

Use of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients With Type 2 Diabetes and the Incidence of Retinal Vein Occlusion in Taiwan

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PURPOSE. The purpose of this study was to evaluate the risk of newly diagnosed retinal vein occlusion (RVO) in patients with type 2 diabetes (T2D) using sodium-glucose cotransporter-2 inhibitors (SGLT-2i) compared to dipeptidyl peptidase-4 inhibitors (DPP-4i).

METHODS. Claims data from the National Health Insurance Research Database of Taiwan were used in this nationwide retrospective cohort study. A target trial emulation framework was applied. Patients with T2D with no prior diagnosis of RVO who had newly commenced treatment with SGLT-2i or DPP-4i between May 1, 2016, and December 31, 2020, were included. Potential systematic differences in baseline characteristics between the paired groups were controlled using stabilized inverse probability of treatment weighting. The outcome of interest was incident RVO. The hazard ratio (HR) for SGLT-2i compared with that of DPP-4i was estimated using a Cox regression model.

RESULTS. Data from 123,567 and 578,665 patients receiving SGLT-2i and DPP-4i, respectively, were analyzed. The incidence of RVO was lower in patients newly receiving SGLT-2i (0.59 events per 1000 person-years) compared to those receiving DPP-4i (0.77 events per 1000 person-years) over a mean follow-up of 1.61 years. SGLT-2i users had a significantly lower risk of developing RVO compared with DPP-4i users (HR = 0.76, 95% confidence interval [CI] = 0.59–0.98). In the individual outcome analysis, SGLT-2i use was significantly associated with a lower risk of branch RVO (HR = 0.71, 95% CI = 0.52–0.96), but not central RVO (HR = 0.84, 95% CI = 0.57–1.24).

CONCLUSIONS. The risk of developing RVO was lower in patients with T2D receiving SGLT-2i compared with that in those receiving DPP-4i.

Keywords: retinal vein occlusion (RVO), sodium glucose co-transporter 2 inhibitors (SGLT-2i), cohort study

Type 2 diabetes (T2D) is a prominent public health concern affecting approximately 6.3% of the global population.¹ Several ophthalmic diseases, in addition to macro- and micro-vascular complications, have been associated with prolonged hyperglycemia.² Diabetic retinopathy (DR) and retinal vein occlusion (RVO), both being major retinal vascular diseases, may cause vision impairment among patients with T2D. RVO constitutes a significant source of visual morbidity and blindness, particularly among older individuals.^{3,4} RVO has been reported in 3.4% of patients with T2D.⁵ The relative risk of RVO in patients

with T2D has been reported to be 1.76 times higher than that in the healthy cohort in Taiwan after adjusting for age, sex, and potential confounding factors.⁶ Thus, identifying the factors or treatment strategies that elevate or reduce the likelihood of developing RVO in patients with T2D is crucial.

Sodium-glucose cotransporter-2 inhibitor (SGLT-2i) are a relatively novel class of glucose-lowering agents that increase urinary glucose excretion by suppressing renal glucose reabsorption, which leads to a reduction in the blood glucose levels.⁷ SGLT-2i have emerged as



a promising therapeutic choice for patients with T2D, given their protective effects on the renal and cardiovascular systems.⁸ However, SGLT-2i may induce mild diuresis, which can result in volume depletion and elevated blood viscosity, which could elevate the risk of RVO.^{9–11} Moreover, the US Food and Drug Administration (FDA) has flagged the use of SGLT-2i as a potential cause of severe thromboembolic events.¹² However, SGLT-2i also possesses the ability to reduce the systemic levels of proinflammatory cytokines and improve endothelial function, thereby potentially mitigating the risk of RVO.^{13,14}

Although a previous observational study¹⁰ has reported an increased risk of RVO associated with SGLT-2i use among patients with T2D, current evidence regarding this issue is limited. Whether SGLT-2i use increases or decreases the risk of RVO in patients with T2D remains unclear. Therefore, this study aimed to evaluate the risk of developing RVO among patients who recently commenced treatment with SGLT-2i compared with that in those who recently commenced treatment with dipeptidyl peptidase-4 inhibitors (DPP-4i).

METHODS

Data Source and Ethical Approval

This nationwide population-based study was conducted using claims-based data from the National Health Insurance Research Database (NHIRD) of Taiwan. The NHIRD encompasses roughly 23.6 million insured individuals, representing more than 99.6% of the population of Taiwan, and is managed by the National Health Insurance (NHI) Program, a government administered, compulsory, single-payer health program established in 1995.¹⁵ The database contains comprehensive health and medical treatment information for all enrollees, including the demographic characteristics, medical claims, and medication dispensation records. The data used in this study were de-identified prior to being made available for research purposes to protect patient privacy.¹⁶ The procedure and diagnostic codes were based on the International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) until 2016, and the ICD, Tenth Revision, and CM (ICD-10-CM) subsequently. The study protocol was approved by the Research Ethics Committee (REC) of the Hualien Tzu Chi Hospital (REC number: IRB110-170-C). The requirement for obtaining informed consent was waived owing to the anonymization of data via the encryption of the identification numbers provided by the Health and Welfare Data Science Center in Taiwan.

Study Population

A target trial design was used to simulate the conditions of a randomized controlled trial using observational data. Supplementary Table S1 presents the specific methods for emulating this target trial.^{17–19} All patients diagnosed with T2D aged ≥ 20 years who commenced treatment with anti-diabetic medications, specifically SGLT-2i or DPP-4i, between May 1, 2016, and December 31, 2020, were included in this study. The diagnosis of T2D was established based on specific diagnostic codes, particularly, the ICD-9-CM code 250 (except 250.x1 and 250.x3) or the ICD-10-CM codes

E08 to E13 (except E10), applied at least once during an inpatient service or twice during an outpatient service.²⁰ The medications were identified via anatomic therapeutic chemical codes. The patients were categorized into two groups based on the first oral antidiabetic medication they were prescribed: the SGLT-2i and DPP-4i cohorts. The index date for each patient was defined as the date of the first prescription of SGLT-2i or DPP-4i after May 1, 2016, when SGLT-2i were initially approved in Taiwan. Participants with a prior diagnosis of RVO were excluded from the study to ensure that only newly diagnosed cases of RVO were captured during the follow-up period. In addition, individuals who had received DPP-4i before April 30, 2016, were also excluded to ensure that only patients who had newly commenced treatment with DPP-4i were enrolled in the study. The patients prescribed SGLT-2i and DPP-4i simultaneously on the index date were also excluded from the analysis.

Outcome Measures

The primary study outcomes were the diagnosis of new-onset RVO, including central RVO (CRVO; ICD-9-CM code: 362.35; and ICD-10-CM codes: H34.811, H34.812, H34.813, and H34.819) and branch RVO (BRVO; ICD-9-CM code: 362.36; and ICD-10-CM codes: H34.831, H34.832, H34.833, and H34.839) based on the inpatient or outpatient diagnostic codes assigned by ophthalmologists after the index date. A target trial with a per-protocol design was emulated using an on-treatment approach. The follow-up period extended from the index date until the incidence of any of the following events: the onset of RVO; simultaneous use of SGLT-2i and DPP-4i; shift to another medication type; discontinuation of drugs for a period of 3 months; death; and December 31, 2020, which marked the end of the data available from the database, whichever came first. Individual analyses for CRVO and BRVO were also conducted.

Covariates and Confounders

Pre-existing comorbidities, adapted diabetes complication severity index score (aDCSI), and baseline medication use, as presented in Table 1, were selected as potential confounders based on a literature review.^{21,22} Pre-existing comorbidities were defined as medical conditions that had been diagnosed via one hospitalization or 2 outpatient visits in the year preceding the index date, with the diagnostic and procedural codes from ICD-9-CM and ICD-10-CM. Supplementary Table S2 lists the diagnostic codes of the comorbidities. The general comorbidity condition within each group was assessed using the Charlson Comorbidity Index.²³ Medication use at baseline was defined as the prescription of a drug for a duration of at least 30 days within 6 months preceding the index date. The aDCSI, which encompasses a scale of seven diabetes-related complications, was used to determine the severity of diabetes. The aDCSI score increases according to the escalating severity of diabetes.^{24,25}

Subgroup and Stratified Analyses

The SGLT-2i cohort was further subdivided into distinct groups, namely, those receiving dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin. Each of these subgroups,

TABLE 1. Demographic Data of the Study Population After Stabilized Inverse Probability of Treatment Weighting

Characteristic [†]	SGLT-2i (n = 123,567)	DPP-4i (n = 578,665)	SMD [‡]
Mean age (SD), y	60.4 (12.8)	61.0 (13.8)	0.047
Sex, %			
Male	61.3	59.4	0.040
Female	38.7	40.6	0.040
Index year, %			
2016	12.3	12.8	0.015
2017	20.0	20.5	0.011
2018	21.7	21.8	0.001
2019	23.0	22.7	0.006
2020	23.0	22.3	0.017
No. of ophthalmologic outpatient visits, mean (SD)	1.4 (3.1)	1.4 (3.1)	0.002
aDCSI score, mean (SD)	0.8 (1.1)	0.9 (1.2)	0.028
CCI, mean (SD)	2.0 (1.6)	2.0 (1.7)	0.025
Ophthalmologic conditions, %			
Glaucoma	3.1	3.1	0.001
Cataract	8.8	8.8	0.001
Age-related macular degeneration	0.9	0.9	0.001
Diabetic comorbidities, %			
Retinopathy	2.8	2.8	0.001
Neuropathy	3.5	3.5	0.004
Nephropathy	12.0	12.4	0.014
Cardiovascular comorbidities, %			
Hypertension	56.4	57.2	0.016
Atrial fibrillation	0.9	1.0	0.005
Stroke	7.9	8.1	0.008
Heart failure	3.4	3.7	0.014
Coronary artery disease	12.5	12.9	0.009
Peripheral vascular disease	1.5	1.5	0.002
Other comorbidities, %			
COPD	5.1	5.4	0.014
Cirrhosis	1.5	1.5	0.003
Chronic kidney disease	6.8	7.4	0.021
Hyperlipidemia	53.1	52.3	0.015
Obesity	0.0	0.0	0.000
Autoimmune disease	1.8	1.8	0.001
Obstructive sleep apnea	0.2	0.2	0.001
Malignancy	5.8	6.1	0.010
Other baseline diabetes medications use, %			
Alpha-glucosidase inhibitors	7.9	7.5	0.013
Thiazolidinediones	8.6	8.0	0.022
Meglitinides	3.6	3.8	0.007
Biguanides	64.2	63.1	0.024
GLP-1RA	0.2	0.2	0.001
Sulfonylureas	41.5	40.0	0.031
Insulin	6.6	6.4	0.007
Other concomitant drugs, %			
Systemic steroid	2.8	2.9	0.009
Statins	45.4	44.8	0.013
Diuretic	8.9	9.3	0.014
Antiplatelet	23.4	23.7	0.006
Anticoagulants	1.9	1.9	0.002
Hormone replacement therapy	0.6	0.6	0.004

aDCSI, Adapted Diabetes Complications Severity Index; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMD, standardized mean difference.

Data are expressed as percentages unless otherwise indicated.

[†] All covariates listed were used to calculate the propensity score for inverse probability of treatment weighting.

[‡] A standardized mean difference of <0.1 indicates a negligible difference.

representing a specific SGLT-2i, was compared with the DPP-4i cohort to determine the relative effect on the risk of RVO. Stratified analyses were performed according to age, sex, and the presence of hypertension (HTN), hyperlipidemia, or chronic kidney disease (CKD).

Statistical Analyses

A propensity score method known as stabilized inverse probability of treatment weighting (IPTW) was used to address the potential systematic differences between the

baseline characteristics of the paired groups (SGLT-2i versus DPP-4i).²⁶ The disparities in the baseline characteristics were assessed using the standardized mean difference (SMD), with a value of < 0.1 indicating a negligible difference.²⁷ The Kaplan–Meier method was used to determine the cumulative incidence of outcomes. The log rank tests were used to determine the distinctions between cumulative incidence curves. Cox proportional hazard regression models based on stabilized IPTW were used to estimate the hazard ratio (HR) for each outcome. A P value of < 0.05 was considered statistically significant. All statistical analyses and data management were performed using R (version 4.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Sensitivity Analyses

Sensitivity analyses were performed to evaluate the robustness of the findings. First, a multivariable Cox regression model without propensity score methods was used, and the model was adjusted for all covariates listed in Table 1. Second, an as-started design (analog of intention-to-treat) was used as a sensitivity analysis wherein censoring was not performed when patients switched oral anti-glycemic drugs or discontinued the index oral anti-glycemic treatment after 90 days. Last, a sensitivity analysis limited to patients receiving the index oral anti-glycemic (the initially prescribed oral anti-glycemic) with a high medication possession ratio ($\geq 80\%$) during follow-up was performed. The medication possession ratio for each patient was calculated by dividing the days they received oral anti-glycemic agents by their follow-up in days.²⁸

RESULTS

Characteristics of the Study Cohort

A total of 126,032 and 577,979 patients prescribed SGLT-2i and DPP-4i, respectively, were eligible for inclusion. Follow-

ing the application of the stabilized IPTW, a pseudo-population of 123,567 and 578,665 patients receiving SGLT-2i and DPP-4i was formed to compare the risk of RVO between patients receiving SGLT-2i and those receiving DPP-4i. The majority of the baseline characteristics were comparable between the study groups owing to the application of the stabilized IPTW, with an SMD of < 0.1 (see Table 1). Figure 1 illustrates the patient selection process. Supplementary Table S3 presents the demographic data for the study groups before the application of IPTW.

Risk of Developing RVO, CRVO, and BRVO

In the analyses with stabilized IPTW, 108 and 727 patients in the SGLT-2i and DPP-4i cohorts developed RVO, with an incidence rate of 0.59 and 0.77 per 1,000 person-years, respectively (Table 2). The Cox proportional hazard model revealed that the risk of developing RVO was significantly lower among patients receiving SGLT-2i (HR = 0.76, 95% confidence interval [CI] = 0.59–0.98, $P = 0.032$) than among patients receiving DPP-4i. Analyses of individual outcomes revealed that the risk of developing BRVO was significantly lower among patients receiving SGLT-2i (HR = 0.71, 95% CI = 0.52–0.96, $P = 0.024$) than among those receiving DPP-4is. However, the risk of developing CRVO did not differ significantly between the two groups (HR = 0.84, 95% CI = 0.57–1.24, $P = 0.379$). Figure 2 presents the cumulative incidence curves for the SGLT-2i and DPP-4i cohorts.

Risk of Developing RVO in the SGLT-2i Subgroup

Analyses for the SGLT-2i subgroup revealed that the risk of developing RVO was lower in the dapagliflozin subgroup than in the DPP-4i cohort (HR = 0.72, 95% CI = 0.52–0.99, $P = 0.043$); however, the risk of developing RVO did not decrease significantly in the empagliflozin and canagliflozin subgroups (Table 3).

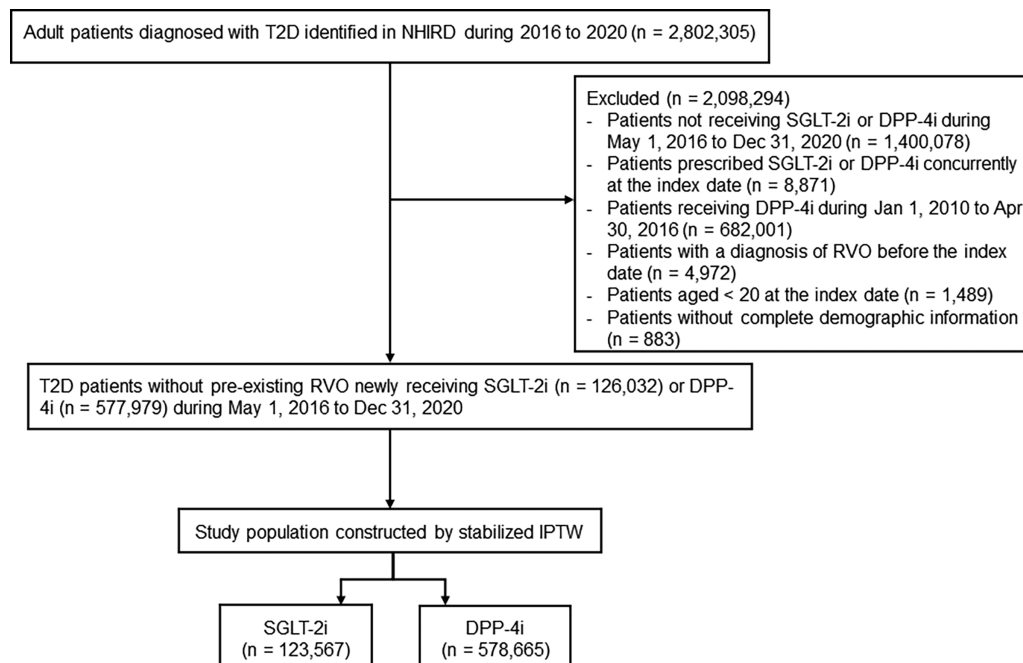


FIGURE 1. Flowchart depicting the patient selection process.

TABLE 2. Risk of Incident RVO, CRVO, and BRVO Among the Patients Receiving SGLT-2i Versus DPP-4i

Comparison/Outcomes	Patients, <i>n</i>	Events, <i>n</i>	Person-Years at Risk	Incidence Rate [†]	HR [‡]	95% CI	<i>P</i> Value
RVO							
SGLT2i cohort	123,567	108	184,209	0.59	0.76	0.59–0.98	0.032
DPP-4i cohort	578,665	727	948,675	0.77	1.00	Reference	
CRVO							
SGLT2i cohort	123,567	53	184,286	0.29	0.84	0.57–1.24	0.379
DPP-4i cohort	578,665	324	949,245	0.34	1.00	Reference	
BRVO							
SGLT2i cohort	123,567	65	184,265	0.35	0.71	0.52–0.96	0.024
DPP-4i cohort	578,665	467	949,055	0.49	1.00	Reference	

BRVO, branch retinal vein occlusion; CI, confidence interval; CRVO, central retinal vein occlusion; DPP-4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; RVO, retinal vein occlusion; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

[†] Per 1000 person-years.

[‡] The hazard ratio was calculated using a univariable Cox regression model considering inverse probability weighting and using the DPP-4i cohort as the reference.

Stratified Analyses According to Age, Sex, HTN, Hyperlipidemia, and CKD

Stratified analyses revealed that the lower risk of developing RVO following the use of SGLT-2i was similar to that observed in the primary analysis; however, certain stratification outcomes did not attain statistical significance (Supplementary Table S4). The decreased risk of incident RVO associated with the use of SGLT-2i remained significant among individuals aged < 60 years (HR = 0.66, 95% CI = 0.47–0.97, *P* = 0.035), individuals with HTN receiving SGLT-2i (HR = 0.72, 95% CI = 0.53–0.98, *P* = 0.038), and individuals with hyperlipidemia (HR = 0.69, 95% CI = 0.50–0.96, *P* = 0.028).

Results of the Sensitivity Analyses

The results of the sensitivity analyses were consistent with those of the primary analyses when a multivariable Cox regression model considering all covariates listed in Table 1 was used and the analysis was restricted to patients with a high medication possession ratio (MPR; Supplementary Table S5). However, with the application of an as-started design, the risk of developing RVO was not significantly lower among patients receiving SGLT-2i than among those receiving DPP-4i.

DISCUSSION

This nationwide cohort study comprising 704,011 patients with T2D revealed that the risk of developing RVO among patients receiving SGLT-2i was 24% lower than that among those receiving DPP-4i. Furthermore, the individual outcome analysis revealed that the use of SGLT-2i was associated with a decreased risk of incident BRVO but not incident CRVO. The subanalyses for different types of SGLT-2i revealed an association between dapagliflozin and reduced risk of developing RVO. The sensitivity analyses using a multivariable Cox regression model and limited to those with a high MPR also supported the findings of the present study findings. Few studies have compared the effect of the use of SGLT-2i and DPP-4i with respect to the risk of developing RVO. Therefore, a large-scale nationwide cohort was conducted to address this knowledge gap.

The exact mechanisms underlying the better outcomes observed in the patients receiving SGLT-2i compared to

those receiving DPP-4i remain unclear; however, several factors may explain these findings. Although both SGLT-2i and DPP-4i exhibit comparable effects on glycemic control, their impacts on cardiometabolic markers differ significantly.²⁹ For instance, the utilization of SGLT-2i may offer advantages to patients presenting with HTN and dyslipidemia, both recognized risk factors for RVO. Prior network meta-analyses of clinical trials³⁰ have illustrated that SGLT-2i demonstrate a superior reduction in systolic blood pressure (SBP) ranging from 2.3 to 5.8 mm Hg compared to DPP-4i. Further corroborating this observation, another real-world study²⁹ found that SGLT-2i were associated with a 1.9 mm Hg greater reduction in SBP compared to DPP-4i among real-world patients. The plausible rationale behind the more pronounced reduction in SBP with SGLT-2i may be attributed to their osmotic diuretic and mild natriuretic effects.³¹ Moreover, one study³² has suggested that specific SGLT-2i, such as dapagliflozin, exhibit the capacity to suppress potent atherogenic small dense low-density lipoprotein cholesterol (sdLDL-C) and elevate high-density lipoprotein subclass 2 cholesterol (HDL2-C), a favorable cardiometabolic marker. Recent clinical investigations³³ have additionally proposed that SGLT-2i (ipragliflozin) may exert an anti-atherogenic effect through the modulation of HDL-C and apolipoprotein E compared to DPP-4i (sitagliptin), altering triglycerides (TGs) and apolipoprotein B48, CII, and CIII levels in patients diagnosed with T2D. Given the aforementioned favorable pleiotropic effects of SGLT-2i, such as greater improvements in SBP and dyslipidemia when compared to DPP-4i, SGLT-2i may have beneficial effect in the development of RVO. Nonetheless, the mechanism through which SGLT-2i influences the development of RVO must be investigated further.

To the best of our knowledge, evidence regarding the association between SGLT-2i and RVO was limited,¹⁰ which revealed an increased risk of developing RVO among patients receiving SGLT-2i compared with that among those receiving glucose-lowering drugs (HR = 1.26, 95% CI = 1.06–1.51), particularly among older patients and those with CKD. Inconsistent with these results, a protective effect of SGLT-2i against RVO was observed in patients with T2D than that in patients receiving DPP-4i in the present study. These discrepancies may be attributed to the differences in the comparators used in the analysis. The study by Lee et al.¹⁰ used glucose-lowering drugs, such as insulin, sulfonylurea, metformin, thiazolidinedione, and DPP-4i, as references. In

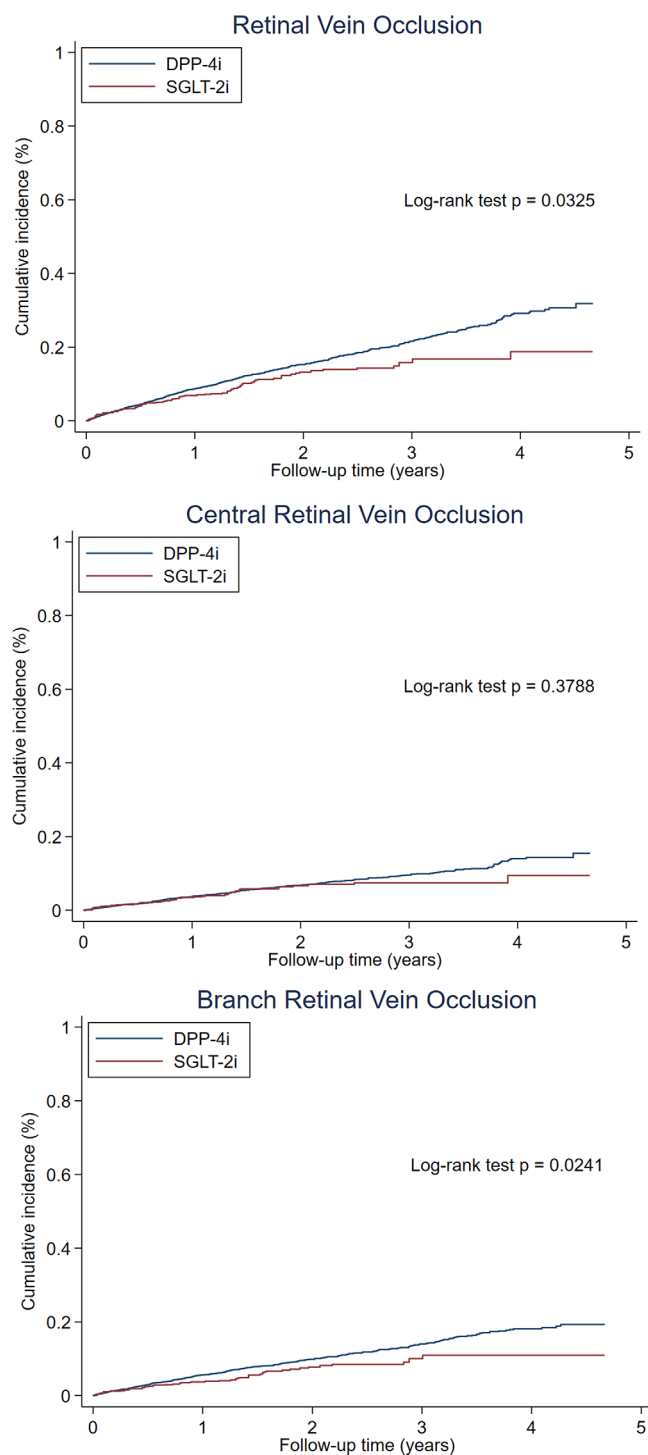


FIGURE 2. The cumulative incidence curves of RVO, CRVO, and BRVO estimated by the cox proportional hazard models for patients receiving SGLT-2i and DPP-4i after stabilized inverse probability of treatment weighting. BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DPP-4i, dipeptidyl peptidase-4 inhibitors; RVO, retinal vein occlusion; SGLT-2i, sodium-glucose co-transporters.

contrast, the present study emulated a target trial design and used only DPP-4i as a reference, as they are prescribed at a similar stage of T2D as SGLT-2i. Moreover, both drugs were prescribed as part of intensified anti-glycemic treatment according to the reimbursement system in Taiwan, ensuring group comparability.

Individual outcome analysis revealed a 29% decrease in the risk of developing BRVO and no significant decrease in the risk of developing CRVO among the patients receiving SGLT-2i. CRVO and BRVO differ in terms of risk factors, pathophysiology, and clinical manifestations.^{34–36} For instance, arteriosclerosis and elevated blood pressure, which are crucial elements in RVO, tend to be more prevalent in cases of BRVO.^{21,36} SGLT-2i may have better pleiotropic effects in reducing blood pressure, body mass index, and blood lipids compared to DPP-4i; thus, their positive impact would be more noticeable in the prevention of BRVO.^{29,30,32,33} However, further studies must be conducted to substantiate this observation.

Stratified analysis revealed that the risk of developing RVO in patients receiving SGLT-2i was significantly lower only in patients aged < 60 years. Older age is a strong factor affecting the development of RVO. Moreover, elderly individuals using SGLT-2i appear to face increased susceptibility to volume depletion, potentially predisposing them to RVO.^{37–40} Consequently, the protective impact of SGLT-2i against RVO incidence might be comparatively modest among older patient cohorts. In the sex-stratified analyses, the trend of a lower risk of RVO associated with SGLT-2i use remains consistent in both male and female subgroups. Although none of them reach statistical significance, further research with larger sample sizes for subgroup/stratified analyses is still needed to confirm this trend. The risk of incident RVO among patients with T2D with concomitant HTN or hyperlipidemia receiving SGLT-2i was significantly lower; however, this association was not observed in individuals without HTN or hyperlipidemia. A recent meta-analysis suggested that 48% of cases of RVO can be attributed to HTN, 20% to hyperlipidemia, and 5% to diabetes.⁴¹ The expected beneficial effect on the development of RVO may be more prominent in patients with T2D with co-existing risk factors owing to the off-target effects of SGLT-2i, particularly their ability to lower blood pressure and lipids.^{29,30,32,33}

A key strength of the present study is the large-scale nationwide analysis conducted using real-world data from routine clinical practice. However, this study has some limitations. First, in observational studies, it is challenging to completely eliminate the possibility of confounding by indication. In addition, the study used an administrative database that lacked granular data on clinical characteristics, such as smoking, lifestyle, physical activity, body mass index, and laboratory results. Although the stabilized IPTW method was used to adjust for several important parameters related to clinical outcomes, bias related to unmeasured confounders may still exist. Second, the ascertainment of RVO was based on ICD codes instead of directly assessing patients. Consequently, some patients with outcomes may not have been identified in the claims database as they did not seek medical assistance. However, under-reporting of outcome events is expected to occur non-differentially in each treatment cohort, thereby biasing the effect estimates toward the null.^{42,43} Therefore, the difference in the risk of developing RVO among the patients receiving SGLT-2i and DPP-4i may be more significant. Third, the use of ertugliflozin was not evaluated due to insufficient patient

TABLE 3. Risk of Incident Retinal Vein Occlusion Among Patients Treated With Individual SGLT-2i Versus DPP-4i

Comparison/Outcomes	Patients, <i>n</i>	Events, <i>n</i>	Person-Years at Risk	Incidence Rate [†]	HR [‡]	95% CI	<i>P</i> Value
Dapagliflozin versus DPP-4i							
Dapagliflozin cohort	67,299	57	101,466	0.56	0.72	0.52–0.99	0.043
DPP-4i cohort	578,237	743	963,495	0.77	1.00	Reference	
Empagliflozin versus DPP-4i							
Empagliflozin cohort	46,679	45	70,469	0.64	0.82	0.53–1.24	0.344
DPP-4i cohort	578,108	750	967,390	0.78	1.00	Reference	
Canagliflozin versus DPP-4i							
Canagliflozin cohort	5,792	6	6,180	0.98	1.18	0.39–3.56	0.775
DPP-4i cohort	577,993	758	971,464	0.78	1.00	Reference	

CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitors.

[†] Per 1000 person-years.

[‡] The hazard ratio was calculated using a univariable Cox regression model considering inverse probability weighting and using the DPP-4i cohort as the reference.

numbers, and its unavailability in the NHI program of Taiwan until 2019. Furthermore, the risk of incident RVO in the empagliflozin and canagliflozin subgroups was not significantly reduced than that in the DPP-4i cohort. Therefore, these findings should be interpreted with caution, given that the implementation of stratification leads to a diminished sample size and concomitant limitations in statistical robustness. Last, a significantly lower risk of developing RVO was not observed among the patients receiving SGLT-2i in the as-started design analysis. Patients in real-world practice may discontinue or not adhere to SGLT-2i treatment; thus, the misclassified cases in the cohort may bias the results to null.

In conclusion, this population-based cohort study demonstrated a reduced risk of developing RVO in patients with T2D receiving SGLT-2i compared with that in those receiving DPP-4i, especially those aged < 65 years or those with concomitant HTN or hyperlipidemia. Individual outcome analyses indicated that compared with DPP-4i, SGLT-2i might protect against the incidence of BRVO. Nonetheless, further studies must be conducted to establish the causality of these findings and elucidate the underlying mechanisms.

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