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Cost-effectiveness of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors among patients with type 2 diabetes with and without established cardiovascular diseases: A model-based simulation analysis using 10-year real-world data and targeted literature review

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Abstract

Aim: We conducted a model-based economic analysis of sodium-glucose cotransporter-2 inhibitors (SGLT2is) versus dipeptidyl peptidase-4 inhibitors (DPP4is) in patients with type 2 diabetes (T2D), with and without established cardiovascular diseases (CVDs), 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 $3244 and $4186 per QALY gained for patients with T2D, with and without established CVDs, respectively. Results were robust across a series of sensitivity and scenario analyses, showing ICERs between $-1074 (cost-saving) and $8467 per QALY gained for patients with T2D with established CVDs and between $369 and $37 122 per QALY gained for patients with T2D without established CVDs.

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

Zi-Yang Peng and Chun-Ting Yang contributed equally.

1 | INTRODUCTION

A substantial burden attributable to cardiovascular diseases (CVDs) among patients with type 2 diabetes (T2D), particularly those without optimal glycaemic 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 CV system.[5,6] Compared with dipeptidyl peptidase-4 inhibitors (DPP4is), which are widely used as add-on oral GLAs for patients with T2D 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 because of 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 about tailoring a treatment for 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 patients with T2D 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 updated evidence on the cost-effectiveness of using SGLT2is versus DPP4is for patients with T2D.

2 | MATERIALS AND METHODS

2.1 | Base-case model structure and assumptions

Because of 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 the cost-effectiveness of SGLT2is versus DPP4is, which focused the CVD progression of T2D based on substantial evidence on CV 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 modelling analyses based on patient characteristics reported in a previous Taiwanese study[21]: patients with T2D with 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.

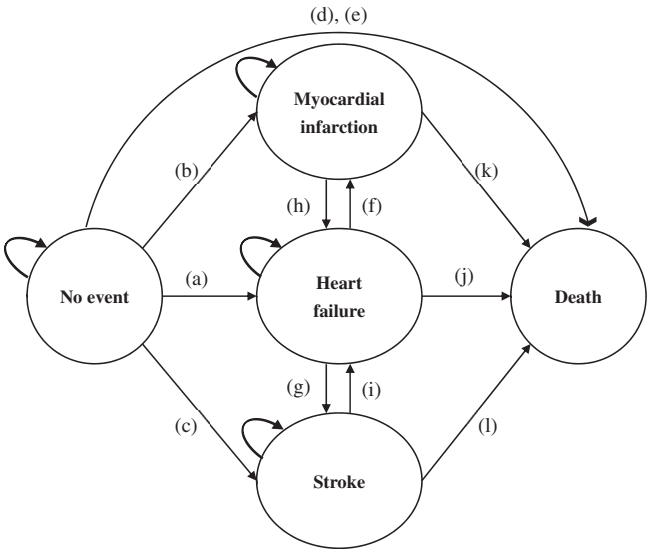

FIGURE 1 Model structure

2.2 | 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 patients with T2D.

The cost parameters associated with different health states were based on a population-based study of Taiwanese patients with T2D, which estimated the mean annual healthcare cost that 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 modelling analyses are detailed in Table S1.

2.3 | Transition probabilities between health states

To reflect the real-world effectiveness of SGLT2is versus DPP4is in Taiwan, transition probabilities between modelled health states were derived from Taiwan's National Health Insurance Research Database (NHIRD) and the published literature on the Taiwanese population.[21,26,27] In particular, in the DPP4i group, patients with T2D who initiated DPP4is in 2010 were identified from the NHIRD and followed until death or the end of the database (i.e. 31 December 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 patients with T2D as a function of patient sociodemographics, lifestyle behaviours 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. 31 December 2018), whichever came first. Estimation procedures and the data of transition probabilities for each model pathway between health states are detailed in Tables S2-S4.

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 $0 < \text{ICER} \leq$ 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.[22] The impact inventory for the components considered in the CEAs is provided in Table S5.

2.5 | 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 Tables S1, S3 and S4) were applied, and the key drivers of ICERs were identified as the parameters whose variations yielded a change >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 varied simultaneously in the plausible ranges with pre-defined distributions (Tables S1, S3 and S4) that were determined by the characteristics of the parameters and their levels of certainty.

2.6 | 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 modelled subjects that mirrored the average or common values of the characteristics of the Taiwanese T2D population (as shown in Table S2) were used in the risk score system[26] to estimate the mortality risk, which contributed 0 points in the risk score

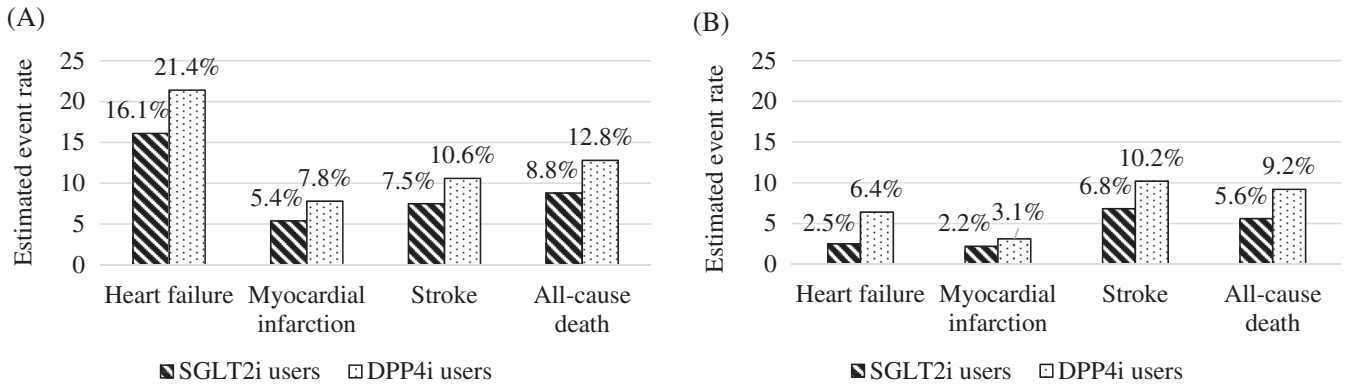

FIGURE 2 Estimated event rates of cardiovascular diseases and all-cause death over 10-year simulation horizon in patients (A) with and (B) without a cardiovascular disease history. DPP4is, dipeptidyl peptidase 4 inhibitors; SGLT2is, sodium-glucose cotransporter-2 inhibitors

calculation. This assumption might thus underestimate the mortality of our modelled 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 patients with T2D. Third, CVD risks (i.e. pathways a, b and c) varied a range of ±25% to account for disease progression rates that may change with the ageing 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 patients with T2D with a follow-up of ≥12 weeks to assess the 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. The Bayesian hierarchical network meta-analysis was then 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%-50% of the base-case value against the ICERs to show 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). The economic analyses were reported in compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS),[31] which is available in Table S6.

3 | RESULTS

3.1 | Base-case analyses

Over a 10-year simulation, HF was the most common CVD among patients with T2D with a CVD history and stroke was the most common CVD among patients with T2D without a 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 3244 per QALY gained) for patients with T2D with a CVD history, and 0.245 QALYs gained at an additional cost of USD 1025 (ICER: USD 4185 per QALY gained) for patients with T2D without a CVD history (Table 1).

3.2 | 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 patients with T2D and a CVD history, and the annual drug costs of DPP4is and the hazard ratio of SGLT2is versus DPP4is on all-cause death for those without a CVD history. An ICER plane from the PSA under 10 000 model iterations of study data in a 10-year simulation was provided in Figure S1 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 patients with T2D without a CVD history (Table 1 and Figure 4).

3.3 | Scenario analyses

The results of the scenario analyses are generally consistent with those of the base-case analyses, which were shown as highly cost-effective for using SGLT2i versus DPP4is, except for the result of the analysis based on a 1-year simulation of patients with T2D without a 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 patients with T2D with a CVD history, and USD 257 for those without a CVD history (Figure S2).

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

	QALYs			Costs (USD)			ICER (USD per QALY gained)	Probability of being highly cost-effective[a] for SGLT2is vs. DPP4is in PSA (%)
	SGLT2is	DPP4is	Incremental	SGLT2is	DPP4is	Incremental		
Base-case analyses (10-year simulation)								
With a CVD history	6.492	6.294	0.198	11 306	10 661	644	3244.07	100.0
Without a CVD history	8.154	7.909	0.245	9147	8122	1025	4185.64	100.0
Scenario analyses								
With a CVD history								
Mortality considering diabetes-related risk factors with values over average levels[b]	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	2908.77	100.0
Decreased CVD risks in DPP4i group (25% reduction)	6.540	6.348	0.191	10 991	10 270	720	3770.20	100.0
Treatment effects of SGLT2is from NMA of clinical trials	6.421	6.294	0.127	11 480	10 662	818	6439.57	100.0
1-year simulation	0.782	0.778	0.003	1238	1251	23	7659.27	85.6
2-year simulation	1.530	1.518	0.012	2492	2440	52	4383.65	99.0
3-year simulation	2.247	2.221	0.026	3684	3574	109	4281.99	99.8
5-year simulation	3.591	3.527	0.064	5.991	5.748	243	3797.91	100.0
20-year simulation	10.579	10.021	0.557	20 423	18 918	1505	2700.90	100.0
30-year simulation	12.710	11.745	0.965	27 335	24 883	2452	2541.73	100.0
Without a CVD history								
Mortality considering diabetes-related risk factors with values over average levels[b]	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	9226	8246	980	3664.73	100.0
Decreased CVD risks in DPP4i group (25% reduction)	8.193	7.972	0.220	9068	7993	1074	4864.24	100.0
Treatment effects of SGLT2is from NMA of clinical trials	8.022	7.909	0.113	9355	8122	1232	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	1940	1712	227	18 639.09	88.2

TABLE 1 (Continued)

	QALYs			Costs (USD)			ICER (USD per QALY gained)	Probability of being highly cost-effective[a] for SGLT2is vs. DPP4is in PSA (%)
	SGLT2is	DPP4is	Incremental	SGLT2is	DPP4is	Incremental		
3-year simulation	2.785	2.758	0.027	2887	2552	335	12 548.61	100.0
5-year simulation	4.471	4.401	0.070	4743	4199	543	7753.02	100.0
20-year simulation	13.518	12.734	0.748	16 989	15 085	1903	2427.23	100.0
30-year simulation	16.632	15.155	1.478	23 350	20 485	2865	1938.86	100.0

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

[a]Willingness-to-pay threshold was set asone time the per capita gross domestic product in Taiwan in 2020 (i.e. USD30038).

[b]A 14-point risk score that comprised the following risk factors and score points (with a range of 0-5, indicating no to high impact on patient's mortality) was applied topredict 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 behaviour (1 point), education ≤5 years (2 points), body mass index <18.5 kg/m^2 (1 point), variation of fast plasmaglucose ≥22.3% (1 point), variation of glycated haemoglobin ≥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).

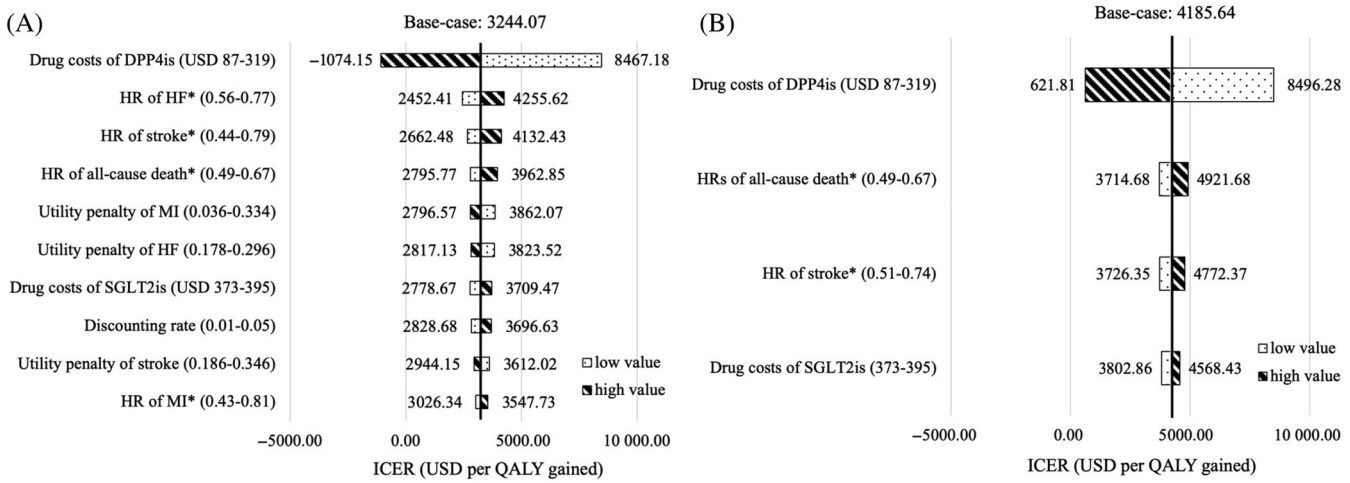

FIGURE 3 Tornado diagram of deterministic sensitivity analyses results in patients with type 2 diabetes, (A) with and (B) without a cardiovascular disease history. DPP4is, dipeptidyl peptidase 4 inhibitors; HF, heart failure; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; MI, myocardial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

4 | 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 patients with T2D in real-world clinical practice regardless of patients' status of CVD history.

Generally, favourable 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 CEA specifically focused on the use of SGLT2is versus DPP4is and the results are comparable with those in the existing literature obtained from the targeted literature review (Table S7 for detailed literature review procedures, Figure S3 for the flow of article selection), which showed 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 Table S8 and Figure S4, 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%. Importantly, 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

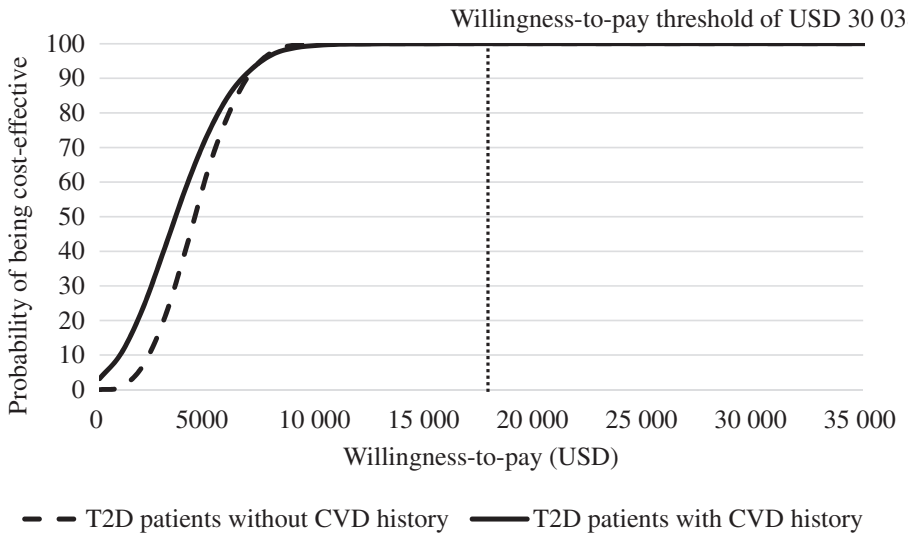

FIGURE 4 Cost-effectiveness acceptability curve of SGLT2is versus DPP4is in patients with T2D, with and without a CVD history, in base-case analyses. CVD, cardiovascular disease; T2D, type 2 diabetes; USD, United States dollar

short-term efficacy data (e.g. biomarker changes) based on highly selective patient populations from clinical trials as clinical effectiveness parameters; 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 the literature or information from the public domains. Only two studies (ours and Reifsnider et al.[18]) performed subgroup CEAs 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 costs (i.e. USD 87-319 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).

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 patients with T2D with established CVDs, followed by utility penalties of CVDs, drug costs of SGLT2is and discount rate. However, for patients with T2D 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 (patients with T2D, with and without CVD history). HF and all-cause death were the two most common events among patients with T2D with a 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 patients with T2D with a CVD history. In contrast, the risk of developing HF was relatively low among patients with T2D without a 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 patients without a 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 a CVD history but not those without a CVD history. This may also be explained by the relatively low CVD risks in patients without a CVD history and thus the QALYs gained, which were contributed by SGLT2i-associated CV benefits, were trivial in this population.

The DSA findings suggest that among patients with T2D with established CVDs whose CV 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 the 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 patients with T2D without a 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 have been shown in this study. Based on our study findings, the use of SGLT2is in real-world practice should be encouraged because of 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. In particular, Figure S2, 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 CVDs and those without a 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 amplified more when the costs of SGLT2is are 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 of prioritizing treatment for the subgroup populations who can benefit more from using SGLT2is clinically and economically. For example, we found that the use of SGLT2is yielded a more favourable cost-effectiveness profile among patients with established CVDs than those without a CVD history, i.e. the ICER estimates were consistently lower in patients with a CVD history versus those without a 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 a 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.

This study had its strengths and limitations. Our economic evaluation attentively applied several study designs that can reflect real-life scenarios, including: (a) derivation of effectiveness parameters (i.e. transition probabilities regarding CVD events) from a large-scale, real-world T2D cohort population; (b) incorporation of time-varying transition probabilities (i.e. annual risks of CVDs, increased mortalities with ageing) in modelling analyses; and (c) stratification of the analyses for patients with established CVDs and those without established CVDs; such a stratification analysis was less often considered in previous CEAs. In addition, to ensure the applicability of the study results in Taiwan's health care setting, we used data from population-based studies that analysed Taiwanese T2D populations for the effectiveness, health utility and cost parameter inputs in the model (i.e. studies by Chen et al.[4] and Kuo et al.,[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 disease and the 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 hypoglycaemia, diabetic ketoacidosis). Second, the analyses were not performed from the societal perspective because costs from informal healthcare and non-healthcare sectors were not included because of 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 conclusion, the use of SGLT2is versus DPP4is for real-world patients with T2D regardless of 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 health care resource allocation.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

ZYP designed the study, performed the targeted literature review, analyzed and interpreted the data, and wrote the manuscript. CTY designed the study, performed the targeted literature review, analyzed and interpreted the data, and wrote the manuscript. HTO provided study materials, designed the study, interpreted the data and wrote the manuscript. SK designed the study, interpreted the data and reviewed/edited the manuscript. All authors approved the final manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14708.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available; the effectiveness data at doi: 10.3389/fendo.2022.836365. reference number (21), doi: 10.1111/dom.14240. reference number (26), and

doi: 10.1371/journal.pmed.1003094. reference number (27); the utility data at doi: 10.1111/jdi.13520. reference number (23); and the cost data at doi: 10.2337/dc20-0072. reference number (2).

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SUPPORTING INFORMATION

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