of the healthcare system. Costs were based on local data, the transitional probabilities were derived from the LEADER trial, and utilities were derived from published studies. Future costs and outcomes were discounted at 3% annually. A series of sensitivity analyses were performed.

Results: Compared to SoC, adding liraglutide incurred higher costs and gained more quality-adjusted life-years (QALYs), yielding incremental cost-effectiveness ratios (ICERs) of above 1 million Thai baht (THB) for the three cohorts. The most influential parameter was the discount rate. When the annual cost of liraglutide reduced from 87,874 to 30,340 THB, 30,116 THB, and 31,617 THB for all people with T2D, people with ASCVD, and people without ASCVD, respectively, the ICER fell below the local threshold of 160,000 THB/QALY. Compared to the SoC treatment, the liraglutide group acquired more clinical benefit in terms of fewer CVD. Sensitivity analyses revealed that with an increase in the level of willingness-to-pay (WTP) threshold, adding liraglutide had an increased chance of being a cost-effective strategy.

Conclusion: Compared to the SoC treatment, adding liraglutide at the current cost is not cost-

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effective at the local WTP. People with T2D with ASCVD would have the most potential gain from adding liraglutide treatment compared to other populations.

Keywords: ASCVD; Cost–utility; Liraglutide; Type 2 diabetes; Quality-adjusted life-years

Key Summary Points
Why carry out this study?
The prevalence of type 2 diabetes (T2D) is increasing, and the associated complications place a substantial cost burden on the healthcare system in Thailand.
Liraglutide has shown significant decrease in the risk of cardiovascular (CV) outcomes which may improve healthcare spending on long-term complications.
However, there is paucity of data on local economic evidence based on the cardiorenal protection benefits from the LEADER study.
What was learned from this study?
Adding-on liraglutide to standard of care (SoC) showed a higher incremental cost-effectiveness ratio (ICER) which was above the local willingness-to-pay (WTP) threshold versus SoC alone but shown to save 77 CV deaths which yielded an ICER above the acceptable ceiling in Thailand.
Liraglutide would be considered cost-effective at an annual treatment cost of around 30,000 THB/year in Thailand.
People with type 2 diabetes (T2D) with atherosclerotic cardiovascular disease (ASCVD) would have the most potential gain from adding liraglutide treatment compared to other populations characterized in this study.

INTRODUCTION

Type 2 diabetes mellitus (T2D) is a growing public health issue globally. In 2021, T2D affected approximately 536.6 million people worldwide, and is estimated to increase to 783.2 million by 2045 [1]. T2D, especially with poor glycemic control, is strongly associated with a risk of micro- and macrovascular complications and mortality [2]. These comorbidities place a substantial cost burden on the healthcare system. In Thailand, 6.1 million adults are affected by diabetes [1]. According to the 5th National Health Examination Survey, almost 8.9% and 10.8% of Thai men and women, respectively, were affected by T2D among which less than half (45.9% and 36.4%, respectively) received any T2D treatment [3]. Additionally, approximately 44% of Thai people with T2D reported a history of microvascular complications, and 6% reported a history of cardiovascular disease (CVD) [4]. About half of the direct medical cost was allocated to hospital care, whereas the cost of medicine accounted for only 14%. Moreover, the cost of treating people with diabetes increased exponentially when those people developed complications [4, 5]. Clinical guidelines recognize the importance of management of people with T2D beyond glycemic control by counting risks and complications [6]. Glucagon-like peptide 1 (GLP-1) receptor agonists and sodium–glucose co-transporter 2 (SGLT2) inhibitors are part of the treatment plans for people with T2D with increased cardiovascular (CV) risks [6]. The current guideline-based practice recommends SGLT2 inhibitors or GLP-1 receptor agonists for adults with T2D and CVD *or* renal disease. For those with established CVD *and* renal disease, the guideline recommends SGLT2 inhibitors and GLP-1 receptor agonists as an alternative [7]. Liraglutide, an analogue of human GLP-1, has been approved for the treatment of T2D [8]. Liraglutide has demonstrated good glucose-lowering effects and is also associated with reductions in body weight and blood pressure [8]. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) is a large CV outcome trial of

liraglutide compared to placebo as an add-on treatment to the standard treatment, including 9340 people with T2D and established CVD or multiple risk factors for CVD [9]. Over the follow-up period of 3.8 years, liraglutide demonstrated a significant reduction in the primary composite CV outcome by 13.0% (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78–0.97; $p = 0.01$ for superiority). Death from CV causes occurred in fewer people in the liraglutide group (HR 0.78; 95% CI 0.66–0.93; $p = 0.007$) versus placebo. The data also suggested beneficial effects on the composite outcome of renal or retinal microvascular events, with results being driven by lower rates of nephropathy with liraglutide compared to placebo (HR 0.78; 95% CI 0.67–0.92; $p = 0.003$) [10]. These clinical benefits of liraglutide could consequently improve healthcare spending on long-term treatment for cardiorenal complications, which generally are associated with high cost. However, there is no local economic evidence based on the cardiorenal protection benefits from the LEADER study. Hence, this analysis of the LEADER trial assessed the cost–utility of adding liraglutide to the standard treatment for treating people with T2D in a Thai context.

METHODS

Cohort Population

The cohort population in this study consisted of people with T2D. The study assessed the cost-effectiveness of liraglutide in three cohorts: (1) all people with T2D; (2) people with T2D with atherosclerotic cardiovascular disease (ASCVD); and (3) people with T2D but no documented ASCVD (no ASCVD).

Intervention and Comparator

The intervention group consisted of people with T2D who received 1.8 mg of liraglutide subcutaneously once-daily as an add-on to standard of care (SoC). The comparator group received SoC for T2D.

Model Structure

A Markov model, as shown in Fig. 1, was developed in Microsoft Excel and based on the CV and renal outcomes of the LEADER trial [9, 10]. The model comprised eight health status: T2D with CV risk, non-fatal myocardial infarction (MI), post-MI, non-fatal stroke, post-stroke, pre-renal replacement therapy (pre-RRT), RRT, and death. The assumption in this model was that MI, stroke, and nephropathy were mutually exclusive events. Deaths included fatal MI, fatal stroke, CV death, non-CV death, and renal death. To capture the long-term costs and outcomes, a lifetime horizon with a yearly cycle length was used for the analyses.

Each cohort was started at the T2D with CV risk health state. People then moved to non-fatal MI, non-fatal stroke, pre-RRT, or death according to the transitional probability of such a health state. People who experienced either non-fatal MI or non-fatal stroke could move to post-MI or post-stroke, respectively, or experience death from CV causes in the next cycle. People with either post-MI or post-stroke could remain in the same health state or get worse and attain death. Another pathway was nephropathy. The cohort could move from the starting health state to the pre-RRT health state or attain death from renal disease. People were then moved to the RRT health state or could remain in the pre-RRT health state or death state according to the transitional probabilities. People in the RRT health state could stay in the RRT health state or get worse and die. Finally, all people could enter the absorbing health state, which is the death state.

Input Parameters

Transitional Probability Inputs

Myocardial Infarction Risk of non-fatal MI was obtained from the LEADER trial [9, 11], which reported 6.02% vs. 6.79% in the liraglutide and SoC groups for all people, 6.88% vs. 7.95% for people with ASCVD, and 3.72% vs. 3.77% for people without ASCVD. The number of fatal MI was fewer than non-fatal MI in all

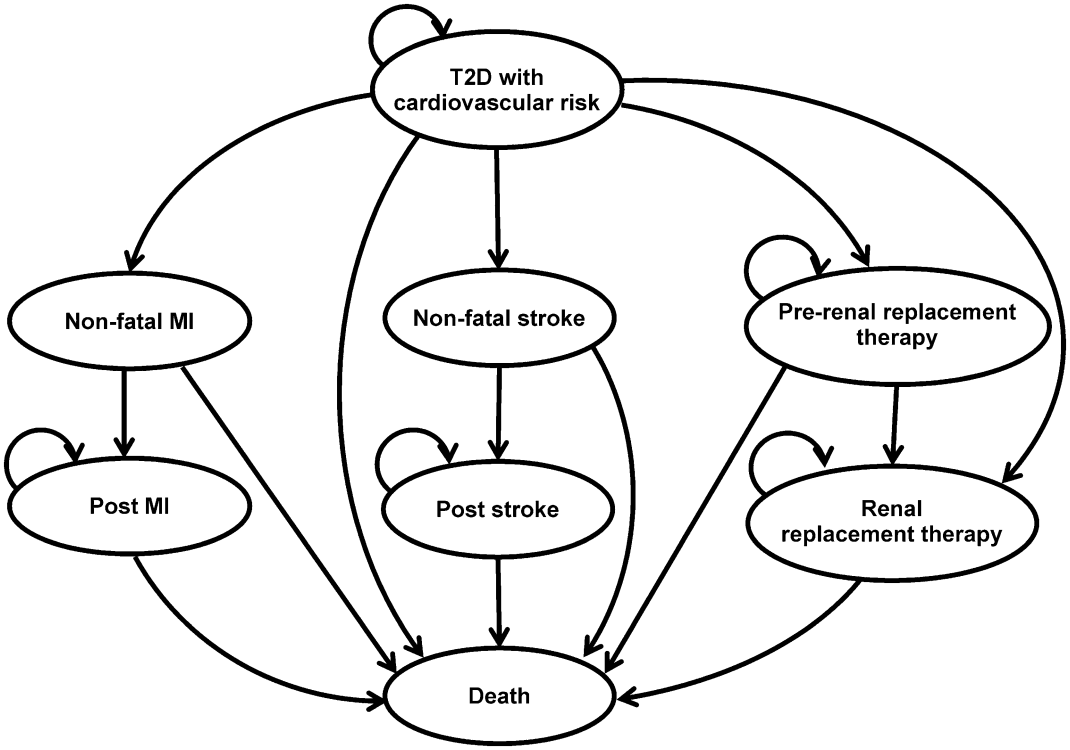

Fig. 1 Markov model of type 2 diabetes people with cardiovascular risk. *T2D* type 2 diabetes, *MI* myocardial infarction

three cohorts. People who received add-on liraglutide had fewer fatal MI than those who received SoC alone in all three cohorts. The reported percentages of fatal MI were 0.36% vs. 0.60% in the liraglutide and SoC groups for all people, 0.38% vs. 0.56% for people with ASCVD, and 0.32% vs. 0.69% for people without ASCVD [9, 11]. All these risks of non-fatal MI and fatal MI were converted into an annual rate, then converted back to an annual probability. The details are shown in Table 1.

Stroke The data on non-fatal stroke and fatal stroke were also obtained from the LEADER trial [9, 11]. The number of non-fatal strokes was higher compared to fatal strokes for all three cohorts. People who received liraglutide treatment had lower percentages of non-fatal stroke versus those who received SoC treatment (3.67% vs. 4.33% for people with ASCVD, 3.41% vs. 3.79% for all people). However, people from the no ASCVD cohort had higher percentages of non-fatal stroke in the liraglutide group than the SoC group (2.69% vs. 2.38%). There were fewer people with fatal stroke in the liraglutide group than in the SoC group for all three cohorts. Risks of fatal stroke in the liraglutide and SoC groups were 0.34% vs. 0.54%, 0.32% vs. 0.56%, and 0.40% vs. 0.46% for all people, people with ASCVD, and people without ASCVD, respectively. All these risks of non-fatal stroke and fatal stroke were converted to an annual rate, then converted back to an annual probability. The details are shown in Table 1.

Cardiovascular Death The mortality rate after the first non-fatal event of MI and stroke in the SoC group was 4.8 per 100 patient-year based on the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) study [12]. The mortality rate due to MI in the liraglutide group was obtained from the mortality rate of the SoC group adjusted by the HR of 0.60 (95% CI 0.33–1.10) for all people [9], 0.67 (95% CI 0.29–1.57) for people with ASCVD, and 0.45 (95% CI 0.14–1.47) for people

Table 1 Probability inputs

Author (year)	Inputs	Base value (range)		Distribution
		Liraglutide and SoC	SoC	
Risk of non-fatal MI				
Marso et al. [9]; Verma et al. [11]	All people with T2D[1]	0.0160 (0.0144–0.0176)	0.0181 (0.0163–0.0199)	Beta
	ASCVD[2]	0.0184 (0.0165–0.0202)	0.0213 (0.0192–0.0235)	
	No ASCVD[3]	0.0098 (0.0088–0.0108)	0.0100 (0.0090–0.0110)	
Risk of fatal MI				
Marso et al. [9]; Verma et al. [11]	All people with T2D[4]	0.0009 (0.0009–0.0010)	0.0016 (0.0014–0.0017)	Beta
	ASCVD[5]	0.0010 (0.0009–0.0011)	0.0015 (0.0013–0.0016)	
	No ASCVD[6]	0.0008 (0.0007–0.0009)	0.0018 (0.0016–0.0020)	
Risk of non-fatal stroke				
Marso et al. [9]; Verma et al. [11]	All people with T2D[7]	0.0090 (0.0081–0.0099)	0.0100 (0.0090–0.0110)	Beta
	ASCVD[8]	0.0097 (0.0087–0.0107)	0.0115 (0.0103–0.0126)	
	No ASCVD[9]	0.0071 (0.0064–0.0078)	0.0063 (0.0056–0.0069)	
Risk of fatal stroke				
Marso et al. [9]; Verma et al. [11]	All people with T2D[10]	0.0009 (0.0008–0.0010)	0.0014 (0.0013–0.0015)	Beta
	ASCVD[11]	0.0008 (0.0008–0.0009)	0.0015 (0.0013–0.0016)	
	No ASCVD[12]	0.0010 (0.0009–0.0011)	0.0012 (0.0011–0.0013)	
Risk of CV death from MI				
White et al. [12]; Marso et al. [9]; Verma et al. [11]	All people with T2D[13]	0.0284 (0.0256–0.0312)	0.0469 (0.0422–0.0516)	Beta
	ASCVD[14]	0.0316 (0.0285–0.0348)	0.0469 (0.0422–0.0516)	
	No ASCVD[15]	0.0214 (0.0192–0.0235)	0.0469 (0.0422–0.0516)	
Risk of CV death from stroke				
White et al. [12]; Marso et al. [9]; Verma et al. [11]	All people with T2D[16]	0.0303 (0.0272–0.0333)	0.0469 (0.0422–0.0516)	Beta
	ASCVD[17]	0.0251 (0.0226–0.0276)	0.0469 (0.0422–0.0516)	
	No ASCVD[18]	0.0404 (0.0364–0.0445)	0.0469 (0.0422–0.0516)	
Risk of nephropathy				
Marso et al. [9]; Verma et al. [11]	All people with T2D[19]	0.0153 (0.0138–0.0168)	0.0193 (0.0174–0.0212)	Beta
	ASCVD[20]	0.0125 (0.0113–0.0138)	0.0173 (0.0156–0.0190)	
	No ASCVD[21]	0.0228 (0.0205–0.0251)	0.0247 (0.0222–0.0272)	

Table 1 continued

Author (year)	Inputs	Base value (range)		Distribution
		Liraglutide and SoC	SoC	
Risk of RRT				
Mann et al. [10]	All people with T2D[22]	0.0031 (0.0028–0.0035)	0.0036 (0.0032–0.0039)	Beta
	ASCVD[23]	0.0021 (0.0019–0.0024)	0.0025 (0.0022–0.0027)	
	No ASCVD[24]	0.0058 (0.0052–0.0064)	0.0065 (0.0058–0.0071)	
Risk of renal death				
Mann et al. [10]	All people with T2D[25]	0.0004 (0.0004–0.0005)	0.0003 (0.0003–0.0003)	Beta
	ASCVD[26]	0.0003 (0.0003–0.0003)	0.0002 (0.0002–0.0003)	
	No ASCVD[27]	0.0008 (0.0007–0.0009)	0.0004 (0.0004–0.0004)	
Risk of pre-RRT				
Mann et al. [10]	All people with T2D[28]	0.0117 (00,106–0.0129)	0.0155 (0.0140–0.0171)	Beta
	ASCVD[29]	0.0101 (0.0091–0.0111)	0.0146 (0.0131–0.0160)	
	No ASCVD[30]	0.0162 (0.0146–0.0179)	0.0179 (0.0162–0.0197)	
Risk of death from RRT				
Adler et al. [13]; Mann et al. [10]	All people with T2D[31]	0.2631 (0.2368–0.2894)	0.1747 (0.1572–0.1922)	Beta
	ASCVD[32]	0.3123 (0.2811–0.3435)	0.1747 (0.1572–0.1922)	
	No ASCVD[33]	0.3267 (0.2940–0.3593)	0.1747 (0.1572–0.1922)	
Risk of death from pre-RRT				
Adler et al. [13]; Mann et al. [10]	All people with T2D[34]	0.0705 (0.0635–0.0776)	0.0450 (0.0405–0.0495)	Beta
	ASCVD[35]	0.0858 (0.0772–0.0944)	0.0450 (0.0405–0.0495)	
	No ASCVD[36]	0.0904 (0.0814–0.0994)	0.0450 (0.0405–0.0495)	
Risk of RRT from pre-RRT				
Adler et al. [13]; Mann et al. [10]	All people with T2D[37]	0.0198 (0.0178–0.0218)	0.0227 (0.0205–0.0250)	Beta
	ASCVD[38]	0.0194 (0.0174–0.0213)	0.0227 (0.0205–0.0250)	
	No ASCVD[39]	0.0205 (0.0184–0.0225)	0.0227 (0.0205–0.0250)	

Table 1 continued

ASCVD atherosclerotic cardiovascular disease, *CV* cardiovascular, *MI* myocardial infarction, *Pre-RRT* pre-renal replacement therapy, *RRT* renal replacement therapy, *SoC* standard of care

[1]Rate in liraglutide and SoC group = − (ln(1 − 281/4668))/3.84 = 0.0162; risk = 1 − exp(− 0.0162) = 0.0160; rate in SoC group = − (ln(1 − 317/4672)/3.84 = 0.0183; risk = 1 − exp(− 0.0183) = 0.0181

[2]Rate in liraglutide and SoC group = − (ln(1 − 234/3403))/3.84 = 0.0186; risk = 1 − exp(− 0.0186) = 0.0184; rate in SoC group = − (ln(1 − 268/3372)/3.84 = 0.0216; risk = 1 − exp(− 0.0183) = 0.0213

[3]Rate in liraglutide and SoC group = − (ln(1 − 47/1265))/3.84 = 0.0099; risk = 1 − exp(− 0.0099) = 0.0098; rate in SoC group = − (ln(1 − 49/1300)/3.84 = 0.0100; risk = 1 − exp(− 0.0100) = 0.0100

[4]Rate in liraglutide and SoC group = − (ln(1 − 17/4668))/3.84 = 0.0010; risk = 1 − exp(− 0.0010) = 0.0009; rate in SoC group = − (ln(1 − 28/4672)/3.84 = 0.0016; risk = 1 − exp(− 0.0016) = 0.0016

[5]Rate in liraglutide and SoC group = − (ln(1 − 13/3403))/3.84 = 0.0010; risk = 1 − exp(− 0.0010) = 0.0010; rate in SoC group = − (ln(1 − 19/3372)/3.84 = 0.0015; risk = 1 − exp(− 0.0015) = 0.0015

[6]Rate in liraglutide and SoC group = − (ln(1 − 4/1265))/3.84 = 0.0008; risk = 1 − exp(− 0.0008) = 0.0008; rate in SoC group = − (ln(1 − 9/1300)/3.84 = 0.0018; risk = 1 − exp(− 0.0018) = 0.0018

[7]Rate in liraglutide and SoC group = − (ln(1 − 159/4668))/3.84 = 0.0090; risk = 1 − exp(− 0.0090) = 0.0090; rate in SoC group = − (ln(1 − 177/4672)/3.84 = 0.0101; risk = 1 − exp(− 0.0101) = 0.0100

[8]Rate in liraglutide and SoC group = − (ln(1 − 125/3403))/3.84 = 0.0097; risk = 1 − exp(− 0.0097) = 0.0097; rate in SoC group = − (ln(1 − 146/3372)/3.84 = 0.0115; risk = 1 − exp(− 0.0115) = 0.0115

[9]Rate in liraglutide and SoC group = − (ln(1 − 34/1265))/3.84 = 0.0071; risk = 1 − exp(− 0.0071) = 0.0071; rate in SoC group = − (ln(1 − 31/1300)/3.84 = 0.0063; risk = 1 − exp(− 0.0063) = 0.0063

[10]Rate in liraglutide and SoC group = − (ln(1 − 16/4668))/3.84 = 0.0009; risk = 1 − exp(− 0.0009) = 0.0009; rate in SoC group = − (ln(1 − 25/4672)/3.84 = 0.0014; risk = 1 − exp(− 0.0014) = 0.0014

[11]Rate in liraglutide and SoC group = − (ln(1 − 11/3403))/3.84 = 0.0008; risk = 1 − exp(− 0.0008) = 0.0008; rate in SoC group = − (ln(1 − 19/3372)/3.84 = 0.0015; risk = 1 − exp(− 0.0015) = 0.0015

[12]Rate in liraglutide and SoC group = − (ln(1 − 5/1265))/3.84 = 0.0010; risk = 1 − exp(− 0.0010) = 0.0010; rate in SoC group = − (ln(1 − 6/1300)/3.84 = 0.0012; risk = 1 − exp(− 0.0012) = 0.0012

[13]Mortality rate in SoC group = 0.048; risk = 1 − exp(− 0.048) = 0.0469; mortality rate in liraglutide and SoC group = 0.6 × 0.048 = 0.0288; risk = 1 − exp(− 0.0288) = 0.0284

[14]Mortality rate in SoC group = 0.048; risk = 1 − exp(− 0.048) = 0.0469; mortality rate in liraglutide and SoC group = 0.67 × 0.048 = 0.0322; risk = 1 − exp(− 0.0322) = 0.0316

[15]Mortality rate in SoC group = 0.048; risk = 1 − exp(− 0.048) = 0.0469; mortality rate in liraglutide and SoC group = 0.45 × 0.048 = 0.0216; risk = 1 − exp(− 0.0216) = 0.0214

[16]Mortality rate in SoC group = 0.048; risk = 1 − exp(− 0.048) = 0.0469; mortality rate in liraglutide and SoC group = 0.64 × 0.048 = 0.0307; risk = 1 − exp(− 0.0307) = 0.0303

[17]Mortality rate in SoC group = 0.048; risk = 1 − exp(− 0.048) = 0.0469; mortality rate in liraglutide and SoC group = 0.53 × 0.048 = 0.0254; risk = 1 − exp(− 0.0254) = 0.0251

[18]Mortality rate in SoC group = 0.048; risk = 1 − exp(− 0.048) = 0.0469; mortality rate in liraglutide and SoC group = 0.86 × 0.048 = 0.0413; risk = 1 − exp(− 0.0413) = 0.0404

[19]Rate in liraglutide and SoC group = − (ln(1 − 268/4668))/3.84 = 0.0154; risk = 1 − exp(− 0.0154) = 0.0153; rate in SoC group = − (ln(1 − 337/4672)/3.84 = 0.0195; risk = 1 − exp(− 0.0195) = 0.0193

[20]Rate in liraglutide and SoC group = − (ln(1 − 161/3403))/3.84 = 0.0126; risk = 1 − exp(− 0.0126) = 0.0125; rate in SoC group = − (ln(1 − 218/3372)/3.84 = 0.0174; risk = 1 − exp(− 0.0174) = 0.0173

[21]Rate in liraglutide and SoC group = − (ln(1 − 107/1265))/3.84 = 0.0230; risk = 1 − exp(− 0.0230) = 0.0228; rate in SoC group = − (ln(1 − 119/1300)/3.84 = 0.0250; risk = 1 − exp(− 0.0250) = 0.0247

[22]Rate in liraglutide and SoC group = − (ln(1 − 56/4668))/3.84 = 0.0030; risk = 1 − exp(− 0.0030) = 0.0031; rate in SoC group = − (ln(1 − 64/4672)/3.84 = 0.0040; risk = 1 − exp(− 0.0040) = 0.0036

Table 1 continued

[23]Rate in liraglutide and SoC group = − (ln(1 − 28/3403))/3.84 = 0.0020; risk = 1 − exp(− 0.0020) = 0.0021; rate in SoC group = − (ln(1 − 32/3372)/3.84 = 0.0020; risk = 1 − exp(− 0.0020) = 0.0025
[24]Rate in liraglutide and SoC group = − (ln(1 − 28/1265))/3.84 = 0.0060; risk = 1 − exp(− 0.0060) = 0.0058; rate in SoC group = − (ln(1 − 32/1300)/3.84 = 0.0060; risk = 1 − exp(− 0.0060) = 0.0065
[25]Rate in liraglutide and SoC group = − (ln(1 − 8/4668))/3.84 = 0.0004; risk = 1 − exp(− 0.0004) = 0.0004; rate in SoC group = − (ln(1 − 5/4672)/3.84 = 0.0004; risk = 1 − exp(− 0.0004) = 0.0004
[26]Rate in liraglutide and SoC group = − (ln(1 − 4/3403))/3.84 = 0.0003; risk = 1 − exp(− 0.0003) = 0.0003; rate in SoC group = − (ln(1 − 3/3372)/3.84 = 0.0002; risk = 1 − exp(− 0.0002) = 0.0002
[27]Rate in liraglutide and SoC group = − (ln(1 − 4/1265))/3.84 = 0.0008; risk = 1 − exp(− 0.0008) = 0.0008; rate in SoC group = − (ln(1 − 2/1300)/3.84 = 0.0004; risk = 1 − exp(− 0.0004) = 0.0004
[28]Rate in liraglutide and SoC group = 0.0154 − 0.003 − 0.0004 = 0.0118; risk = 1 − exp(− 0.0118) = 0.0117; rate in SoC group = 0.0195 − 0.004 − 0.0003 = 0.0156; risk = 1 − exp(− 0.0156) = 0.0155
[29]Rate in liraglutide and SoC group = 0.0126 − 0.002 − 0.0003 = 0.0102; risk = 1 − exp(− 0.0102) = 0.0101; rate in SoC group = 0.0174 − 0.002 − 0.0002 = 0.0147; risk = 1 − exp(− 0.0147) = 0.0146
[30]Rate in liraglutide and SoC group = 0.0230 − 0.006 − 0.0008 = 0.0164; risk = 1 − exp(− 0.0164) = 0.0162; rate in SoC group = 0.0250 − 0.006 − 0.0004 = 0.0181; risk = 1 − exp(− 0.0181) = 0.0179
[31]Mortality rate in SoC group = 0.192; risk = 1 − exp(− 0.192) = 0.1747; mortality rate in liraglutide and SoC group = 1.59 × 0.192 = 0.3053; risk = 1 − exp(− 0.3053) = 0.2631
[32]Mortality rate in SoC group = 0.192; risk = 1 − exp(− 0.192) = 0.1747; mortality rate in liraglutide and SoC group = 1.95 × 0.192 = 0.3744; risk = 1 − exp(− 0.3744) = 0.3123
[33]Mortality rate in SoC group = 0.192; risk = 1 − exp(− 0.192) = 0.1747; mortality rate in liraglutide and SoC group = 2.06 × 0.192 = 0.3955; risk = 1 − exp(− 0.3955) = 0.3267
[34]Mortality rate in SoC group = 0.046; risk = 1 − exp(− 0.046) = 0.045; mortality rate in liraglutide and SoC group = 1.59 × 0.046 = 0.0731; risk = 1 − exp(− 0.0731) = 0.07051
[35]Mortality rate in SoC group = 0.046; risk = 1 − exp(− 0.046) = 0.045; mortality rate in liraglutide and SoC group = 1.95 × 0.046 = 0.0897; risk = 1 − exp(− 0.089) = 0.0858
[36]Mortality rate in SoC group = 0.046; risk = 1 − exp(− 0.046) = 0.045; mortality rate in liraglutide and SoC group = 2.06 × 0.046 = 0.0948; risk = 1 − exp(− 0.0948) = 0.0904
[37]Mortality rate in SoC group = 0.023; risk = 1 − exp(− 0.023) = 0.0227; mortality rate in liraglutide and SoC group = 0.87 × 0.023 = 0.0200; risk = 1 − exp(− 0.0200) = 0.0198
[38]Mortality rate in SoC group = 0.023; risk = 1 − exp(− 0.023) = 0.0227; mortality rate in liraglutide and SoC group = 0.85 × 0.023 = 0.0196; risk = 1 − exp(− 0.0196) = 0.0194
[39]Mortality rate in SoC group = 0.023; risk = 1 − exp(− 0.023) = 0.0227; mortality rate in liraglutide and SoC group = 0.90 × 0.023 = 0.0207; risk = 1 − exp(− 0.0207) = 0.0205

without ASCVD [11]. All rates were finally converted into risk. The details are shown in Table 1.

RRT and Pre-RRT The LEADER trial [10] reported one of the renal outcomes as the number of people needing RRT. People with ASCVD had a lower risk of RRT than those with no ASCVD for both the liraglutide and SoC groups. In addition, people who received liraglutide treatment had lower risk of RRT than those who received SoC in all three cohorts. The percentages of RRT in the liraglutide and SoC groups were 1.20% vs. 1.37%, 0.82% vs. 0.95%, and 2.21% vs. 2.46% for all people, people with ASCVD, and people without ASCVD, respectively. All these risks were converted to an annual rate, then to an annual probability. The details are shown in Table 1.

Since the renal outcomes reported from the LEADER trial [10] did not clearly show the rate of pre-RRT, we estimated this rate from the rate of all renal outcomes minus RRT and renal death. Then, the estimated rate of pre-RRT was converted into an annual probability. The details are shown in Table 1.

Renal Death The mortality rates from pre-RRT and RRT of the SoC group were obtained from the United Kingdom Prospective Diabetes Study (UKPDS-64) [13], then adjusted by the HR from the LEADER trial [10]. All rates were finally converted into risk. Renal death from the initial health state and T2D with CV risk were also considered. People who received liraglutide treatment had a numerically higher risk of renal death than those who received SoC treatment. although the difference was not statistically significant and based on very low occurrence. This risk was more evident in people without ASCVD than those with ASCVD. The risk of renal death in the liraglutide and SoC groups was 0.17% vs. 0.11%, 0.12% vs. 0.09%, and 0.32% vs. 0.15% for all people, people with ASCVD, and people without ASCVD, respectively [10].

Cost Inputs

This study was conducted from a healthcare system perspective; therefore, only direct medical costs were included. The direct medical costs included costs of liraglutide and other antihyperglycemic agents for people who did not meet the recommended target for glycemic control [14, 15], cost of adverse event treatment, costs of complication treatment, and costs of CV events (including CV death).

The acquisition costs of liraglutide and other antihyperglycemic agents were obtained from the Drug and Medical Supply Information Center (DMSIC), Thailand Ministry of Public Health [16]. Liraglutide 3 mL sterile solution of 6 mg/mL costs 2407 Thai baht (THB), resulting in an annual cost of 87,874 THB. For other antihyperglycemic agents where a product was supplied by several pharmaceutical companies, the median price from the median list of all pharmaceutical companies was used, in accordance with the Thai Health Technology Assessment (HTA) Guideline [17]. The total cost was the product of unit cost of individual antihyperglycemic agent mentioned above and the resource use obtained from the LEADER trial [9]. The difference in total cost of antihyperglycemic agents from both strategies was included for data analysis. Since people discontinued liraglutide treatment at a rate of 5.23% per year, we factored it into the total cost calculation. Treatment costs of adverse events and complications were based on a published study [18] or a large university-affiliated hospital database [19] (Certificate of Approval No. EXEMPTION-6811/2019). All costs were inflated to the year 2021, using the consumer price index for the medical-care category [20].

Utility Inputs

Utility is a health-related quality-of-life measure that varies from zero, representing death, to one, representing perfect health. The lifetime was weighted by utility values to estimate the quality-adjusted life-year (QALY) associated with health states after treatments. The baseline utility was based on people without diabetes-related complications, which was 0.753 [21]. Utility decrements associated with CV and renal complications were obtained from published studies and applied in the model. Table 2 shows the utility and disutility values used in the model.

Health Outcomes

The predicted long-term costs and outcomes of interest in this study were clinical outcomes, such as number of CV deaths and renal deaths, the incremental costs, life-years gained, QALY gained, and incremental cost-effectiveness ratio (ICER).

Data Analyses

Base-Case Analysis

Of all three cohorts, the expected lifetime total cost and outcomes of add-on liraglutide to existing regimen compared to SoC in each population were calculated and discounted at an annual rate of 3% [22]. The ICER was

Table 2 Cost and utility inputs

Author (year)	Inputs	Base value	Range	Distribution
Costs (per year)				
DMSIC [16]	Liraglutide	87,874	70,299–105,449	Gamma
DMSIC [16]	Other antidiabetic agents	345	276–414	Gamma
Hospital database	MI			Gamma
	First year	297,980	238,384–357,576	
	Subsequent year	25,043	20,034–30,051	
Hospital database	Stroke			Gamma
	First year	180,298	144,239–216,358	
	Subsequent year	211,625	169,300–253,950	
Deerochanawong et al. [24]	Hypoglycemia[1] (per event)	51,410	41,128–61,692	Gamma
IMRTA [25]	Gallstone[2] (per event)	19,101	15,280–22,921	Gamma
Hospital database	Death			Gamma
	CV causes	194,525	142,385–246,666	
	MI	1,133,472	906,778–1,360,167	
	Stroke	50,992	40,794–61,190	
Pattanaprateep et al. [26]	Pre-RRT	49,799	42,924–56,674	Gamma
Permsuwan et al. [27]	RRT			Gamma
Nephrology Society of Thailand [28]	First year	492,439	393,951–590,926	
	Subsequent year	438,242	350,593–525,890	
Utility				
Kranenburg et al. [21]	Diabetes	0.753	0.678–0.828	Beta
Srisubat et al. [29]	Pre-RRT	0.720	0.648–0.792	Beta
Utility decrement				
Kranenburg et al. [21], Selvin et al. [30]	Stroke			Gamma
	At time of event	0.052	0.047–0.057	
	Subsequent year	0.040	0.036–0.044	
Kranenburg et al. [21], Selvin et al. [30]	MI			Gamma
	At time of event	0.041	0.037–0.045	
	Subsequent year	0.012	0.011–0.013	

Table 2 continued

Author (year)	Inputs	Base value	Range	Distribution
Selvin et al. [30], Turnbull et al. [31]	RRT			Gamma
	At time of event	0.060	0.054–0.066	
	Subsequent year	0.263	0.237–0.289	

CV cardiovascular, *DMSIC* Drug and Medical Supply Information Center, *IMRTA* Institute of Medical Research and Technology Assessment, *MI* myocardial infarction, *Pre-RRT* pre-renal replacement therapy, *RRT* renal replacement therapy
[1]Cost of hypoglycemia treatment in liraglutide group = 51,410 × 0.006 = 330 THB; cost of hypoglycemia in SoC group = 51,410 × 0.009 = 444 THB
[2]Cost of gallstone treatment in liraglutide group = 19,101 × 0.008 = 156 THB; cost of gallstone treatment in SoC group = 19,101 × 0.005 = 97 THB

calculated using the differences in lifetime total cost divided by the difference in outcome for both strategies. When the estimated ICER fell below the accepted threshold in Thailand (160,000 THB/QALY), the add-on liraglutide strategy was considered cost-effective.

Sensitivity Analyses

One-way sensitivity analyses under which each parameter varied were conducted to assess the robustness of the cost-effectiveness analysis. The key input parameters varied among plausible ranges. When available, the standard deviation or 95% CI was used as a range for the one-way sensitivity analysis. When no such data were available, costs, probabilities, and utilities were varied within a range of ± 20%, ± 10%, and ± 10%, respectively. All plausible ranges are summarized in Tables 1 and 2. The discount rate varied from 0 to 6%, following the recommendation of the Thai HTA Guideline [22]. The results were displayed as a tornado diagram. Willingness-to-pay (WTP) threshold analysis was conducted to estimate the cost of liraglutide that yielded ICER equal to the accepted threshold in Thailand (160,000 THB/QALY).

In addition, a probabilistic sensitivity analysis was conducted, whereby individual sets of parameter values were drawn from an appropriate statistical distribution (Tables 1 and 2), with results generated for 1000 simulation runs. The results of the analysis were displayed as a scatterplot and a cost-effectiveness acceptability curve, which graphically represented the probability of add-on liraglutide being cost-effective, compared to SoC alone, for different defined WTP thresholds.

Compliance with Ethics Guidelines

This article is been approved ethics committees and was performed in accordance with the Helsinki Declaration of 1964.

RESULTS

Base-Case Result

All People with T2D

The lifetime total cost in the add-on liraglutide group was higher than in the SoC group (2,333,111 THB vs. 1,381,347 THB), resulting in an incremental cost of 951,764 THB. After disaggregation of the total costs, the major component cost of the total cost was the cost of liraglutide. However, liraglutide was shown to save 77 CV deaths per 1000 people with a gain of 0.91 years and 0.72 QALYs when compared with the SoC. This yielded an ICER of 1,051,626 THB/life-years or 1,326,197 THB/QALY, which is much above the acceptable ceiling ratio of 160,000 THB/QALY (Table 3).

Table 3 Base-case results

	All people with T2D			ASCVD population			No ASCVD population		
	Liraglutide and SoC	SoC	Difference[1]	Liraglutide and SoC	SoC	Difference[1]	Liraglutide and SoC	SoC	Difference[1]
Lifetime total costs	2,333,111	1,381,347	951,764	2,394,153	1,422,284	971,868	2,074,152	1,270,556	803,596
Drug cost	1,278,291	6041	1,272,250	1,285,089	6034	1,279,055	1,215,744	6056	1,209,688
Adverse events	7464	7805	− 341	7504	7796	− 292	7097	7824	− 726
MI or stroke	363,080	324,867	38,213	410,698	366,877	43,821	252,113	207,312	44,801
CV death	553,371	832,615	− 279,244	602,057	867,357	− 265,300	425,762	738,192	− 312,430
Pre-RRT	48,901	69,746	− 20,845	38,150	64,140	− 25,989	59,614	85,561	− 25,947
RRT	82,003	140,272	− 58,269	50,655	110,080	− 59,426	113,820	225,611	− 111,791
Lifetime outcomes									
CV death (per 1000)	214	291	− 77	237	323	− 86	153	200	− 47
Renal death (per 1000)	200	202	− 2	169	174	− 5	319	285	34
Life-year	15.35	14.44	0.91	15.43	14.43	1.00	14.60	14.48	0.12
QALY	11.41	10.69	0.72	11.48	10.69	0.80	10.85	10.69	0.16
ICER[2] (THB/QALY)	1,051,626			968,404			6,769,724		
ICER[3] (THB/QALY)	1,326,197			1,222,381			5,086,153		

ASCVD atherosclerotic cardiovascular disease, *CV* cardiovascular death, *ICER* incremental cost-effectiveness ratio, *MI* myocardial infarction, *QALY* quality-adjusted life-year, *RRT* renal replacement therapy, *SoC* standard of care, *THB* Thai baht

[1]Difference = liraglutide and SoC − SoC

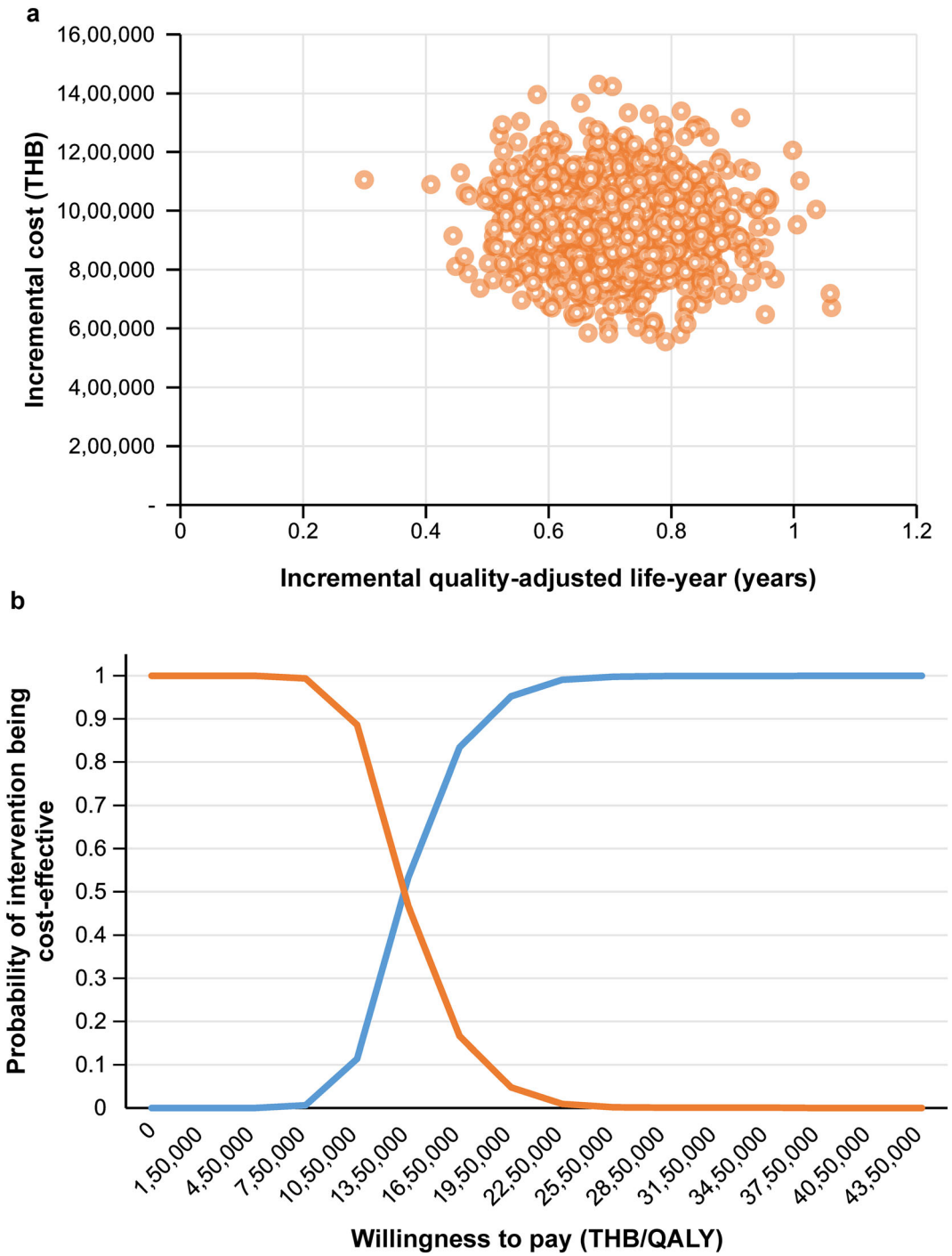

Fig. 2 Probabilistic sensitivity analysis of add-on liraglutide compared to standard of care alone in all people with type 2 diabetes and high cardiovascular risk. *QALY* quality-adjusted life-year, *THB* Thai baht

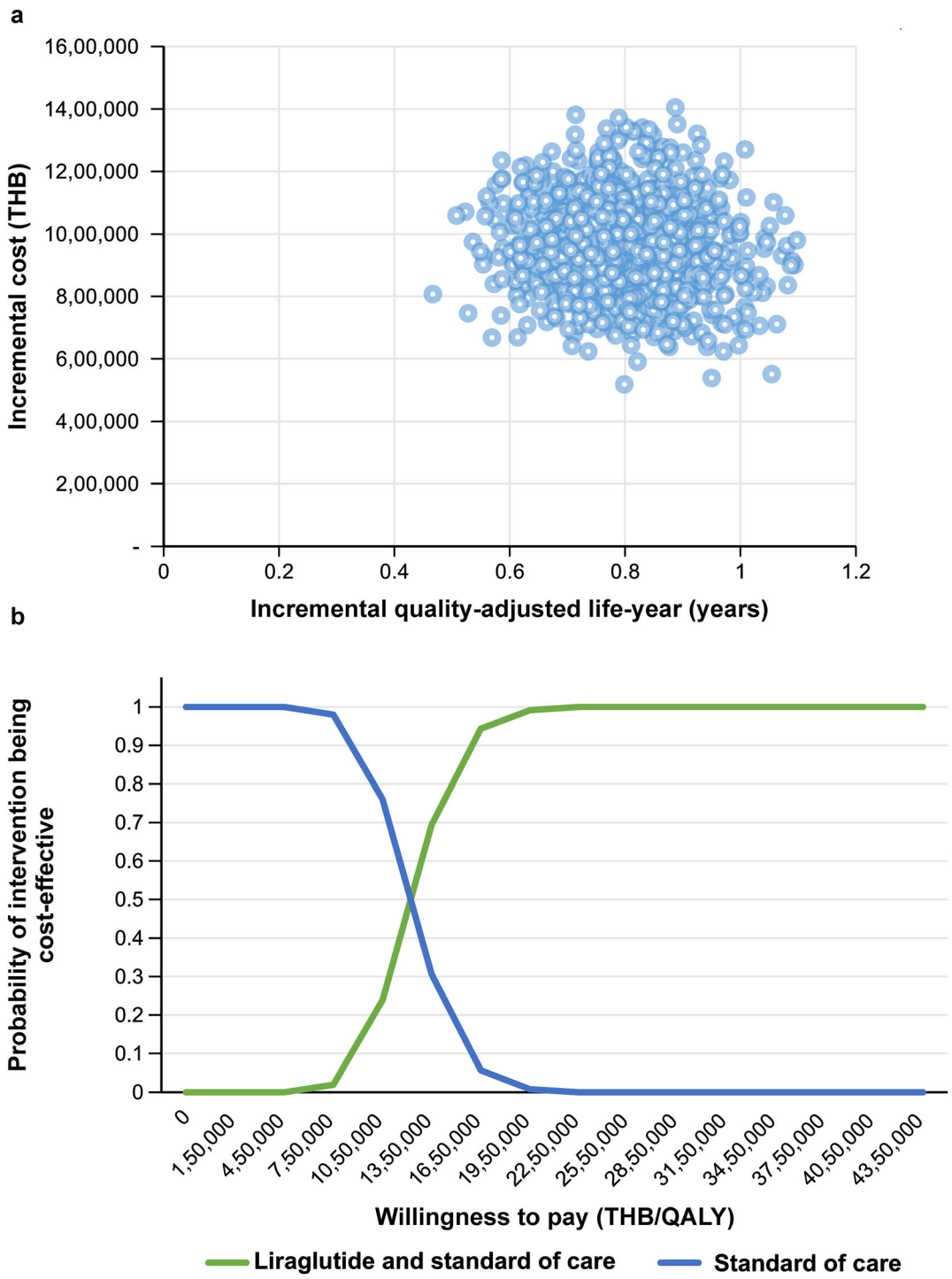

Fig. 3 Probabilistic sensitivity analysis of add-on liraglutide compared to standard of care alone in people with atherosclerotic cardiovascular disease. *QALY* quality-adjusted life-year, *THB* Thai baht

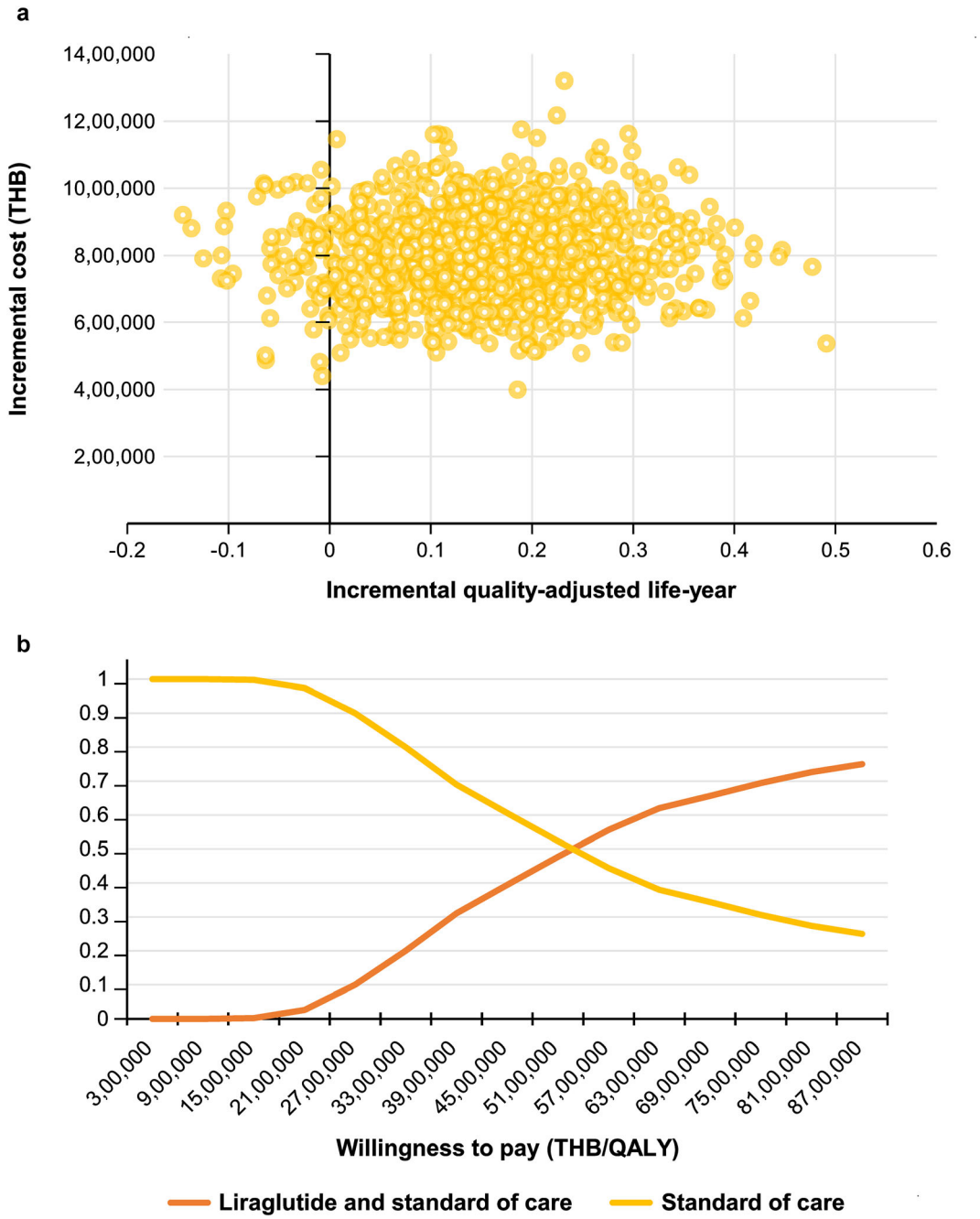

Fig. 4 Probabilistic sensitivity analysis of add-on liraglutide compared to standard of care alone in people without atherosclerotic cardiovascular disease. *QALY* quality-adjusted life-year, *THB* Thai baht

ASCVD Population

The lifetime total cost in the add-on liraglutide group was higher than in the SoC group (2,394,153 THB vs. 1,422,284 THB), resulting in an incremental cost of 971,868 THB. The cost of liraglutide made the greatest contribution to the lifetime total cost. However, liraglutide was shown to save 86 CV deaths per 1000 people and 5 renal deaths per 1000 people with a gain

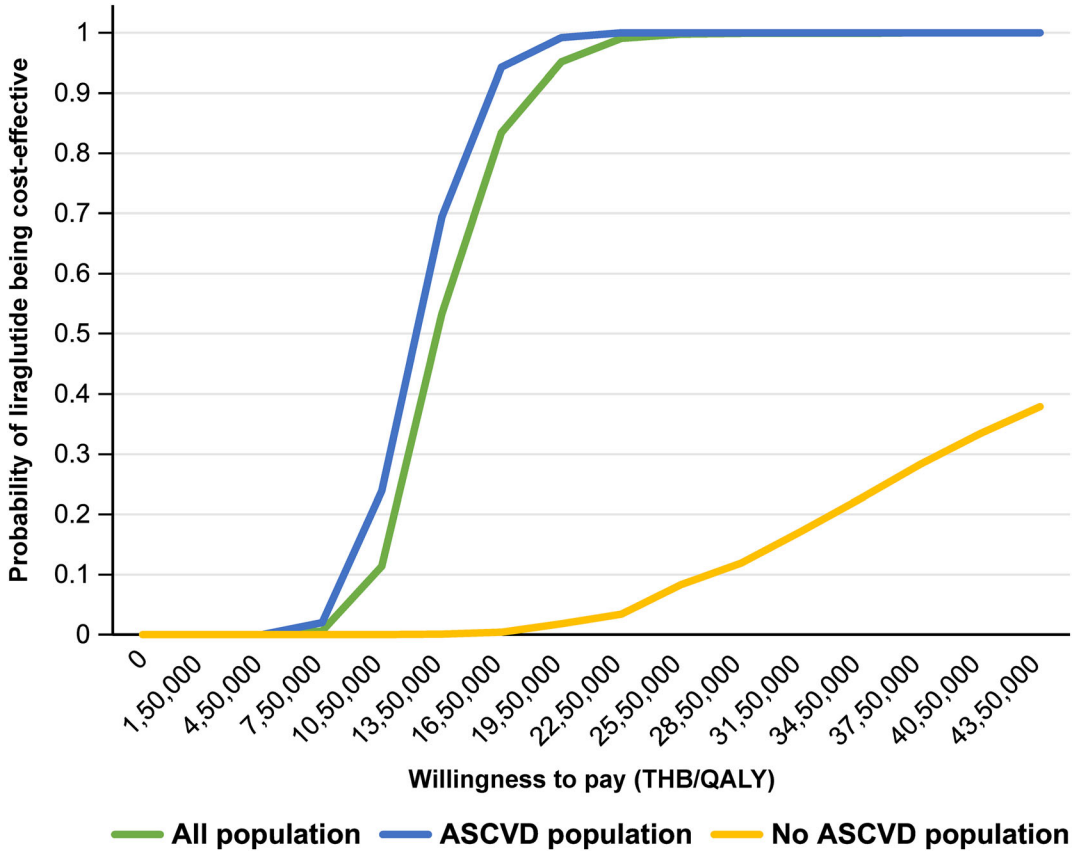

Fig. 5 Cost-effectiveness acceptability curves of three cohort populations. *ASCVD* atherosclerotic cardiovascular disease, *QALY* quality-adjusted life-year, *THB* Thai baht

of 1.00 years and 0.80 QALYs when compared with the SoC. This yielded an ICER of 968,404 THB/life-years or 1,222,381 THB/QALY, which is much above the acceptable ceiling ratio of 160,000 THB/QALY (Table 3).

No ASCVD Population

The lifetime total cost in the add-on liraglutide group was higher than in the SoC group (2,074,152 THB vs. 1,270,556 THB), resulting in an incremental cost of 803,596 THB. The cost of liraglutide accounted for the greatest component of the lifetime total cost. Compared to the SoC, people treated with liraglutide had a lower number of CV deaths per 1000 people (153 vs. 200) and a higher number of renal deaths per 1000 people (319 vs. 285). However, the add-on liraglutide group gained 0.12 more life-years or 0.16 QALYs than the SoC group. This yielded an ICER of 6,769,724 THB/life-years or 5,086,153 THB/QALY, which is much above the acceptable ceiling ratio of 160,000 THB/QALY (Table 3).

Sensitivity Analysis

The scatterplot on the cost-effectiveness plane showed that compared to the SoC treatment, add-on liraglutide treatment incurred higher costs for all three populations, with more QALY gain in two populations (all people with T2D and people with ASCVD). However, approximately 31% of a thousand iterations in people without ASCVD had fewer QALY in the add-on liraglutide group compared to the SoC group (Figs. 2, 3, and 4). At the WTP of 160,000 THB/

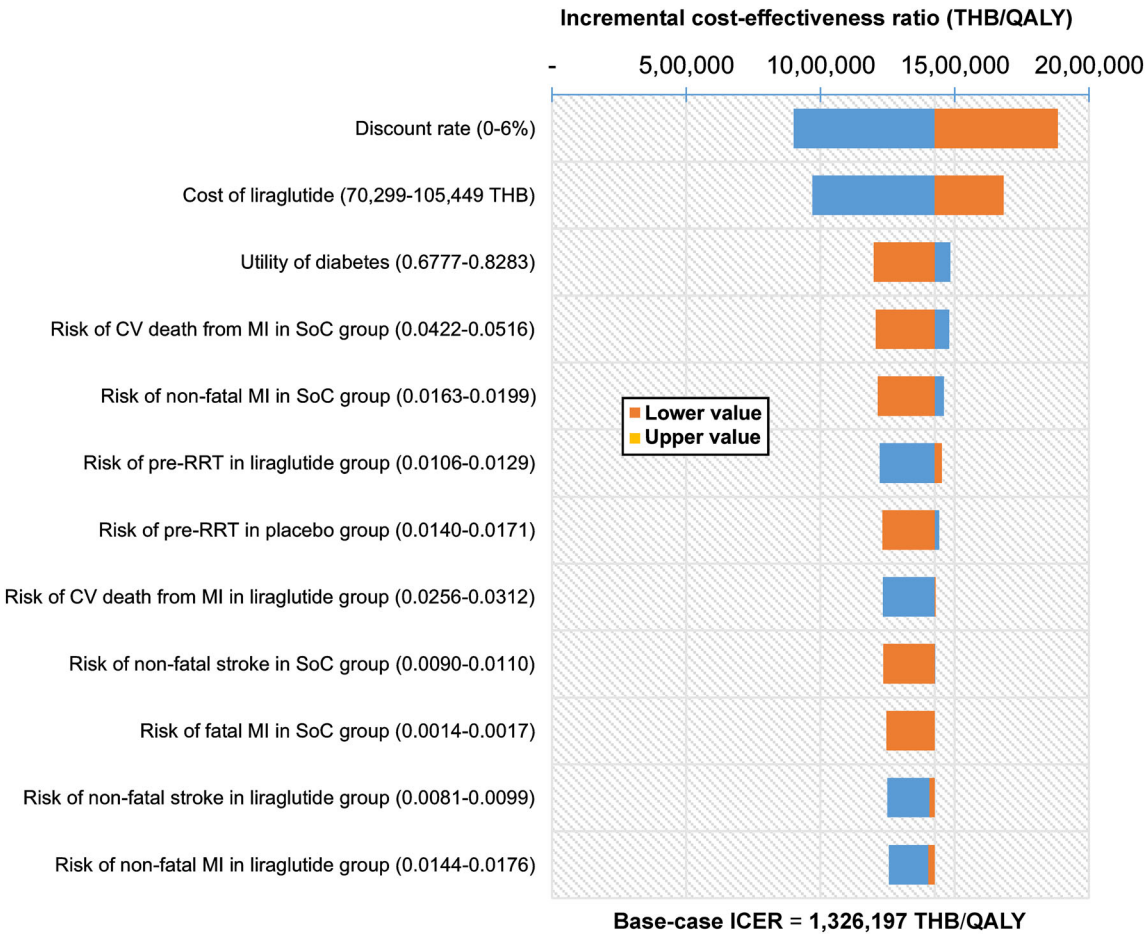

Fig. 6 Tornado diagram of add-on liraglutide compared to standard of care alone in all people with type 2 diabetes. *CV* cardiovascular, *ICER* incremental cost-effectiveness ratio, *MI* myocardial infarction, *QALY* quality-adjusted life-year, *RRT* renal replacement therapy, *SoC* standard of care, *THB* Thai baht

QALY, it was unlikely that an add-on liraglutide treatment was a cost-effective strategy in the three cohort populations. The probability of add-on liraglutide being a cost-effective alternative was shown to increase with higher levels of WTP threshold (Figs. 2, 3, and 4). Of the three cohorts, an add-on liraglutide treatment in people with ASCVD yielded the highest percentage of being cost-effective at the same level of WTP (Fig. 5).

The results of one-way sensitivity analysis in all people with T2D and people with ASCVD showed that discount rate and cost of liraglutide were the top two parameters that had an impact on the estimated ICER (Figs. 6 and 7). For people without ASCVD, risk of pre-RRT was the most influential parameter, followed by the discount rate and risk of RRT (Fig. 8). When the annual cost of liraglutide reduced by 10%, the estimated ICERs declined accordingly, especially in people without ASCVD (Fig. 9). To yield the ICER of 160,000 THB/QALY, an annual cost of liraglutide should be equal to 65.5% (30,340 THB), 65.7% (30,116 THB), and 64.0% (31,617 THB) for all people with T2D, people with ASCVD, and people without ASCVD, respectively.

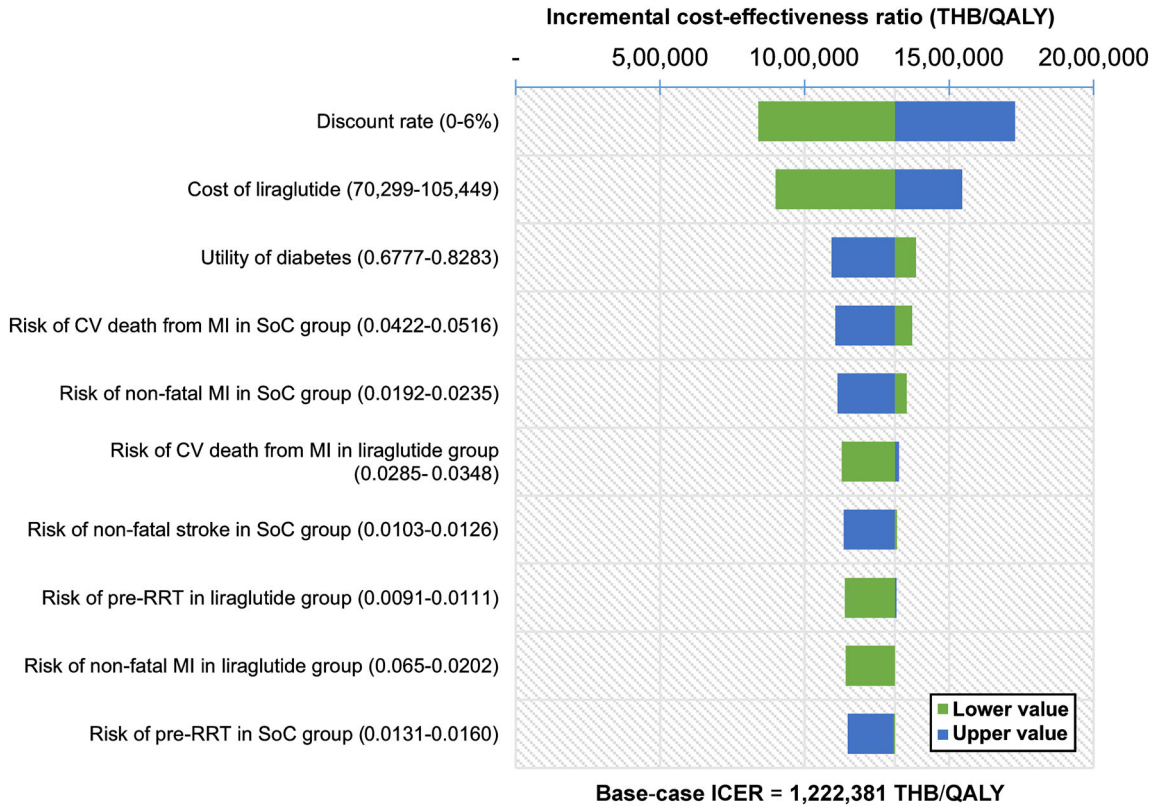

Fig. 7 Tornado diagram of add-on liraglutide compared to standard of care alone in people with atherosclerotic cardiovascular disease. *CV* cardiovascular, *ICER* incremental cost-effectiveness ratio, *MI* myocardial infarction, *QALY* quality-adjusted life-year, *RRT* renal replacement therapy, *SoC* standard of care, *THB* Thai baht

DISCUSSION

The clinical evidence from the landmark LEADER trial [9, 10] showed that, when added to the SoC, liraglutide resulted in lower rate of the first occurrence of death from CV causes, non-fatal MI, and non-fatal stroke among people with T2D with ASCVD risk, and the development and progression of diabetic kidney disease. This evident clinical benefit was taken into consideration with overall costs of treatment for people with T2D in three cohorts (all people with T2D, people with ASCVD, and people without ASCVD). The findings of this study indicated that add-on liraglutide use had an ICER above the local WTP threshold of 160,000 THB/QALY compared to the SoC treatment alone for all three cohorts. Therefore, adding liraglutide may not be a cost-effective strategy with the current setting on total cost and WTP threshold. Among the three cohorts, adding liraglutide showed the most value for money in ASCVD populations. The findings indicated the lower rate of CV deaths, resulting in cost saving, in the add-on liraglutide treatment compared to the SoC treatment for all three cohorts. In addition, the lower rate of progression of diabetic kidney disease could be observed from the lower costs of pre-RRT and RRT treatment in the add-on liraglutide group compared to the SoC group (Table 3) for all three cohorts. However, the cost saving accrued from the lower rate of CV death and progression of diabetic kidney disease could not offset the acquisition cost of liraglutide, resulting in an abundant incremental cost and ICER. The annual cost of liraglutide should be reduced by 65.5%, 65.7%, and 64.0% for all people with T2D, people with ASCVD, and people without

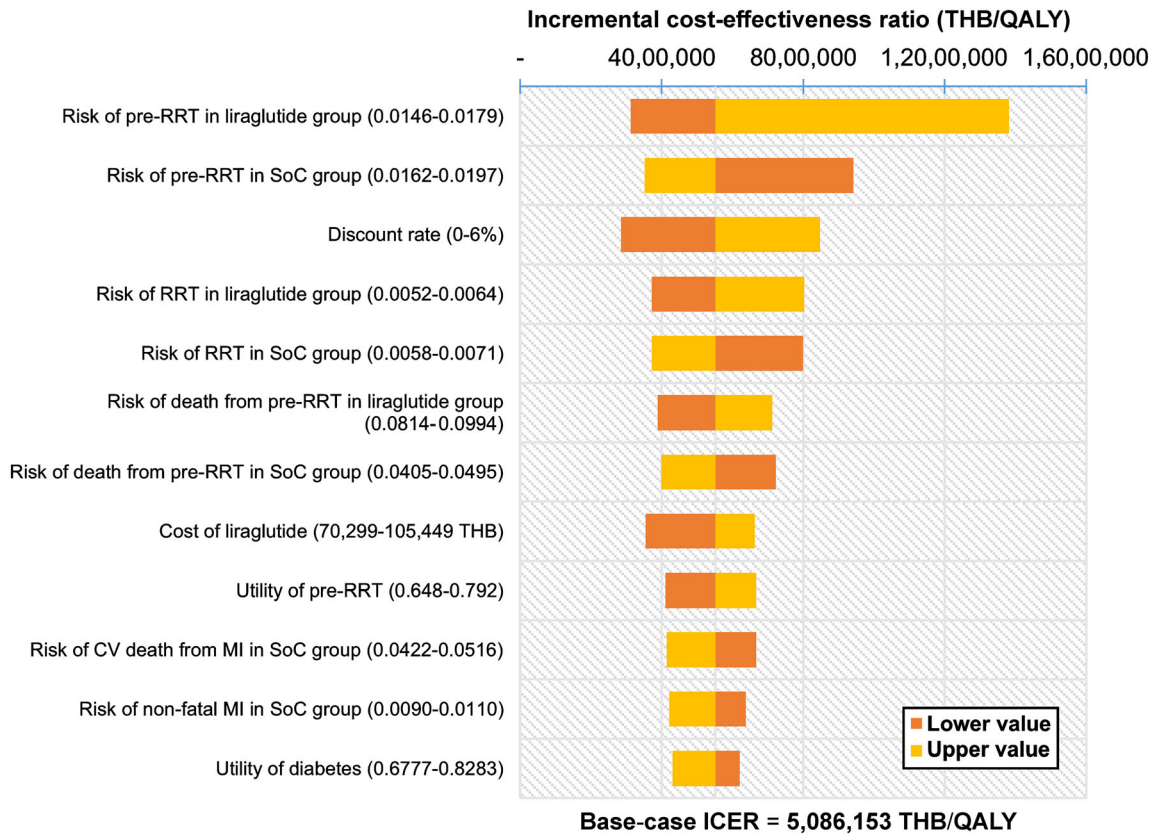

Fig. 8 Tornado diagram of add-on liraglutide compared to standard of care alone in people without atherosclerotic cardiovascular disease. *CV* cardiovascular, *ICER* incremental cost-effectiveness ratio, *MI* myocardial infarction, *QALY* quality-adjusted life-year, *RRT* renal replacement therapy, *SoC* standard of care, *THB* Thai baht

ASCVD, respectively, to yield the ICER within the local Thai threshold.

A cost-effectiveness study conducted in the USA [23] using data from the LEADER trial reported that liraglutide was a cost-effective strategy for people with T2D with established CVD or elevated CV risk compared to the SoC, with an ICER of US$106,749/QALY. The WTP threshold to justify the cost-effectiveness used in this study was US$150,000/QALY. Although the data from the LEADER trial was used in the two studies, the results could be different owing to several factors such as the difference in model structure, costs of treatment, and WTP threshold. When the incremental cost and incremental QALY were considered, the findings of the all people cohort in this study incurred lower incremental cost and gained more QALYs than those in the US study. With the huge difference in the level of acceptable threshold in these two studies, it is not surprising that the results were not consistent.

Several strengths and limitations were taken into consideration. First, the developed Markov model used in this study captured the long-term CV and renal outcomes of liraglutide; however, the transitional probabilities were derived from the median time of 3.84 years from the LEADER clinical trial [9] and carried forward the constant transitional probabilities. This might not truly reflect the real situation. The disease is likely to progress exponentially, especially in people with T2D and high risk of ASCVD. These people would gain benefit from early liraglutide treatment. Second, this study incorporated the cost of CV death into the analysis. Liraglutide treatment resulted in cost saving from the

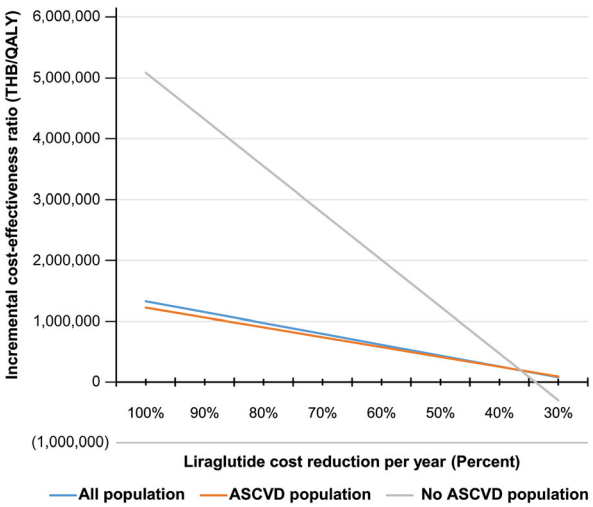

Fig. 9 Effect of liraglutide cost reduction on the incremental cost-effectiveness ratio for three populations. *ASCVD* atherosclerotic cardiovascular disease, *QALY* quality-adjusted life-year, *THB* Thai baht

significantly lower CV death compared to the SoC treatment.

CONCLUSION

On the basis of the clinical evidence from the LEADER clinical trial with 3.84 years of median follow-up duration and the current cost of liraglutide, add-on liraglutide has an ICER of 1.3 million THB for all people with T2D, 1.2 million THB for people with T2D and ASCVD, and 5 million THB for people with T2D without ASCVD. People with T2D and ASCVD would have the most potential gain from adding liraglutide treatment compared to other populations.

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Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors were responsible for the conception and design of the study, and for the acquisition, analysis, and interpretation of data. Unchalee Permsuwan analyzed the data and drafted the manuscript. All authors contributed substantially to drafting and revising of the manuscript. All authors have reviewed and approved the final version of the manuscript for submission to *Diabetes Therapy* and agree to be accountable for its contents.

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Compliance with Ethics Guidelines. This article is been approved ethics committees and was performed in accordance with the Helsinki Declaration of 1964.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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