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Risk of Retinal Vein Occlusion between Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes

A Retrospective Cohort Study

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Objective: To evaluate whether glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reduced retinal vein occlusion (RVO) risk compared with dipeptidyl peptidase-4 (DPP-4) inhibitors in patients with type 2 diabetes mellitus (T2DM).

Design: A multinational, retrospective cohort study.

Participants: Adults with T2DM newly prescribed GLP-1RAs or DPP-4 inhibitors between 2006 and 2023 were included in our analysis.

Methods: This study leveraged data from populations across 21 countries. Propensity score matching at a 1:1 ratio balanced age, sex, race, glycated hemoglobin (HbA1c), body mass index (BMI), estimated glomerular filtration rate, medications, and comorbidities between GLP-1RA and DPP4 inhibitor users.

Main Outcomes Measures: We observed the occurrence of incident RVO and branch RVO (BRVO) in the overall population and in subpopulations stratified by age, sex, race, GLP-1RA type, baseline HbA1c, BMI, and diabetes duration.

Results: Among 79 486 matched participants, GLP-1RA use is associated with a lower risk of RVO (hazard ratio [HR], 0.73; 95% confidence interval [CI], 0.54–0.98) and BRVO (HR, 0.62; 95% CI, 0.41–0.95) over 5 years compared with DPP-4 inhibitor use. This association is consistent among patients aged ≥50 years, Blacks, those prescribed human-analog GLP-1RAs, and those with baseline HbA1c ≥8%, BMI ≥30 kg/m^2, and diabetes duration ≥3 years.

Conclusions: Glucagon-like peptide-1 receptor agonist use was linked to reduced RVO and BRVO risks in patients with T2DM when compared with DPP-4 inhibitor use, particularly in high-risk populations, suggesting potential benefits of GLP-1RAs over DPP-4 inhibitors in managing ocular complications in T2DM.

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Retinal vein occlusion (RVO) is the second most prevalent retinal vascular disorder after diabetic retinopathy and is a leading cause of vision loss globally.[1,2] Retinal vein occlusion can be categorized into central RVO (CRVO) and branch RVO (BRVO) based on the location of the occlusion, with BRVO being more prevalent.[3] Risk factors for RVO generally overlap with those for other vascular occlusions, such as older age, hypertension, and type 2 diabetes mellitus (T2DM).[1,4]

In patients with T2DM, the function of incretin hormones in regulating glucose homeostasis is markedly impaired or absent.[5] Incretin-based therapies, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, address this deficiency by stimulating glucagon-like peptide-1 (GLP-1) receptors and enhancing insulin secretion. Both GLP-1RAs and DPP-4 inhibitors have been introduced for a decade and have become the fundamental treatment options for T2DM.[6,7] Although GLP-1RAs and DPP-4 inhibitors manage T2DM through similar mechanisms, they differ in their delivery routes, dosing frequency, pleiotropic effects, and adverse event profiles.[7,8] Glucagon-like peptide-1 receptor agonists have demonstrated efficacy in reducing the risk of stroke, myocardial infarction, diabetic retinopathy, and glaucoma

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among patients with T2DM.[9–12] A post hoc analysis of the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN) 6 and the trial investigating Peptide Innovation for Early Diabetes Treatment (PIONEER) 6 suggested that GLP-1RAs reduced the incidence of small vessel occlusions, likely through reducing inflammation, vascular smooth muscle proliferation, oxidative stress, and increasing microvascular blood flow.[13] Dipeptidyl peptidase-4 inhibitors, though lacking clear cardiovascular benefits, are characterized by their neutral effect on weight, convenient oral dosing, good tolerability, and low risk of hypoglycemia.[14] Given that previous studies have suggested a reduced risk of vascular occlusions with GLP-1RAs, we hypothesized that GLP-1RAs may reduce the risk of RVO compared with DPP-4 inhibitors. However, the current literature lacks head-to-head comparisons of GLP-1RAs and DPP-4 inhibitors on ocular microvascular complications, specifically RVO, in patients with T2DM.[11,12]

To address this knowledge gap, we conducted a cohort study using electronic medical records from a large, multinational population spanning 21 countries that compares the impact of GLP-1RAs and DPP-4 inhibitors on the risk of RVO in patients with T2DM. Given the differing pleiotropic effects and adverse profiles of GLP-1RAs and DPP-4 inhibitors, selecting the most appropriate treatment for each patient requires consideration of numerous factors. Our study aims to provide evidence that assists clinical practitioners in optimizing treatment strategies for patients with T2DM.

Methods

Data Source

This retrospective cohort study analyzed deidentified electronic medical records from the Global Collaborative Network within the TriNetX platform, which contains data on >200 million patients from 160 health care organizations across 21 countries.[15] TriNetX provides extensive patient data, including demographic information, diagnoses, treatments, laboratory results, and genomic information. Data analyses were conducted within the platform, and results were exported for further evaluation. To protect patient privacy, the exact numbers for outcomes occurring in ≤10 patients were not disclosed. Hazard ratios (HRs) and 95% confidence intervals (CIs) could not be calculated when there are 0 events in 1 or both groups. TriNetX complies with US Health Insurance Portability and Accountability Act guidelines, ensuring secure management of health care data.

Study Population

The study included patients with T2DM who received prescriptions of GLP-1RAs or DPP-4 inhibitors between 2006 and 2023 for the first time. Given that the first GLP-1RA (exenatide) was approved by the US Food and Drug Administration in 2005 and the first DPP-4 inhibitor (sitagliptin) in 2006, study enrollment began in 2006 to mitigate disparities in follow-up durations.

The inclusion criteria for the participants were as follows: (1) patients aged ≥18 years; (2) patients coded with a diagnosis of T2DM (International Classification of Diseases 10, Clinical Modification code: E11) before the index date; (3) patients who were prescribed with GLP-1RAs or DPP-4 inhibitors for the first time between 2006 and 2023; (4) individuals who had either a refill or an ongoing prescription for the medication between 3 and 12 months after the initial prescription; and (5) individuals with available data on glycated hemoglobin (HbA1c), body mass index (BMI), and estimated glomerular filtration rate (eGFR) within 1 year before the index date. This approach was done to ensure that these data reflect the updated condition of each participant, which enables accurate propensity score matching at baseline. Value of eGFR was computed based on the Chronic Kidney Disease Epidemiology Collaboration equation.

The exclusion criteria were as follows: (1) patients coded with a diagnosis of any retinal vascular disease (e.g., RVO, BRVO, CRVO, or retinal artery occlusion) before the index date, (2) patients in the GLP-1RA group who are concurrently prescribed with DPP-4 inhibitors during the study period, and (3) patients in the DPP-4 inhibitor group who are concurrently prescribed with GLP-1RAs within the study period.

Outcome Measures

The outcomes evaluated in this study were incident RVO, BRVO, and CRVO. The index event was defined as the initiation of GLP-1RA or DPP-4 inhibitor therapy. Patients were followed for up to 5 years, until the outcome event, or until the study period's end, whichever occurred first.

Statistical Analysis

Participants prescribed with GLP-1RAs and DPP-4 inhibitors were propensity score matched in a 1:1 ratio using greedy nearest neighbor matching algorithm with a caliper of 0.1 pooled standard deviations (SDs). A standardized mean difference of <0.1 reflects a small difference between groups, indicating a well-balanced comparison. Baseline covariates, including age, sex (female), race (White, Black, and Asian), smoking history, laboratory values (HbA1c, BMI, and eGFR), medications (lipid-lowering medications, metformin, sulfonylureas, thiazolidinediones, sodium–glucose cotransporter-2 inhibitors, insulin, contraceptives, warfarin, aspirin, and direct factor Xa inhibitors), and comorbidities (hypertension, ischemic heart disease, cerebral infarction, heart failure, atrial fibrillation and flutter, neoplasm, dyslipidemia, end-stage renal disease, obstructive sleep apnea, chronic obstructive pulmonary disease, coagulation disorder, and open-angle glaucoma) were used for matching. Matching was restricted to medications and diagnoses coded within 1 year before the index date to ensure they reflected each patient's most recent clinical condition. When multiple laboratory values were recorded within that year, the most recent data were used for propensity score matching. The *International Classification of Diseases, 10th Revision, Clinical Modification*, Anatomical Therapeutic Chemical Classification, and additional codes for determining prescriptions and diagnoses are detailed in Table S1 (available at www.ophthalmologyscience.org).

Analyses were conducted in October 2024 to evaluate the risk of outcome development across different follow-up durations and stratifications. Follow-up periods included 1, 2, 3, 4, and 5 years. In the 5-year follow-up analysis, participants were further stratified by age (<50 and ≥50 years), sex (female and male), race (White, Black, and Asian), type of GLP-1RA used (human-analog and exendin-based GLP-1RAs), baseline HbA1c (<8% and ≥8%), baseline BMI (<30 and ≥30 kg/m^2), and T2DM duration (<3 and ≥3 years) to assess potential outcome variabilities across different patient characteristics. A 50-year cutoff was chosen for stratification because studies have shown a significantly higher incidence of RVO among individuals older than 50 years.[4,16] The cutoff values

for baseline HbA1c, BMI, and diabetes duration were adapted from previous publications.[17–19] For GLP-1RA type-specific analysis, human-analog GLP-1RAs (e.g., semaglutide, liraglutide, dulaglutide, and albiglutide) were defined as those derived from modified native GLP-1, whereas exendin-based GLP-1RAs (e.g., exenatide and lixisenatide) were those derived from exendin-4.[20,21] Diabetes duration was defined as the interval from the first coded T2DM diagnosis to the index date.

We applied Cox regression models to estimate HRs and 95% CIs. Kaplan–Meier analysis assessed event-free survival probabilities for outcomes over the 5-year follow-up period. The TriNetX provides data analysis functions directly through an online platform. Statistical outputs were generated using Apache Commons Math v3.6.1 in Java (v11.0.16; Oracle Corporation); the Hmisc v1.1 and Survival v3.2-3 packages in R (v4.0.2; R Core Team 2024); lifelines v0.22.4, matplotlib v3.5.1, numpy v1.21.5, pandas v1.3.5, scipy v1.7.3, and statsmodels v0.13.2 in Python (v3.7; Python Software Foundation). Further details regarding the underlying technology are proprietary and protected by TriNetX's trade secrets. Participants with outcomes occurring before the index date were excluded from the final analysis.

Patients are censored in Kaplan–Meier analyses when they no longer contribute to additional data, such as after the last clinical event recorded within the time window of the analysis. Mortality is not considered a censoring event if it occurs during the observation period. The data on the TriNetX platform directly reflect how information is recorded, and TriNetX generally does not impute or estimate missing clinical values in patients' medical records. However, there are 2 exceptions: (1) an encounter date is assigned for each clinical or laboratory observation and (2) an eGFR is calculated for every reported serum, plasma, or blood creatinine value, provided that the patient's sex as well as age (for adults aged $\geq$18 years) or height (for individuals $<$18 years of age) is available. The TriNetX platform lacks a feature to directly calculate the proportion of participants lost to follow-up during the study observation period.

Our study protocol for retrospective data collection through the TriNetX Analytics Network was approved by the Institutional Review Board of Taichung Veterans General Hospital under the registration number CE24430C. Informed consent was not obtained because TriNetX, as a federated network that only processes deidentified patient information, received a waiver from the Western Institutional Review Board. The authors confirm that all procedures in this study comply with the Declaration of Helsinki. Our study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology statements for cohort studies (Table S2, available at www.ophthalmologyscience.org).

Sensitivity Analysis

We conducted several sensitivity analyses on January 2025 to further strengthen our findings. Given that microvascular retinopathy is a shared pathogenic mechanism between RVO and diabetic retinopathy, diabetic retinopathy could influence the results and act as a potential confounder in assessing the risk of developing RVO. Therefore, we incorporated the presence and severity of diabetic retinopathy (mild, moderate, severe nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy) as a covariate in the propensity score matching process. To address the possibility of unrecorded outcomes among participants with insufficient follow-up periods, we also conducted a sensitivity analysis by including only patients with a minimum follow-up duration of 1 year. Additionally, we performed a sensitivity analysis among the subpopulation of those who had documented ophthalmic examinations during the study period. This approach was intended to ensure that all participants had been examined by ophthalmologists, thereby reducing the risk of disease misclassification.

Results

After propensity score matching, the final analysis includes 39 743 participants prescribed with GLP-1RAs and 39 743 participants prescribed with DPP-4 inhibitors. The study flowchart is illustrated in Figure 1. The mean ages are similar between groups, with the GLP-1RA group averaging 62.2 years (SD, 11.7) and the DPP-4 inhibitor group averaging 62.2 years (SD, 12.5). The mean follow-up duration (SD) is 984.30 (550.83) days for the GLP-1RA group and 1334.64 (579.61) days for the DPP-4 inhibitor group. Baseline characteristics, including demographics, laboratory measurements, medication use, and comorbidities, are well-balanced between the GLP-1RA and DPP-4 inhibitor groups with all standardized mean difference values $<$0.1 (Table 3). The study design and results are illustrated in the graphical abstract within the supplementary appendix (Fig S2, available at www.ophthalmologyscience.org).

Risk of RVO over Specified Follow-up Intervals

Participants were followed for up to 5 years to assess the risk of incident RVO, BRVO, and CRVO. Compared with patients prescribed DPP-4 inhibitors, those on GLP-1RAs demonstrate a significantly reduced risk of RVO at 1-year (HR, 0.59; 95% CI, 0.36–0.98), 2-year (HR, 0.66; 95% CI, 0.45–0.97), 3-year (HR, 0.65; 95% CI, 0.47–0.91), 4-year (HR, 0.71; 95% CI, 0.52–0.97), and 5-year (HR, 0.73; 95% CI, 0.54–0.98) follow-up periods. For BRVO, the GLP-1RA group shows significantly lower risk than the DPP-4 inhibitor group in 3 years (HR, 0.61; 95% CI, 0.38–0.98), 4 years (HR, 0.61; 95% CI, 0.39–0.95), and 5 years (HR, 0.62; 95% CI, 0.41–0.95) of follow-up (Fig 3). No statistically significant differences are observed between the GLP-1RA and DPP-4 inhibitor groups in the risk of CRVO across all follow-up periods (Fig S4, available at www.ophthalmologyscience.org).

Kaplan–Meier Survival Analysis

The Kaplan–Meier survival analysis over a 5-year period indicates that GLP-1RA users have a significantly higher event-free survival probability for RVO and BRVO compared with DPP-4 inhibitor users. For RVO, the 5-year survival probability is 99.66% (95% CI, 99.56%–99.74%) in the GLP-1RA group and 99.57% (95% CI, 99.49%–99.64%) in the DPP-4 inhibitor group, with a log-rank P value of 0.0332 (Fig 5A). For BRVO, the 5-year survival probability is 99.85% (95% CI, 99.77%–99.90%) for GLP-1RA users and 99.77% (95% CI, 99.71%–99.82%) for DPP-4 inhibitor users, with a log-rank P value of 0.0276 (Fig 5B).

Stratified Analyses by Patient Characteristics

To further understand the differential effects of GLP-1RAs compared with DPP-4 inhibitors, stratified analyses were

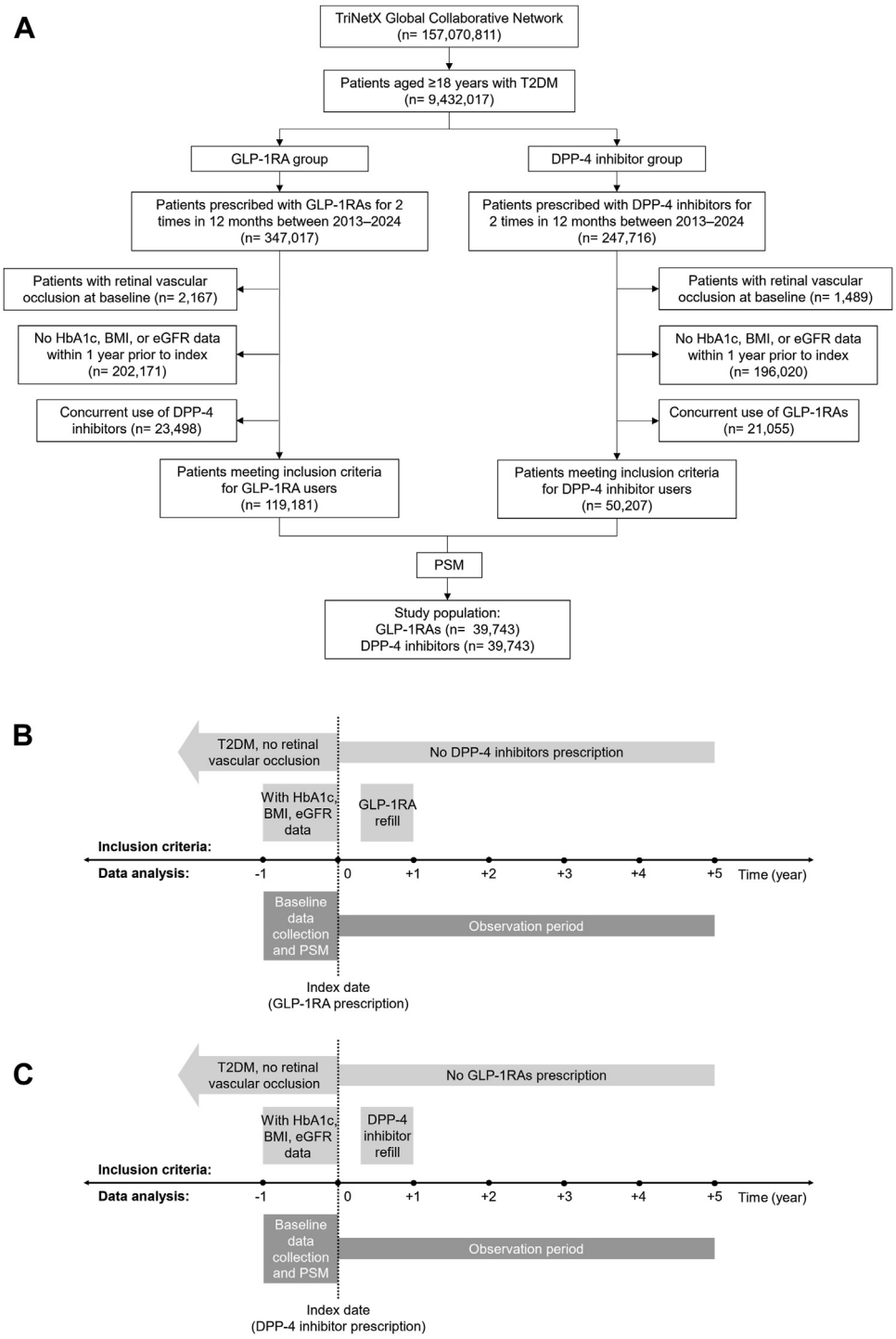

Figure 1. Study flowchart and timeline. **A,** The study flowchart illustrates the selection process. **B,** The study timeline shows the patient selection process for the GLP-1RA group. **C,** The study timeline shows the patient selection process for the DPP-4 inhibitor group. Participants with an index event occurring between January 2006 and December 2023 were eligible for inclusion. BMI = body mass index; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; PSM = propensity score matching; T2DM = type 2 diabetes mellitus.

conducted across participants of different demographics. The baseline characteristics for each stratification are well-balanced and presented in Table S4 (available at www.ophthalmologyscience.org). The reduced RVO risk associated with GLP-1RAs is statistically significant among participants aged ≥50 years (HR, 0.63; 95% CI,

Table 3. Baseline Characteristics of Study Population

	Before PSM			After PSM		
	GLP-1RAs	*DPP-4 inhibitors*	*SMD*	*GLP-1RAs*	*DPP-4 inhibitors*	*SMD*
Total number	119 181	50 207		39 743	39 743	
Age (yrs), mean (SD)	57.4 (12.4)	64.2 (12.8)	0.537	62.2 (11.7)	62.2 (12.5)	0.002
Female, n (%)	65 565 (55.0)	24 279 (48.4)	0.133	19 555 (49.2)	19 761 (49.7)	0.010
Race, n (%)						
White	77 893 (65.4)	29 111 (58.0)	0.152	24 929 (62.7)	25 044 (63.0)	0.006
Black	25 178 (21.1)	8 707 (17.3)	0.096	7426 (18.7)	7494 (18.9)	0.004
Asian	6456 (5.4)	9066 (18.1)	0.401	4563 (11.5)	4322 (10.9)	0.019
Smoking, n (%)	5809 (4.9)	1641 (3.3)	0.081	1488 (3.7)	1463 (3.7)	0.003
Laboratory parameters, mean (SD)						
HbA1c (%)	8.2 (2.1)	8.0 (2.0)	0.105	8.1 (2.0)	8.1 (2.0)	0.015
BMI (kg/m^2)	36.6 (8.1)	31.2 (7.4)	0.695	33.4 (7.4)	32.7 (7.3)	0.096
eGFR (ml/min/1.73 m^2)	82.3 (25.6)	72.9 (27.5)	0.355	76.2 (25.7)	75.6 (27.1)	0.020
Medications, n (%)						
Lipid-lowering agents	72 013 (60.4)	31 153 (62.0)	0.033	24 758 (62.3)	24 612 (61.9)	0.008
Metformin	69 639 (58.4)	27 444 (54.7)	0.076	22 461 (56.5)	22 276 (56.1)	0.009
Sulfonylureas	26 528 (22.3)	16 058 (32.0)	0.220	12 043 (30.3)	11 755 (29.6)	0.016
Thiazolidinediones	4986 (4.2)	3371 (6.7)	0.112	2479 (6.2)	2407 (6.1)	0.008
SGLT2 inhibitors	20 307 (17.0)	3427 (6.8)	0.319	3679 (9.3)	3283 (8.3)	0.035
Insulin	47 514 (39.9)	15 897 (31.7)	0.172	13 171 (33.1)	13 025 (32.8)	0.008
Contraceptives	3573 (3.0)	1237 (2.5)	0.033	946 (2.4)	900 (2.3)	0.008
Warfarin	2922 (2.5)	2310 (4.6)	0.117	1434 (3.6)	1445 (3.6)	0.001
Aspirin	24 345 (20.4)	13 017 (25.9)	0.131	9790 (24.6)	9738 (24.5)	0.003
Factor Xa inhibitors	6443 (5.4)	2278 (4.5)	0.040	1883 (4.7)	1821 (4.6)	0.007
Comorbidities, n (%)						
Hypertension	86 065 (72.2)	37 493 (74.7)	0.056	29 663 (74.6)	29 671 (74.7)	<0.001
IHD	20 860 (17.5)	11 524 (23.0)	0.136	8359 (21.0)	8279 (20.8)	0.005
Cerebral infarction	4197 (3.5)	2567 (5.1)	0.078	1783 (4.5)	1760 (4.4)	0.003
Heart failure	11 392 (9.6)	6124 (12.2)	0.085	4279 (10.8)	4299 (10.8)	0.002
Atrial fibrillation	7877 (6.6)	4797 (9.6)	0.108	3235 (8.1)	3227 (8.1)	0.001
Neoplasm	23 170 (19.4)	10 668 (21.2)	0.045	8106 (20.4)	8074 (20.3)	0.002
Dyslipidemia	82 961 (69.6)	36 161 (72.0)	0.053	28 922 (72.8)	28 830 (72.5)	0.005
ESRD	2956 (2.5)	2391 (4.8)	0.122	1587 (4.0)	1572 (4.0)	0.002
OSA	25 348 (21.3)	5123 (10.2)	0.307	5000 (12.6)	4864 (12.2)	0.010
COPD	7463 (6.3)	4092 (8.2)	0.073	2998 (7.5)	2988 (7.5)	0.001
Coagulation defect	5038 (4.2)	2585 (5.1)	0.044	1864 (4.7)	1867 (4.7)	<0.001
Open-angle glaucoma	1141 (1.0)	643 (1.3)	0.031	501 (1.3)	480 (1.2)	0.005

BMI = body mass index; COPD = chronic obstructive pulmonary disease; DPP-4 = dipeptidyl peptidase 4; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated hemoglobin; IHD = ischemic heart disease; OSA = obstructive sleep apnea; PSM = propensity score matching; SD = standard deviation; SGLT2 = sodium–glucose cotransporter-2; SMD = standardized mean difference.

0.47–0.86), females (HR, 0.62; 95% CI, 0.40–0.96), Blacks (HR, 0.49; 95% CI, 0.26–0.94), Asians (HR, 0.27; 95% CI, 0.08–0.96), individuals prescribed human-analog GLP-1RAs (HR, 0.73; 95% CI, 0.54–0.99), and those with baseline HbA1c ≥8% (HR, 0.58; 95% CI, 0.38–0.87), BMI ≥30 kg/m^2 (HR, 0.61; 95% CI, 0.42–0.89), and diabetes duration ≥3 years (HR, 0.65; 95% CI, 0.43–0.98) compared with DPP-4 inhibitors. For BRVO, GLP-1RAs are associated with a significantly lower risk in individuals aged ≥50 years (HR, 0.59; 95% CI, 0.39–0.90), Blacks (HR, 0.19; 95% CI, 0.06–0.63), human-analog GLP-1RA recipients (HR, 0.55; 95% CI, 0.35–0.86), and participants with baseline HbA1c ≥8% (HR, 0.54; 95% CI, 0.30–0.96), BMI ≥30 kg/m^2 (HR, 0.48; 95% CI, 0.27–0.85), and diabetes duration ≥3 years (HR, 0.45; 95% CI, 0.24–0.84) compared with DPP-4 inhibitors. Results for each stratified analysis are presented in Figure 6.

Sensitivity Analysis

We performed several sensitivity analyses with the baseline characteristics of these analyses provided in Table S5 (available at www.ophthalmologyscience.org). After adding diabetic retinopathy into our propensity score matching process, the risk of developing RVO (HR, 0.71; 95% CI, 0.53–0.95), BRVO (HR, 0.61; 95% CI, 0.41–0.93), and CRVO (HR, 0.84; 95% CI, 0.57–1.24) within 5 years are consistent with that of the main analysis (Fig S7A, available at www.ophthalmologyscience.org).

Among patients with a follow-up duration of at least 1 year, the 5-year risks of developing RVO (HR, 0.72; 95% CI, 0.54–0.95), BRVO (HR, 0.67; 95% CI, 0.45–0.99), and CRVO (HR, 0.72; 95% CI, 0.48–1.06) are consistent with the findings from the main analysis (Fig S7B).

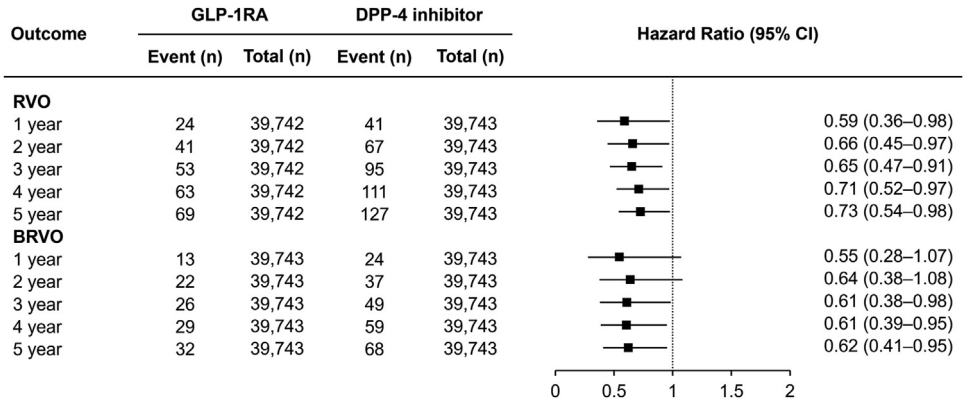

Figure 3. The forest plot depicts the comparative associations of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors with the risk of incident retinal vein occlusion (RVO) and branch RVO (BRVO) across 1 to 5 years. A lower hazard ratio indicates a reduced risk of the outcome with GLP-1RA users compared with DPP-4 inhibitor users. CI = confidence interval.

Among the subpopulation with documented ophthalmic examinations during the study period, the findings remain consistent with those of the main analysis. Compared with participants prescribed with DPP-4 inhibitors, those on GLP-1RAs are associated with a significantly reduced risk of developing RVO and BRVO among those who had visited ophthalmologists for once (RVO: HR, 0.57; 95% CI, 0.40−0.83; BRVO: HR, 0.52; 95% CI, 0.32−0.85), 3 times (RVO: HR, 0.58; 95% CI, 0.39−0.86; BRVO: HR, 0.53; 95% CI, 0.32−0.88), or 5 times (RVO: HR, 0.59; 95% CI, 0.39−0.89; BRVO: HR, 0.54; 95% CI, 0.31−0.92). The results are outlined in Figure S7C.

Discussion

Our study demonstrates that compared with DPP-4 inhibitors, GLP-1RAs are associated with a significantly lower risk of developing RVO, including its subtype BRVO, in patients with T2DM. These results are consistent across several sensitivity analyses. Notably, the association between GLP-1RAs and reduced RVO and BRVO risk when compared with DPP-4 inhibitors remains consistent in participants aged ≥50 years, Blacks, those prescribed human-analog GLP-1RAs, and those with baseline HbA1c ≥8%, BMI ≥30 kg/m^2, and diabetes duration ≥3 years.

Cardiovascular Protective Effects of GLP-1RAs Compared with DPP-4 Inhibitors

GLP-1RAs, widely recognized for their cardiovascular benefits, are commonly used second-line glucose-lowering medications that offer vascular protective effects, especially in older adults with T2DM.[9,22–25] Dipeptidyl peptidase-4 inhibitors, on the other hand, have not shown clear evidence of cardiovascular benefits.[26] A study in Italy found that rates of myocardial infarction and all-cause mortality were lower among GLP-1RA users compared with those using DPP-4 inhibitors.[27] In fact, some studies suggested that DPP-4 inhibitors may increase the risk of heart failure, potentially through the activation of stromal cell−derived factor 1, neuropeptide Y, and substance P, which stimulate the sympathetic nervous system, enhance β-receptor signaling, and lead to cardiomyocyte cell death.[28] Additionally, some

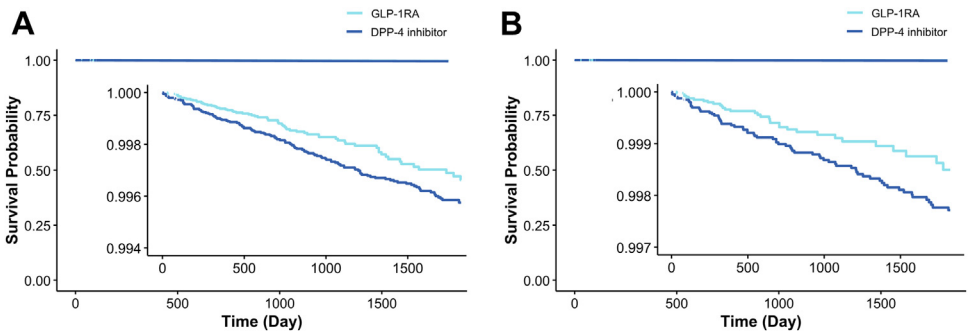

Figure 5. The Kaplan−Meier survival plot illustrates the 5-year event-free survival probability for (**A**) RVO and (**B**) BRVO in patients prescribed with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors. A zoomed-in view is provided in the lower right corner of each figure. The light blue line represents patients prescribed with GLP-1RAs, whereas the dark blue line represents those on DPP-4 inhibitors. BRVO = branch retinal vein occlusion; RVO = retinal vein occlusion.

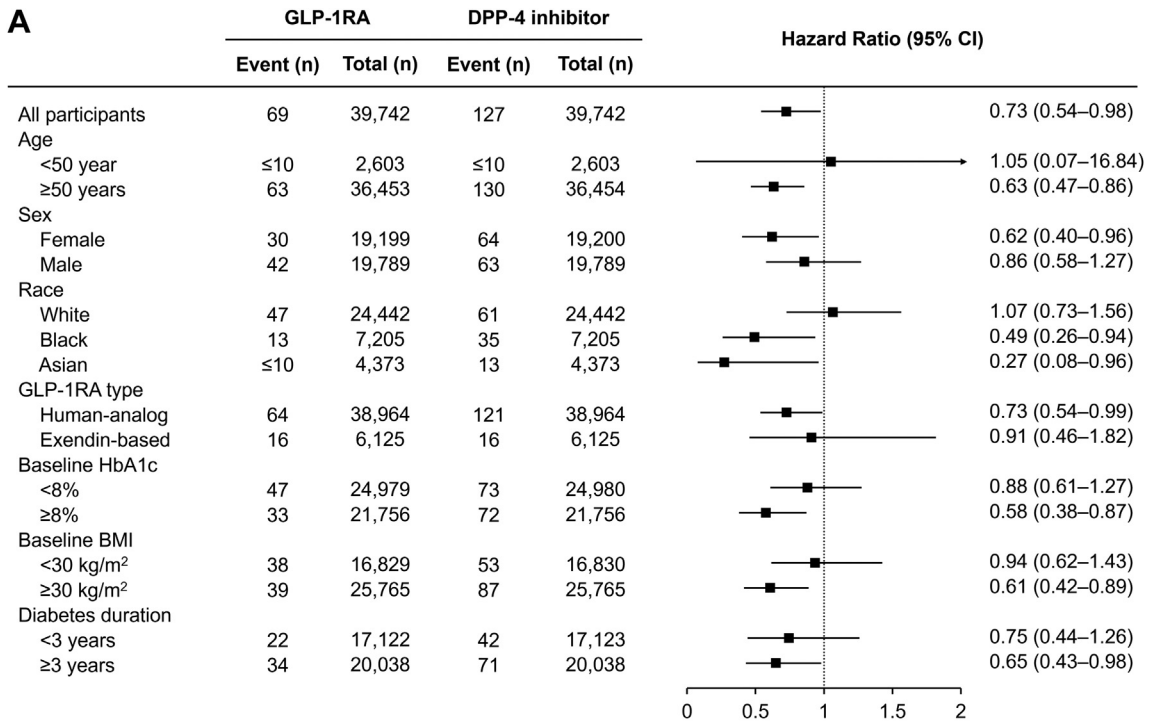

Figure 6. The forest plots illustrates the associations between glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase 4 (DPP-4) inhibitors on (**A**) retinal vein occlusion (RVO) and (**B**) branch RVO (BRVO), stratified by age, sex, race, GLP-1RA type, baseline glycated hemoglobin (HbA1c), body mass index (BMI), and diabetes duration. For privacy, the TriNetX platform conceals exact event numbers for groups with 10 or fewer events. CI = confidence interval; N/A = not applicable.

randomized controlled trials[29,30] have demonstrated that GLP-1RAs led to greater reductions in HbA1c and body weight than DPP-4 inhibitors. These effects may indirectly influence the risks of vascular occlusion because poor glycemic control and obesity are both established risk factors for atherosclerotic diseases.[31]

The cardiovascular benefits of GLP-1RAs may stem from reduced atherosclerosis, improved blood flow, and enhanced cardiac cell protection as proposed by animal studies. A mouse study showed that GLP-1RAs reduced atherosclerotic lesions by suppressing macrophage infiltration, foam cell formation, and smooth muscle proliferation within the aortic wall.[32] In addition, GLP-1RAs have also been shown to enhance vascular blood flow through nitric oxide-mediated cyclic guanosine monophosphate release, resulting in increased coronary perfusion, dilated mesenteric artery, and enhanced microvascular volume.[33,34] Moreover, studies have shown that GLP-1RAs enhance cardiac cell survival, reduce infarct size, improve ventricular function, and decrease oxidative stress,[35] which may be attributed to both GLP-1 receptor activation in cardiac atrial and endothelial cells, as well as receptor-independent actions from GLP-1 metabolites.[33]

Retinal Microvascular Benefits of GLP-1RAs Compared with DPP-4 Inhibitors

Based on the aforementioned animal studies demonstrating an association between GLP-1RAs and endothelial function, there may be a potential link between GLP-1RAs and retinal microcirculation. In studies using retinal models from rats, GLP-1 receptors were identified in the endothelial cells of retinal capillaries through immunofluorescence staining.[36,37] In a study that collected blocked retinal capillaries from rats with ischemia–reperfusion injuries, the authors observed that administering GLP-1RAs could reverse these injuries by relaxing contracted pericytes and dilating the narrowed capillaries. They proposed that this effect could be attributed to the GLP-1 receptor-activated nitric oxide-cyclic guanosine monophosphate pathway, which induces vasodilation.[36] Another mouse study observed a downregulation of GLP-1 receptor expression in retinal endothelial cells under diabetic status, which was restored after GLP-1RA treatment. The restoration of GLP-1 receptor expression led to improvements in retinal degeneration and vascular integrity in diabetic mice, potentially through the protection of endothelial junctions via inhibition of the stimulator of interferon gene signaling.[37] Therefore, GLP-1RAs may reduce the risk of retinal vascular occlusion through retinal endothelial cell protection, aligning with our findings that suggest a reduced risk of RVO in patients prescribed with GLP-1RAs compared with DPP-4 inhibitors. Further research is required to explore why GLP-1RAs are associated with a reduced risk of RVO compared with DPP-4 inhibitors.[38]

Our findings indicate that the effect of GLP-1RAs in reducing RVO compared with DPP-4 inhibitors may largely stem from a reduced risk of BRVO but not CRVO. This distinction could be attributed to differences in the pathophysiology between BRVO and CRVO. Branch RVO is primarily associated with the compression of a branch retinal vein by the atherosclerosis of a neighboring retinal artery, typically at an arteriovenous crossing. In contrast, CRVO results from thrombus composed of fibrin and platelets blocking the central retinal vein, usually forming at a point posterior to or within the lamina cribrosa.[39–41] Given that GLP-1RAs could reduce atherosclerosis[32] and BRVO is more closely associated with arteriosclerotic changes,[39,40,42] it is plausible that GLP-1RAs may provide greater risk reduction for BRVO than for CRVO.

Insights from Stratified Analyses

The stratified analysis reveals that the reduced RVO risk associated with GLP-1RA compared with DPP-4 inhibitors remains statistically significant in participants aged $\geq$50 years, females, Blacks, Asians, and in those with HbA1c $\geq$8%, BMI $\geq$30 kg/m^2, and diabetes diagnosis for $\geq$3 years, which may contribute to the higher baseline RVO risk in these populations. Prior epidemiologic data have indicated that the incidence of RVO is notably higher in individuals aged above 50 years.[4,16] Studies that investigated racial disparities in the incidence of RVO showed that Blacks and Asians have a higher prevalence, whereas Whites exhibit the lowest prevalence. The prevalence of RVO, standardized by age and sex, was 3.7 per 1000 in White populations, 3.9 per 1000 in Black populations, and 5.7 per 1000 in Asian populations.[43] Individuals with higher HbA1c, BMI, and prolonged diabetes also exhibit an increased risk of RVO, likely because these factors are recognized metabolic and vascular risk factors for RVO.[16,44] Given the elevated risk of RVO in these populations, they may particularly benefit from treatments such as GLP-1RAs that help mitigate RVO risk compared with DPP-4 inhibitors.

Furthermore, our findings highlight distinct effects across human-analog and exendin-based GLP-1RAs. Human-analog GLP-1RAs refer to GLP-1RAs that are directly modified from the native GLP-1, whereas exendin-based GLP-1RAs are derived from exendin-4, a peptide found in lizard saliva that shares a structural resemblance to GLP-1.[20] Although human-analog GLP-1RAs exhibit over 90% homology to native GLP-1, exendin-based GLP-1RAs have a homology of only 50%.[45] The differences in homology are reflected in studies showing that human-analog GLP-1RAs are more effective than exendin-based GLP-1RAs in lowering HbA1c, fasting blood glucose levels, and reducing the risk of adverse cardiovascular outcomes.[46,47] The high homology of human-analog GLP-1RAs to native GLP-1 may help explain their association with reduced RVO and BRVO risk when compared with DPP-4 inhibitors.

Strengths and Limitations

This study has several strengths. First, utilizing data from a large, global database increases the statistical power of our analyses and enhances the generalizability of our findings across diverse populations. Second, instead of limiting our focus on RVO, we examined other specific outcomes, including BRVO and CRVO. Third, rather than comparing the newer second-line glucose-lowering medications to first-line treatments such as metformin, we conducted an

active comparison between second-line therapies, including GLP-1RAs and DPP-4 inhibitors. Fourth, we assessed outcome risks over varying follow-up periods, allowing for a more detailed understanding of how these medications influence the risk of RVO over time. Fifth, we performed stratified analyses by age, sex, race, type of GLP-1RAs, and additional patient characteristics, supporting more tailored risk assessments and a deeper insight into RVO risk across different subpopulations. Finally, we conducted several sensitivity analyses to enhance the robustness of our findings, and the results consistently align with those of the main analysis.

However, this study has some limitations. First, as a retrospective cohort study, it is susceptible to biases arising from prescription preferences or differing indications for GLP-1RAs and DPP-4 inhibitors in the clinical setting. To minimize the impact of this limitation, we incorporated a range of covariates in the propensity score matching. Second, given that TriNetX is a deidentified database, we are unable to review the medical records of each patient to confirm the diagnosis of T2DM and RVO. Although we conducted a sensitivity analysis that included only patients with documented ophthalmology visits and observed results consistent with those of the main analysis, the potential risk of disease misclassification or coding errors influencing our findings cannot be fully excluded. Third, we could not assess the proportion of participants lost to follow-up during the study observation period due to a limitation of the TriNetX Analytics platform. However, we conducted a sensitivity analysis by restricting the inclusion to participants with at least 1 year of follow-up, and the results remain consistent with those of the original analysis. Fourth, the TriNetX platform limited our ability to evaluate the effects of varying dosages of GLP-1RAs on RVO because there was insufficient information regarding the cumulative dose of prescriptions.

Contributions

This study contributes to the research field by translating the retinal microvascular protective effects of GLP-1RAs observed in animal models into a clinical context, providing evidence of their potential benefits for RVO compared with DPP-4 inhibitors in patients with T2DM. To date, studies exploring the association between GLP-1RAs or DPP-4 inhibitors and RVO risk in patients with T2DM remain limited. Our findings address this gap and suggest that clinical practitioners may consider GLP-1RAs as a therapeutic option over DPP-4 inhibitors for patients with T2DM who are at heightened risk of developing RVO.

In patients with T2DM, those prescribed GLP-1RAs exhibit a significantly lower risk of developing RVO, particularly for BRVO, compared with those on DPP-4 inhibitors. These findings suggest that GLP-1RAs may be an option worth considering for patients with T2DM who are at risk of RVO, potentially contributing to favorable long-term ocular outcomes and reducing the burden of visual impairment in this population.

Footnotes and Disclosures

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Disclosures:

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HUMAN SUBJECTS: No human subjects were included in this study. Our study protocol for retrospective data collection through the TriNetX Analytics Network was approved by the Institutional Review Board of Taichung Veterans General Hospital under the registration number CE24430C. Informed consent was not obtained because TriNetX, as a federated network that only processes deidentified patient information, received a waiver from the Western Institutional Review Board. The authors confirm that all procedures in this study comply with the Declaration of Helsinki.

Our study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology statements for cohort studies (Table S2).

No animal subjects were included in this study.

Author Contributions:

Conception and design: Pan, Weng, Tsai, Chou

Data collection: Pan

Analysis and interpretation: Pan, Chou

Obtained funding: Chou

Overall responsibility: Pan, Weng, Tsai, Sheen, Hui-Ju Lin, Tien, Jun-Fu Lin, Ching-Heng Lin, Wang, Chou

Abbreviations and Acronyms:
BMI = body mass index; **BRVO** = branch retinal vein occlusion; **CI** = confidence interval; **CRVO** = central retinal vein occlusion; **DPP-4** = dipeptidyl peptidase 4; **eGFR** = estimated glomerular filtration rate; **GLP-1** = glucagon-like peptide-1; **GLP-1RA** = glucagon-like peptide-1 receptor agonist; **HbA1c** = glycated hemoglobin; **HR** = hazard ratio; **RVO** = retinal vein occlusion; **SD** = standard deviation; **T2DM** = type 2 diabetes mellitus.

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References

1. Cugati S, Wang JJ, Rochtchina E, Mitchell P. Ten-year incidence of retinal vein occlusion in an older population: the Blue Mountains Eye Study. *Arch Ophthalmol*. 2006;124:726–732.
2. Jaulim A, Ahmed B, Khanam T, Chatziralli IP. Branch retinal vein occlusion: epidemiology, pathogenesis, risk factors, clinical features, diagnosis, and complications. An update of the literature. *Retina*. 2013;33:901–910.
3. Karia N. Retinal vein occlusion: pathophysiology and treatment options. *Clin Ophthalmol*. 2010;4:809–816.
4. Chang YS, Ho CH, Chu CC, et al. Risk of retinal vein occlusion in patients with diabetes mellitus: a retrospective cohort study. *Diabetes Res Clin Pract*. 2021;171:108607.
5. Nauck MA, Müller TD. Incretin hormones and type 2 diabetes. *Diabetologia*. 2023;66:1780–1795.
6. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol*. 2016;4:525–536.
7. Reid T. Choosing GLP-1 receptor agonists or DPP-4 inhibitors: weighing the clinical trial evidence. *Clin Diabetes*. 2012;30:3–12.
8. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368:1696–1705.
9. Pan SY, Su EL, Huang CJ, et al. Evaluation of glucose-lowering medications in older people: a comprehensive systematic review and network meta-analysis of randomized controlled trials. *Age Ageing*. 2024;53:afae175.
10. Cherney DZI, Udell JA, Drucker DJ. Cardiorenal mechanisms of action of glucagon-like-peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors. *Med*. 2021;2:1203–1230.
11. Wang T, Lu W, Tang H, et al. Assessing the association between GLP-1 receptor agonist use and diabetic retinopathy through the FDA adverse event reporting system. *Diabetes Care*. 2019;42:e21–e23.
12. Muayad J, Loya A, Hussain ZS, et al. Comparative effects of glucagon-like peptide 1 receptor agonists and metformin on glaucoma risk in patients with type 2 diabetes. *Ophthalmology*. 2025;132:271–279.
13. Strain WD, Frenkel O, James MA, et al. Effects of semaglutide on stroke subtypes in type 2 diabetes: post hoc analysis of the randomized SUSTAIN 6 and PIONEER 6. *Stroke*. 2022;53:2749–2757.
14. Kendall DM, Cuddihy RM, Bergenstal RM. Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. *Am J Med*. 2009;122(suppl):S37–S50.
15. Palchuk MB, London JW, Perez-Rey D, et al. A global federated real-world data and analytics platform for research. *JAMIA Open*. 2023;6:ooad035.
16. Yao Y, Wang Q, Yang J, et al. Prevalence and risk factors of retinal vein occlusion in individuals with diabetes: the kailuan eye study. *Diab Vasc Dis Res*. 2024;21:14791641241271899.
17. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:1228–1239.
18. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (harmony outcomes): a double-blind, randomised placebo-controlled trial. *Lancet*. 2018;392:1519–1529.
19. Ko SH, Park SA, Cho JH, et al. Influence of the duration of diabetes on the outcome of a diabetes self-management education program. *Diabetes Metab J*. 2012;36:222–229.
20. Aroda VR. A review of GLP-1 receptor agonists: evolution and advancement, through the lens of randomised controlled trials. *Diabetes Obes Metab*. 2018;20(suppl 1):22–33.
21. Pradhan R, Montastruc F, Rousseau V, et al. Exendin-based glucagon-like peptide-1 receptor agonists and anaphylactic reactions: a pharmacovigilance analysis. *Lancet Diabetes Endocrinol*. 2020;8:13–14.
22. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834–1844.
23. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311–322.
24. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394:121–130.
25. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: standards of care in diabetes—2024. *Diabetes Care*. 2023;47(suppl 1):S179–S218.
26. Mannucci E, Mosenzon O, Avogaro A. Analyses of results from cardiovascular safety trials with DPP-4 inhibitors: cardiovascular outcomes, predefined safety outcomes, and pooled

analysis and meta-analysis. *Diabetes Care*. 2016;39(suppl 2): S196−S204.
27. Longato E, Di Camillo B, Sparacino G, et al. Better cardiovascular outcomes of type 2 diabetic patients treated with GLP-1 receptor agonists versus DPP-4 inhibitors in clinical practice. *Cardiovasc Diabetol*. 2020;19:74.
28. Packer M. Do DPP-4 inhibitors cause heart failure events by promoting adrenergically mediated cardiotoxicity? Clues from laboratory models and clinical trials. *Circ Res*. 2018;122: 928−932.
29. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet*. 2010;375: 1447−1456.
30. Arnolds S, Dellweg S, Clair J, et al. Further improvement in postprandial glucose control with addition of exenatide or sitagliptin to combination therapy with insulin glargine and metformin: a proof-of-concept study. *Diabetes Care*. 2010;33: 1509−1515.
31. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e563−e595.
32. Nagashima M, Watanabe T, Terasaki M, et al. Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice. *Diabetologia*. 2011;54:2649−2659.
33. Ban K, Noyan-Ashraf MH, Hoefer J, et al. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor−dependent and −independent pathways. *Circulation*. 2008;117:2340−2350.
34. Chai W, Dong Z, Wang N, et al. Glucagon-like peptide 1 recruits microvasculature and increases glucose use in muscle via a nitric oxide−dependent mechanism. *Diabetes*. 2012;61:888−896.
35. Drucker DJ. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab*. 2016;24:15−30.
36. Zhai R, Xu H, Hu F, et al. Exendin-4, a GLP-1 receptor agonist regulates retinal capillary tone and restores microvascular patency after ischaemia-reperfusion injury. *Br J Pharmacol*. 2020;177:3389−3402.
37. He X, Wen S, Tang X, et al. Glucagon-like peptide-1 receptor agonists rescued diabetic vascular endothelial damage through suppression of aberrant STING signaling. *Acta Pharm Sin B*. 2024;14:2613−2630.
38. Goldney J, Sargeant JA, Davies MJ. Incretins and microvascular complications of diabetes: neuropathy, nephropathy, retinopathy and microangiopathy. *Diabetologia*. 2023;66: 1832−1845.
39. O'Mahoney PRA, Wong DT, Ray JG. Retinal vein occlusion and traditional risk factors for atherosclerosis. *Arch Ophthalmol*. 2008;126:692−699.
40. McCannel CA, Berrocal AM, Kim SJ, et al. *2021-2022 Basic and Clinical Science Course, Section 12: Retina and Vitreous*. San Francisco, CA: American Academy of Ophthalmology; 2021.
41. Green WR, Chan CC, Hutchins GM, Terry JM. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Trans Am Ophthalmol Soc*. 1981;79:371−422.
42. Tsai H-R, Lin Y-J, Yeh J-I, et al. Use of sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes and the incidence of retinal vein occlusion in Taiwan. *Invest Ophthalmol Vis Sci*. 2024;65:19.
43. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology*. 2010;117:313−319.e1.
44. Nguyen NT, Nguyen XMT, Lane J, Wang P. Relationship between obesity and diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey, 1999-2006. *Obes Surg*. 2011;21:351−355.
45. Cornell S. A review of GLP-1 receptor agonists in type 2 diabetes: a focus on the mechanism of action of once-weekly agents. *J Clin Pharm Ther*. 2020;45(suppl 1):17−27.
46. Yao H, Zhang A, Li D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. *BMJ*. 2024;384:e076410.
47. Banerjee M, Pal R, Mukhopadhyay S, Nair K. GLP-1 receptor agonists and risk of adverse cerebrovascular outcomes in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab*. 2023;108: 1806−1812.