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Cost-effectiveness of SGLT2is versus DPP4is among type 2 diabetes patients with and without established cardiovascular disease: A model-based simulation analysis using 10-year real-world data and targeted literature review

Short title: Real-world cost-effectiveness of SGLT2is

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Abstract

Aims: We conducted a model-based economic analysis of sodium-glucose cotransporter-2 inhibitors (SGLT2is) versus dipeptidyl peptidase-4 inhibitors (DPP4is) in type 2 diabetes (T2D) patients with and without established cardiovascular disease (CVD) using 10-year real-world data.

Materials and Methods: A Markov model was utilized to estimate healthcare costs and quality-adjusted life-years (QALYs) over a 10-year simulation time horizon from a healthcare sector perspective, with both costs and QALYs discounted at 3% annually. Model inputs were derived from analyses of Taiwan's National Health Insurance Research Database or published studies of Taiwanese populations. The primary outcome measure was the incremental cost-effectiveness ratios (ICERs). Incorporated with our study findings, a targeted literature review was conducted to synthesize updated evidence on the cost-effectiveness of SGLT2is versus DPP4is.

Results: Over 10 years, use of SGLT2is versus DPP4is yielded ICERs of $3,244 and $4,186 per QALY gained for T2D patients with and without established CVD, respectively. Results were robust across a series of sensitivity and scenario analyses, showing ICERs between $-1,074 (cost-saving) and $8,467 per QALY gained for T2D patients with established CVD and between $369 and $37,122 per QALY gained for T2D patients without established CVD.

Conclusions: Use of SGLT2is versus DPP4is was highly cost-effective for T2D patients regardless of patients' CVD history in real-world clinical practice. Our results extend current evidence by demonstrating SGLT2is as an economically rational alternative over DPP4is for T2D treatment in routine care. Future research is warranted to explore heterogenous economic benefits of SGLT2is given diverse patient characteristics in clinical settings.

Introduction

A substantial burden attributable to cardiovascular diseases (CVDs) among patients with type 2 diabetes (T2D), especially those without optimal glycemic control (1, 2), remains a major challenge for healthcare systems globally (3, 4). Sodium-glucose cotransporter-2 inhibitors (SGLT2is), originally developed as glucose-lowering agents (GLAs), have shown beneficial effects on the cardiovascular system (5, 6). Compared with dipeptidyl peptidase-4 inhibitors (DPP4is), which are widely used as add-on oral GLAs for T2D patients who failed metformin therapy (7-10), the use of SGLT2is substantially reduces the risks of CVDs and mortality (11).

A growing body of evidence on the cost-effectiveness analysis (CEA) of SGLT2is versus DPP4is suggests that the use of SGLT2is is cost-effective or even cost-saving compared with DPP4is (12-20). However, research gaps remain due to the marked heterogeneity of treatment experiences in different regions and the data or analysis limitations of existing studies. Most of these studies adopted treatment efficacy data from clinical trials with limited short-term follow-ups to project long-term outcomes in model-based simulation economic analyses. The applicability of results from these CEA studies, which were based on selective and homogeneous patient populations in clinical trials, to diverse patient populations in the real world remains unclear. Furthermore, considering that health utility and healthcare cost estimates could be sensitive to study regions, settings and populations (e.g., countries and healthcare systems), the CEA results using health utility and cost data not specific to the given study settings/populations may limit generalizability to inform local clinical care and health policy decisions (14-16, 20). Moreover, given differences in the disease progression of T2D between patients with and without pre-existing CVDs, which were not differentiated in previous CEA studies (12-17, 19, 20), the results remain inconclusive to inform personalized medicine on tailoring a treatment to patients' CVD risks.

Against this background, we conducted an economic analysis study using a model-based

simulation analysis integrated with 10-year real-world data to evaluate the cost-effectiveness of SGLT2is versus DPP4is in T2D patients from a healthcare sector perspective in Taiwan. We employed population- and setting-specific model inputs to enhance the generalizability of study results to usual clinical practice settings in Taiwan, and stratified analyses based on patients' CVD history to provide informative evidence for individualized treatment decisions. Moreover, a targeted literature review was conducted to incorporate our study findings for providing the updated evidence on the cost-effectiveness of using SGLT2is versus DPP4is for T2D patients.

Materials and Methods

Base-case model structure and assumptions

Due to the lack of economic models which have been developed or validated specifically for the T2D populations in Taiwan, the present study adapted a state-transition Markov model with a yearly cycle length for assessing cost-effectiveness of SGLT2is versus DPP4is which focused the CVD progression of T2D based on substantial evidence on cardiovascular benefit of SGLT2i use and reflected the clinical context of Taiwan as confirmed and supported by local experts. The model comprised five health states: T2D without any CVD events, heart failure (HF), myocardial infarction (MI), stroke, and all-cause death (Figure 1). A hypothetical cohort was assumed for the modeling analyses based on patient characteristics reported in a previous Taiwanese study (21): T2D patients with a diabetes duration of 8 years and the initiation of SGLT2is or DPP4is at 55 years old. Patients could progress from T2D without any CVD events to other health states in a yearly cycle over a 10-year simulation horizon. Quality-adjusted life-years (QALYs) and healthcare costs were rewarded in each cycle and discounted at 3% annually over the simulation horizon, which was recommended by the Center of Drug Evaluation/Health Technology Assessment in Taiwan (22). All analyses, including model inputs (i.e., transition probability, health utility, and cost parameters) and economic evaluations, were separately conducted with stratification of CVD history and thus two incremental cost-effectiveness ratios (ICERs) were generated accordingly.

Health utility and healthcare costs

The health utility parameters in the model were based on a population-based study that estimated the mean health utility score of Taiwanese patients with T2D along with health utility penalties attributable to patient demographic and clinical characteristics (23). Specifically, the health utility inputs were estimated by subtracting the utility penalties of

given patient characteristics from the mean health utility score of T2D patients.

The cost parameters associated with different health states were based on a population-based study of Taiwanese T2D patients that estimated the mean annual healthcare cost which comprised the reimbursement fees of diagnosis, treatments (e.g., examinations, procedures), pharmaceutical services, and medications as well as copayments paid by patients for T2D, and cost multipliers associated with patient demographic and clinical characteristics (3). Healthcare costs for a given health state in the model were estimated by multiplying the mean annual healthcare cost with cost multipliers of patient characteristics associated with that health state. Moreover, the drug cost of SGLT2is (or DPP4is) was estimated as the average drug cost of all available SGLT2is (or DPP4is) reimbursed by Taiwan's National Health Insurance (NHI) program in 2017 (24). Costs were converted to 2020 values using the medical component of the consumer price index in Taiwan and are presented in USD (25). The health utility and cost input parameters used in the modeling analyses are detailed in Supplementary Table 1.

Transition probabilities between health states

To reflect the real-world effectiveness of SGLT2is versus DPP4is in Taiwan, transition probabilities between modeled health states were derived from Taiwan's National Health Insurance Research Database (NHIRD) and the published literature on the Taiwanese population (21, 26, 27). Specifically, in the DPP4i group, T2D patients who newly initiated DPP4is in 2010 were identified from the NHIRD and followed until death or the end of the database (i.e., December 31, 2018), whichever came first, to estimate CVD risks in each follow-up year as the model inputs for transition probabilities of progressing from T2D without any CVD events to HF, MI, and stroke. Regarding transition probabilities from other health states to death, the mortality estimates were obtained from a risk score system that has been established for the prediction of CVD-specific and all-cause mortalities in Taiwanese

T2D patients as a function of patient socio-demographics, lifestyle behaviors, and diabetes-related clinical characteristics (e.g., treatments and biomarkers) (26).

In the SGLT2i group, the comparative treatment effects (i.e., relative hazards) of SGLT2is versus DPP4is on risks of CVDs and death were incorporated with the transition probabilities of the DPP4i group to convert the transition probabilities of the SGLT2i group using the ProbToProb function in TreeAge. Briefly, the treatment effects were derived from our previous study (21) which was a retrospective cohort study using the active comparator and new user design to include the stable users of SGLT2is or DPP4is identified from Taiwan's NHIRD in 2017 and follow them up to 2019. To ensure the comparability between drug groups, one-to-one propensity score (PS)-matched SGLT2i and DPP4i users were identified using the 5-to-1 digit greedy PS matching approach. The relative hazards were estimated using Cox proportional hazard models for analyses of the PS-matched pairs of new SGLT2i or DPP4i users from the initiation of study drugs until the occurrence of study outcomes (i.e., HF, MI, stroke, and death) or the end of the database (i.e., December 31, 2018), whichever came first. Estimation procedures and the data of transition probabilities for each model pathway between health states are detailed in Supplementary Tables 2-4.

Base-case analysis

The total QALYs and healthcare costs of a patient in each treatment group were simulated over a 10-year time horizon from a healthcare sector perspective. The 10-year cost-effectiveness of SGLT2i and DPP4i treatments was then measured in terms of the ICERs, calculated as incremental total healthcare costs divided by incremental total QALYs. As recommended by the World Health Organization (28) for the country without a pre-defined willingness-to-pay (WTP) threshold for CEAs, one and three times the per capita gross domestic product (GDP) of Taiwan in 2020 were adopted in this study, which were USD 30,038 and USD 90,114 (29), respectively, to determine whether the use of SGLT2is versus

DPP4is was highly cost-effective (i.e., USD 0 < ICER ≤ USD 30,038) or cost-effective (i.e., USD 30,038 < ICER ≤ USD 90,114). Using one and three times the per country's capita GDP in CEAs is also recommended by Taiwan's Center of Drug Evaluation/Health Technology Assessment (CDE/HTA) (22). The impact inventory for the components considered in the cost-effectiveness analyses is provided in Supplementary Table 5.

Sensitivity analyses

Deterministic sensitivity analyses (DSAs) and probabilistic sensitivity analyses (PSAs) were conducted to quantify the impact of parameter uncertainties on ICER estimates. In the DSAs, the lower and upper bounds of each model input (i.e., the ranges shown in Supplementary Tables 1, 3, 4) were applied, and the key drivers of ICERs were identified as the parameters whose variations yielded a change of over 15% in ICER estimates, and then illustrated in a tornado diagram. The PSAs were performed using a Monte Carlo simulation with 10,000 iterations, in which all model parameter inputs simultaneously varied in the plausible ranges with pre-defined distributions (Supplementary Tables 1, 3, 4) that were determined by the characteristics of the parameters and their levels of certainty.

Scenario analyses

Several scenario analyses were conducted to confirm the robustness of the study findings. First, the simulation time horizon was extended to 20 and 30 years and shortened to 1, 2, 3, and 5 years to assess the uncertainty that arises from the length of the simulation period. Second, in the base-case analysis, the baseline demographics and laboratory data of modeled subjects that mirrored the average or common values of the characteristics of the Taiwanese T2D population (as shown in Supplementary Table 2) were used in the risk score system (26) to estimate the mortality risk, which contributed 0 points in the risk score calculation. This assumption might thus underestimate the mortality of our modeled subjects.

Therefore, a scenario analysis was conducted to use higher mortalities predicted by a risk score system that assumed the risk factor values to be above the average levels of T2D patients. Third, CVD risks (i.e., pathways a, b, and c) were varied with a range of ±25% to account for disease progression rates that may change with the aging of the patient cohort or the evolution of clinical management over time. Fourth, considering potentially unmeasured confounding effects on the estimates of the relative hazards associated with SGLT2is versus DPP4is in claims-based research (21), the hazard ratios from a network meta-analysis of clinical trials (30) were adopted in a sensitivity analysis. Briefly, the network meta-analysis (30) included the randomized clinical trials of T2D patients with a follow-up of ≥ 12 weeks to assess comparative effects of SGLT2is, glucagon-like peptide-1 receptor agonists and DPP4is on clinical outcomes including all-cause death, CV death, HF, MI and stroke, and the Bayesian hierarchical network meta-analysis was applied to synthesize the trial results (e.g., hazard ratios). Fifth, a break-even cost analysis was conducted, where the drug cost of SGLT2is was varied by 10% to 50% of the base-case value against the ICERs to demonstrate the results of adjusting reimbursement prices for SGLT2is in Taiwan's NHI program.

The model-based economic analyses were performed using TreeAge Pro 2020 decision analysis software (TreeAge Software, LLC, Williamstown, MA). The economic analyses were reported in compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (31) which is available in Supplementary Table 6.

Results

Base-case analyses

Over a 10-year simulation, HF was the most common CVD among T2D patients with CVD history and stroke was the most common CVD among T2D patients without CVD history (as shown in Figure 2). Compared with DPP4is, the use of SGLT2is yielded 0.198 QALYs gained at an additional cost of USD 644 (ICER: USD 3,244 per QALY gained) for T2D patients with CVD history, and 0.245 QALYs gained at an additional cost of USD 1,025 (ICER: USD 4,185 per QALY gained) for T2D patients without CVD history (Table 1).

Sensitivity analyses

The DSA results in Figure 3 show that the top two influential drivers for ICER values were the annual drug costs of DPP4is and the hazard ratio of SGLT2is versus DPP4is on HF for T2D patients with CVD history, and the annual drug costs of DPP4is and the hazard ratio of SGLT2is versus DPP4is on all-cause death for those without CVD history. An ICER plane from the PSA under 10,000 model iterations of study data in a 10-year simulation was provided in Supplementary Figure 1 and shows 100 % of ICER points falling below the WTP threshold of USD 30,038. Other PSA results based on the base-case and scenario analyses against the WTP threshold of USD 30,038 are considered highly cost-effective in 85%-100% of the model iterations, except for the 1-year simulation of T2D patients without CVD history (Table 1 and Figure 4).

Scenario analyses

The results of the scenario analyses are generally consistent with those of the base-case analyses, showing highly cost-effective for using SGLT2i versus DPP4is, except for the result of the analysis based on a 1-year simulation of T2D patients without CVD history (Table 1). The results of break-even analyses show that using SGLT2i versus DPP4i would yield more

QALYs with a lower total healthcare cost (i.e., cost-saving treatment) when the annual drug cost of SGLT2i is lower than USD 304 for T2D patients with CVD history and USD 257 for those without CVD history (Supplementary Figure 2).

Discussion

This economic analysis applied real-world and population-specific data as model inputs to estimate the cost-effectiveness of SGLT2is versus DPP4is for T2D in usual clinical practice settings in Taiwan. The present study findings, together with the targeted literature review results, extend current evidence to promote the use of SGLT2is as an economically reasonable alternative to DPP4is for T2D patients in real-world clinical practice regardless of patients' status of CVD history.

Comparison with current evidence on the cost-effectiveness of SGLT2is versus DPP4is

Generally, favorable economic outcomes of using SGLT2i versus other GLAs (i.e., cost-effective or cost-saving) in individuals with T2D have been reported in previous studies (32-34). This cost-effectiveness analysis specifically focused on the use of SGLT2is versus DPP4is and the results are comparable with those in existing literature obtained from the targeted literature review (Supplementary Table 7 for detailed literature review procedures, Supplementary Figure 3 for the flow of article selection), showing that the use of SGLT2is versus DPP4is for T2D is cost-effective (13-15, 17-19) or even cost-saving (12, 16, 20). Details of individual study characteristics and ICER results were summarized in Supplementary Table 8 and Supplementary Figure 4, respectively. The probabilities of being cost-effective for using SGLT2is versus DPP4is obtained by PSAs from this study and existing literature ranged from 96% to 100%. Of noted, our targeted literature review found that different from our study using the NHIRD to estimate the annual transition probabilities of different health states up to 10 years, all previous studies adopted the short-term efficacy data (e.g., biomarker changes) based on highly selective patient populations from clinical trials as clinical effectiveness parameters, and similar to our study, six previous studies employed the country-specific health utility parameters. Moreover, considering potential variations in the cost data collected from real-world settings which may be attributable from

diverse patient populations and clinical practice, the present CEA adopted the adjusted healthcare costs (i.e., cost multipliers) for a given health state of interest using our previous study in Taiwan (4) which applied the rigorous methodology to adjust for potential influences from diverse patient characteristics on the cost estimates, whereas the majority of previous CEAs mainly used the country-specific crude or unadjusted healthcare costs based on literatures or information from public domains. Only two studies, our study and Reifsnider et al' study (18), performed subgroup cost-effectiveness analyses stratified by the status of CVD history.

Moreover, DPP4i drug cost, the most prominent driver of ICERs identified in our study regardless of patients' status of CVD history, has also been reported in previous studies (18, 19). This may be explained by a wide range of DPP4i drug cost (i.e., USD 87 to USD 319 per year in Taiwan) used as model inputs under Taiwan's NHI system. DPP4is have been reimbursed by Taiwan's NHI program since 2006. The drug reimbursement fees of DPP4is have changed considerably owing to the launch of generic DPP4is, adjustments of drug pricing, and changes in relevant reimbursement policies under the Taiwan NHI Administration's regulations (35). Although variations in the DPP4i drug cost had a great impact on ICER values, the cost-effectiveness results of using SGLT2is versus DPP4is remained robust in our sensitivity analyses (Figure 3).

Comparison of dominant variables for base-case ICERs between T2D patients with and without established CVD

Differences in the drivers of ICERs between study patients with and without established CVD should be acknowledged. For the base-case ICER, the treatment effects (i.e., hazard ratios) of SGLT2is versus DPP4is on HF, stroke, and all-cause death were the dominant drivers, other than DPP4i drug costs, for T2D patients with established CVDs, followed by utility penalties of CVDs, drug costs of SGLT2is, and discount rate. However, for T2D

patients without established CVDs, only the treatment effects of SGLT2is versus DPP4is on stroke and all-cause death and drug costs of SGLT2is affected the base-case ICER by more than 15%.

As shown in Figure 2, there are some discrepancies in the composition of the estimated event rates of CVDs and all-cause death between the two simulated cohorts (T2D patients with and without CVD history). HF and all-cause death were the two most common events among T2D patients with CVD history in our analyses. Given the apparent benefits of SGLT2i use on HF and all-cause death (11), it is expected that CEA results would be affected by the hazard ratios of SGLT2is versus DPP4is on these two outcomes for T2D patients with CVD history. In contrast, the risk of developing HF was relatively low among T2D patients without CVD history, while stroke and all-cause death accounted for most clinical events for this population. As a result, the hazard ratios of SGLT2is versus DPP4is on stroke and all-cause death, instead of HF, were identified as the leading drivers for the ICER in T2D patients without CVD history. This means that the treatment benefits of SGLT2is versus DPP4is on CVDs and death would be more evident when the patients' baseline risks of these clinical events were higher, which would further affect the CEA results. In addition, the utility penalties associated with MI, HF, and stroke had considerable impacts on the ICER for patients with CVD history but not those without CVD history. This may also be explained by the relatively low CVD risks in patients without CVD history, and thus the QALYs gained contributed by SGLT2i-associated cardiovascular benefits were trivial in this population.

The DSA findings suggest that among T2D patients with established CVDs whose cardiovascular risks are considerably higher than those without established CVDs, the economic benefit of SGLT2is versus DPP4is would mainly come from the effectiveness of SGLT2is in lowering risks of CVD events (including HF, MI, and stroke) and all-cause death that subsequently led to improved QALYs and reduced healthcare costs of patients. Conversely, the less beneficial effects of SGLT2is versus DPP4is on CVD events, particularly

HF and MI risks, in T2D patients without CVD history might not meaningfully dominate the CEA results, and in this case, the drug costs of SGLT2is are one of the leading drivers of the ICER.

Clinical and health policy implications

Based on our study findings, the use of SGLT2is in real-world practice should be encouraged owing to its lower risks of major clinical events and economic benefits compared with DPP4is. Moreover, from the perspective of the healthcare sector, this study provides supporting evidence for using SGLT2is to facilitate the cost-effective allocation of healthcare resources. Specifically, Supplementary Figure 2, which shows the ICERs of SGLT2is versus DPP4is against various SGLT2i drug costs, could assist health policy-makers in pricing SGLT2i reimbursement fees. For example, SGLT2is become a cost-saving treatment option compared with DPP4is when the SGLT2i drug costs are lower than USD 304 and USD 257 per year for patients with established CVD and those without CVD history, respectively. These break-even points may serve as a reference for the reimbursement pricing adjustment of SGLT2is. In addition, it is expected that the economic benefit of SGLT2is would be more amplified when the cost of SGLT2is is significantly reduced owing to the launch of their generic drugs.

Differences in the cost-effectiveness of SGLT2is versus DPP4is contributed by patients' CVD history were revealed in this study, suggesting the importance for prioritizing the treatment for subgroup populations who can benefit more from using SGLT2is clinically and economically. For example, we found that the use of SGLT2is yielded a more favorable cost-effectiveness profile among patients with established CVDs than those without CVD history; i.e., the ICER estimates were consistently lower in patients with CVD versus those without CVD history in base-case analyses and most scenario analyses (Table 1). Therefore, given limited healthcare resources, the reimbursement or incentive health policies could be tailored

to prioritize the use of SGLT2is in T2D populations with CVD history. Further research is warranted to identify the subgroup patient populations with specific characteristics (e.g., comorbid chronic kidney disease, elderly patients) who can benefit more from SGLT2i use to optimize healthcare resource allocation.

Strengths and limitations

Our economic evaluation attentively applied several study designs that can reflect real-life scenarios, including 1) derivation of effectiveness parameters (i.e., transition probabilities regarding CVD events) from a large-scale, real-world T2D cohort population, 2) incorporation of time-varying transition probabilities (i.e., annual risks of CVDs, increased mortalities with aging) in modeling analyses, and 3) stratification of the analyses for patients with established CVD and those without established CVD; such a stratification analysis was less often considered in previous CEAs. In addition, to ensure the applicability of the study results in Taiwan's healthcare setting, we used data from population-based studies that analyzed Taiwanese T2D populations for the effectiveness, health utility, and cost parameter inputs in the model (i.e., Chen et al.'s study (4), Kuo et al.'s study (23), and the T2D cohort identified from the NHIRD for costs, utility, and effectiveness parameters (21), respectively). The model inputs derived from the same target population (i.e., the T2D cohort from NHIRD) in our study minimize the uncertainties of CEA results that arise from the heterogeneity of multiple data sources.

Several limitations of our study should be acknowledged. First, our Markov decision model included only health states of CVDs and death without considering other clinical outcomes such as kidney diseases and adverse effects of treatments. Given growing evidence about SGLT2i-associated renal benefits (36, 37), the cost-effectiveness of SGLT2is versus DPP4is revealed in the present study could be underestimated. In addition, the impact of adverse drug effects on the CEA results might be negligible given the low incidence of

adverse effects (e.g., severe hypoglycemia, diabetic ketoacidosis). Second, the analyses were not performed from the societal perspective because costs from informal healthcare and non-healthcare sectors were not included due to data unavailability. Lastly, the improved health-related quality of life associated with the use of SGLT2is other than those contributed by reduced CVD and mortality events were not considered, e.g., the SGLT2i-associated benefit of body weight loss on patients' health-related quality of life (38). We might thus have underestimated the economic value of SGLT2is.

In summary, the use of SGLT2is versus DPP4is for real-world T2D patients regardless of the CVD history status in Taiwan is highly cost-effective. Future research is encouraged to explore the subgroup of patients with specific characteristics regarding their health and economic benefits obtained from SGLT2is to facilitate clinical care and health policy decisions and optimize healthcare resource allocation.

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Authors' contributions

Z.Y.P. designed the study, performed the targeted literature review, analyzed, and interpreted the data, and wrote the manuscript. C.T.Y. designed the study, performed the targeted literature review, analyzed, and interpreted the data, and wrote the manuscript. H.T.O. provided study materials, designed the study, interpreted the data, and wrote the manuscript. S.K. designed the study, interpreted the data, and reviewed/edited the manuscript. All authors approved the final manuscript.

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Conflicts of interest

All authors declare no competing interests regarding this work.

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Legends to figures

Figure 1: Model structure

Figure 2: Estimated event rates of cardiovascular diseases and all-cause death over 10-year simulation horizon in patients (a) with and (b) without cardiovascular disease history
Abbreviations: SGLT2is, sodium-glucose cotransporter-2 inhibitors; DPP4is, dipeptidyl peptidase 4 inhibitors.

Figure 3: Tornado diagram of deterministic sensitivity analyses results in type 2 diabetes patients (a) with and (b) without cardiovascular disease history
Abbreviations: DPP4is, dipeptidyl peptidase 4 inhibitors; USD, United States dollar; HR, hazard ratio; HF, heart failure; MI, myocardial infarction; SGLT2is, sodium-glucose cotransporter-2 inhibitors; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
*The hazard ratios refer to the estimated relative risk of SGLT2is versus DPP4is on CVDs or death.
Note: Only the parameters whose variations (i.e., lower and upper bounds) changed the ICER values by ≥ 15% are presented.

Figure 4. Cost-effectiveness acceptability curve of SGLT2is versus DPP4is in type 2 diabetes patients with and without cardiovascular disease history in base-case analyses
Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes; USD, United States dollar.

Table 1. Results of cost-effectiveness of SGLT2is versus DPP4is in base-case analysis and scenario analyses

	QALYs			Costs (USD)				
	SGLT2is	DPP4is	Incre-mental	SGLT2is	DPP4is	Incre-mental	ICER (USD per QALY gained)	Probability of being highly cost-effective* for SGLT2is vs. DPP4is in PSA
Base-case analyses (10-year simulation)								
With CVD history	6.492	6.294	0.198	11,306	10,661	644	3,244.07	100.0%
Without CVD history	8.154	7.909	0.245	9,147	8,122	1,025	4,185.64	100.0%
Scenario analyses								
With CVD history								
Mortality considering diabetes-related risk factors with values over average levels†	2.519	1.685	0.834	14,733	14,252	480	576.47	100.0%
Elevated CVD risks in DPP4i group (25% increase)	6.448	6.245	0.203	11,598	11,007	591	2,908.77	100.0%
Decreased CVD risks in DPP4i group (25% reduction)	6.540	6.348	0.191	10,991	10,270	720	3,770.20	100.0%
Treatment effects of SGLT2is from NMA of clinical trials	6.421	6.294	0.127	11,480	10,662	818	6,439.57	100.0%
1-year simulation	0.782	0.778	0.003	1,238	1,251	23	7,659.27	85.6%
2-year simulation	1.530	1.518	0.012	2,492	2,440	52	4,383.65	99.0%
3-year simulation	2.247	2.221	0.026	3,684	3,574	109	4,281.99	99.8%
5-year simulation	3.591	3.527	0.064	5.991	5.748	243	3,797.91	100.0%
20-year simulation	10.579	10.021	0.557	20,423	18,918	1,505	2,700.90	100.0%

30-year simulation	12.710	11.745	0.965	27,335	24,883	2,452	2,541.73	100.0%
Without CVD history								
Mortality considering diabetes-related risk factors with values over average levels†	3.613	2.369	1.243	11,655	11,196	459	369.08	100.0%
Elevated CVD risks in DPP4i group (25% increase)	8.115	7.848	0.267	9,226	8,246	980	3,664.73	100.0%
Decreased CVD risks in DPP4i group (25% reduction)	8.193	7.972	0.220	9,068	7,993	1,074	4,864.24	100.0%
Treatment effects of SGLT2is from NMA of clinical trials	8.022	7.909	0.113	9,355	8,122	1,232	10,907.14	100.0%
1-year simulation	0.964	0.961	0.003	976	860	115	37,122.45	27.9%
2-year simulation	1.892	1.880	0.012	1,940	1,712	227	18,639.09	88.2%
3-year simulation	2.785	2.758	0.027	2,887	2,552	335	12,548.61	100.0%
5-year simulation	4.471	4.401	0.070	4,743	4,199	543	7,753.02	100.0%
20-year simulation	13.518	12.734	0.748	16,989	15,085	1,903	2,427.23	100.0%
30-year simulation	16.632	15.155	1.478	23,350	20,485	2,865	1,938.86	100.0%

Abbreviations: SGLT2is, sodium-glucose cotransporter-2 inhibitors; DPP4is, dipeptidyl peptidase 4 inhibitors; QALY, quality-adjusted life-year; PSA, probabilistic sensitivity analysis; USD, United States dollar; ICER, incremental cost-effectiveness ratio; CVD, cardiovascular disease; NMA, network meta-analysis.

*The willingness-to-pay threshold was set as one time the per capita gross domestic product in Taiwan in 2020 (i.e., USD 30,038).

†A 14-point risk score that comprised the following risk factors and score points (with a range of 0 to 5, indicating no to high impact on patient's mortality) was applied to predict the mortality of study cohort patients in the scenario analysis: 55 years old (3 points), diabetes duration of 8

years (2 points), glucose-lowering agents (1 point), smoking behavior (1 point), education ≤ 5 years (2 points), body mass index < 18.5 kg/m^2 (1 point), variation of fast plasma glucose ≥ 22.3% (1 point), variation of glycated hemoglobin ≥ 4.5% (1 point), variation of diastolic blood pressure ≥ 5.5% (1 point), triglycerides ≥ 150 mg/dL (1 point), and presence of peripheral neuropathy (1 point).

Figure 1: Model structure

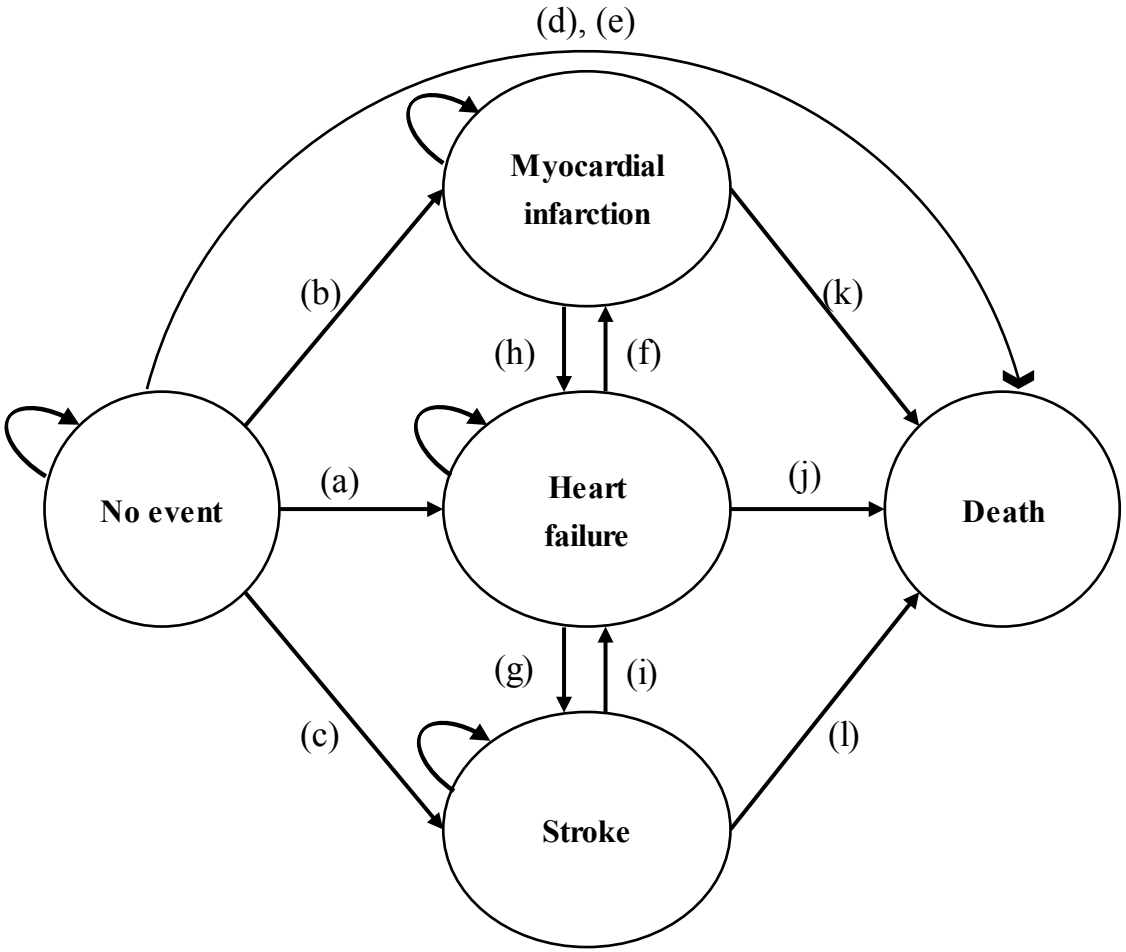
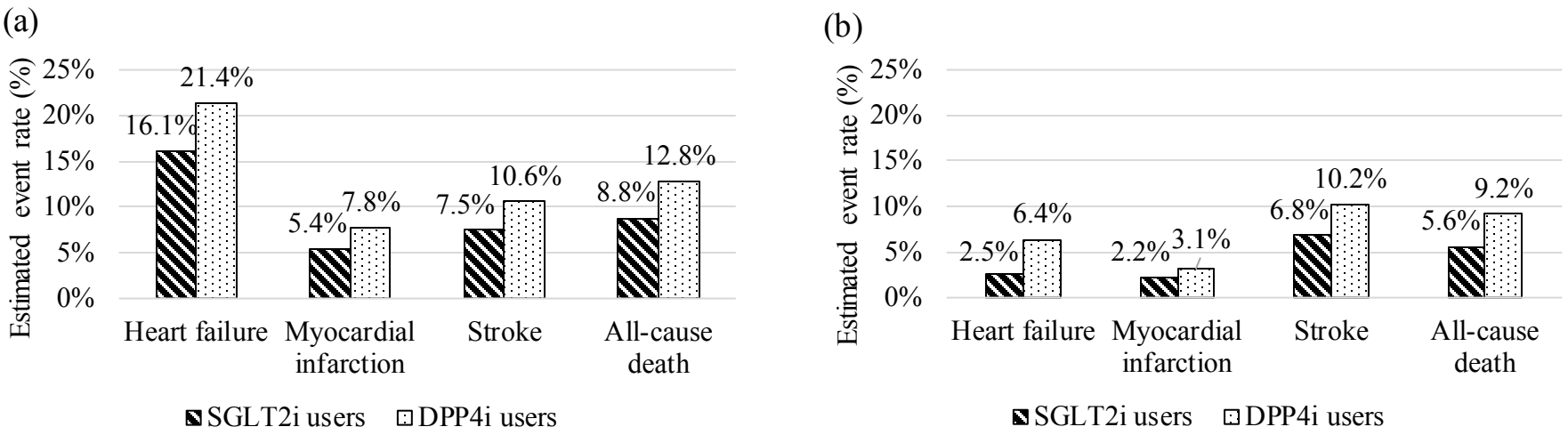
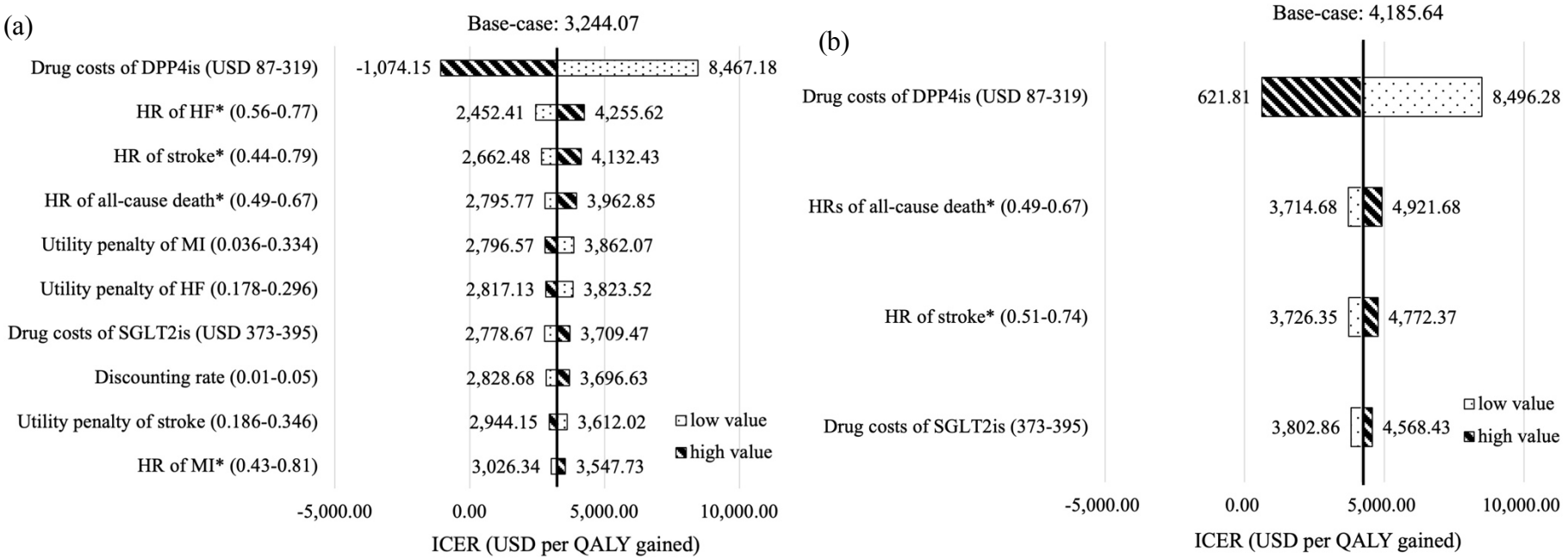


Figure 2. Estimated event rates of cardiovascular diseases and all-cause death over 10-year simulation horizon in patients (a) with and (b) without cardiovascular disease history



Abbreviations: SGLT2is, sodium-glucose cotransporter-2 inhibitors; DPP4is, dipeptidyl peptidase 4 inhibitors.

Figure 3. Tornado diagram of deterministic sensitivity analyses results in type 2 diabetes patients (a) with and (b) without cardiovascular disease history



Abbreviations: DPP4is, dipeptidyl peptidase 4 inhibitors; USD, United States dollar; HR, hazard ratio; HF, heart failure; MI, myocardial infarction; SGLT2is, sodium-glucose cotransporter-2 inhibitors; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

*The hazard ratios refer to the estimated relative risk of SGLT2is versus DPP4is on CVDs or death.

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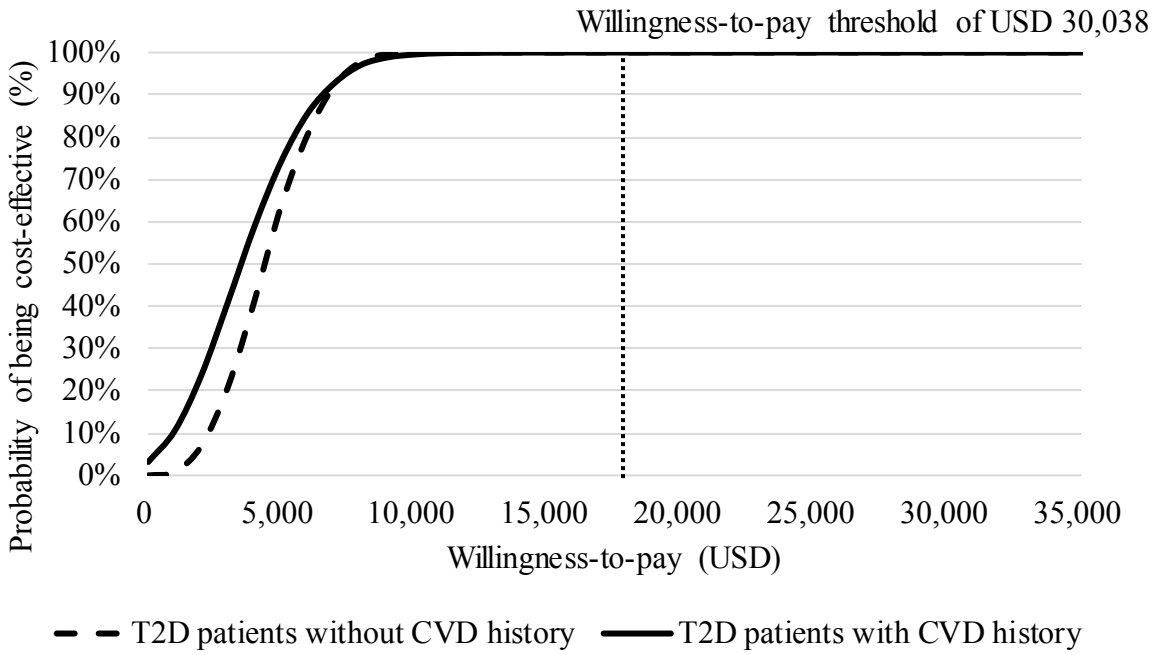
Figure 4. Cost-effectiveness acceptability curve of SGLT2is versus DPP4is in type 2 diabetes patients with and without cardiovascular disease history in base-case analyses



Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes; USD, United States dollar.