Comparing the real-world effects of once-weekly GLP-1 RAs and DPP-4is on ischemic stroke and myocardial infarction in individuals with T2D and ASCVD

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Background and Aims

This study aimed to compare the time to occurrence of ischemic stroke, MI, and 2-point MACE (ischemic stroke and MI) in patients with T2D and ASCVD who initiated a once weekly GLP-1 RA vs a DPP-4i.

Several large CVOTs have demonstrated that GLP-1 RAs significantly reduce adverse cardiovascular events and improve cardiovascular outcomes for patients with T2D.[1-3]

GLP-1 RAs with demonstrated cardiovascular benefit are recommended by multiple diabetes and cardiology guidelines and professional societies for people with T2D and established ASCVD or multiple risk factors for ASCVD, independent of baseline glucose levels.[1-4]

GLP-1 RAs and DPP 4is are therapies that affect the incretin system and are commonly used in clinical practice for individuals with T2D.

- Several head-to-head trials have demonstrated that compared with DPP 4is, GLP 1 RAs are associated with improved glycemic control and greater weight loss in individuals with T2D[5]
- Several GLP-1 RAs have demonstrated cardiovascular benefits in CVOTs, while DPP-4is have not[6]

Real world evidence comparing the effects of OW GLP-1 RAs and DPP4-is on the risk of cardiovascular events in individuals with T2D and ASCVD is limited, though some studies have been conducted.[7]

Methods

Retrospective cohort study using data from Optum® Clinformatics® Data Mart. Study period: 1/1/17-9/30/21.

Index date defined as Rx date of index drug (OW GLP-1 RA or DPP-4i). The baseline was year prior to index; follow-up was the interval between the index and the end of follow-up (≥3 months required).

Patients followed until earliest of: death, end of study, new initiation of SGLT-2i, DPP-4i, or GLP-1RA (depending on the group), the lapse of continuous enrollment, or discontinuation of index drug (>60 days).

Exclusion criteria: baseline GLP-1 RA or DPP-4i use, missing age or sex, pregnancy or claim for T1D at any point during the study.

Inclusion criteria: ≥18 on index date, ≥2 Dx of T2D, history of ASCVD, ≥1 Rx of index drug, persistent use of index drug (≥90 days), continuous enrollment during study period.

Ischemic stroke and MI were identified using ICD-10 codes on inpatient visits.

IPTW was used to reduce selection bias between groups using stabilized average treatment effect weights to balance baseline characteristics.

Summary

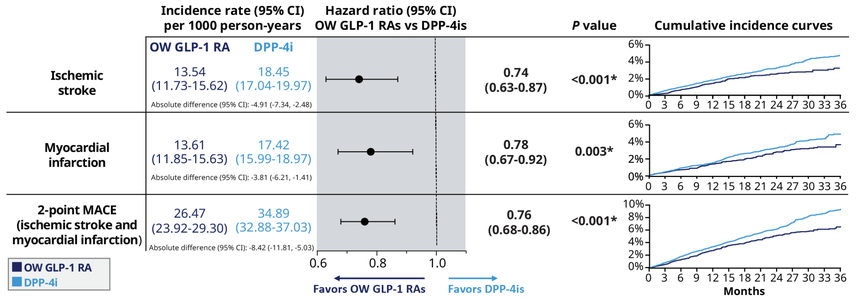
The results of this study demonstrated that OW GLP-1 RAs are more effective than DPP-4is in reducing the risks of ischemic stroke and MI in adults with T2D and ASCVD.

The HRs reported for stroke and MI in the present study were lower than those reported in a recent meta-analysis of outcomes across CVOTs[8] (though the present study included some population differences, including adults of all ages, patients with both T2D and ASCVD, and individuals using the newer generation of GLP-1 RAs).

The effect size identified for reduction in stroke risk (HR=0.74) is comparable to or exceeds that of meta-analyses investigating the effects of lowering blood pressure (RR=0.73), treating hyperlipidemia (RR=0.79), and other interventions in patients with T2D.[9]

Compared with users of DPP-4is, **new users of once weekly GLP-1 RAs** had significantly lower risks of ischemic stroke, MI, and 2-point MACE

Figure 2: Weighted Incidence Rates, Hazard Ratios, and Cumulative Incidence Curves of Clinical Outcomes



This real-world evidence complements existing clinical trial results and **demonstrates the importance of once-weekly GLP-1RAs in the complex treatment of patients with comorbid T2D and ASCVD**

Table 1. Weighted Key Baseline Characteristics

	OW GLP-1 RA (n=25,287)	DPP-4i (n=39,684)	SMD
Continuous variables, mean (SD)			
Age, years	69.68 (10.19)	70.26 (10.32)	0.057
ASCVD duration, years	4.12 (3.78)	4.14 (3.80)	0.005
T2D duration, years	5.47 (4.24)	5.34 (4.14)	0.029
CCI	2.48 (2.19)	2.53 (2.21)	0.026
DCSI	3.26 (2.21)	3.29 (2.19)	0.017
Sex, n (%)			
F	12,387 (49.0)	19,645 (49.5)	0.010
M	12,900 (51.0)	20,039 (50.5)	0.010
Race/ethnicity, n (%)			
White	14,866 (58.8)	22,988 (57.9)	0.017
Black	4137 (16.4)	6457 (16.3)	0.002
Hispanic	4211 (16.7)	6838 (17.2)	0.015
Asian	854 (3.4)	1519 (3.8)	0.024
Unknown	1220 (4.8)	1882 (4.7)	0.004
HbA1c, n (%)			
<7%	2258 (8.9)	3938 (9.9)	0.034
7% to <8%	3061 (12.1)	5043 (12.7)	0.018
8% to <9%	2842 (11.2)	4362 (11.0)	0.008
≥9%	3575 (14.1)	5303 (13.4)	0.023
Unknown	13,551 (53.6)	21,038 (53.0)	0.012
BMI, n (%)			
<25	617 (2.4)	1166 (2.9)	0.031
25 to <30	1771 (7.0)	2874 (7.2)	0.009
30 to <35	2502 (9.9)	3874 (9.8)	0.004
35 to <40	1903 (7.5)	2854 (7.2)	0.013
≥40	2215 (8.8)	3272 (8.3)	0.018
Unknown	16,280 (64.4)	25,643 (64.6)	0.005

Results

Before weighting, the study included 26,430 OW GLP-1 RA users and 39,858 DPP-4i users. After weighting, the sample sizes were 25,287 and 39,684, respectively.

The average follow-up time was similar between the two groups (approximately 11.3 months).

After IPTW weighting, there were no significant differences in baseline characteristics between the OW GLP-1 RA and DPP-4i groups (**Table 1**).

Prior to the index date, approximately 70% and 30% of patients were on metformin and insulin, respectively. Approximately 15% of patients had a history of ischemic stroke and 14.5% had a history of MI.

Incidence rates for stroke, MI, and 2-point MACE were lower in the OW GLP-1 RA group compared with the DPP-4i group. Similar trends were observed in the cumulative incidence curves for these clinical outcomes (**Figure 2**).

Compared with DPP-4is, OW GLP 1 RAs were associated with:

- 26% lower risk of ischemic stroke (HR [95% CI]=0.74 [0.63-0.87]; *P*<0.001)
- 22% lower risk of MI (HR [95% CI]=0.78 [0.67-0.92]; *P*=0.003)
- 24% lower risk of 2-point MACE (HR [95% CI]=0.76 [0.68 0.86]; *P*<0.001)

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Abbreviations: CCI, Charlson Comorbidity Index; DCSI, Diabetes Complications Severity Index; HR, hazard ratio; IPTW, inverse probability of treatment weighting; RR, rate ratio; SMD, standardized mean.

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