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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Aim

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.

Introduction

- 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 DPP-4is on the risk of cardiovascular events in individuals with T2D and ASCVD is limited, though some studies have been conducted[7]
  - Some older daily GLP-1 RAs may be less efficacious in improving cardiovascular outcomes and may confound assessments of the entire GLP-1 RA class.[6] Therefore, it is particularly important to examine the cardiovascular effectiveness of the newer, OW generation of GLP-1 RAs

Methods

- This was a retrospective cohort study using data from the Optum Clinformatics® Data Mart. The study period was from January 1, 2017, to September 30, 2021

Abbreviations:

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CCI, Charlson Comorbidity Index; CVOT, cardiovascular outcome trial; DCSI, Diabetes Complications Severity Index; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HR, hazard ratio; ICD-10 CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; MI, myocardial infarction; OW, once-weekly; RR, rate ratio; SGLT-2, sodium-glucose cotransporter-2; SMD, standardized mean difference; T1D, type 1 diabetes; T2D, type 2 diabetes.

Figure 1. Patient Attrition Flow Chart

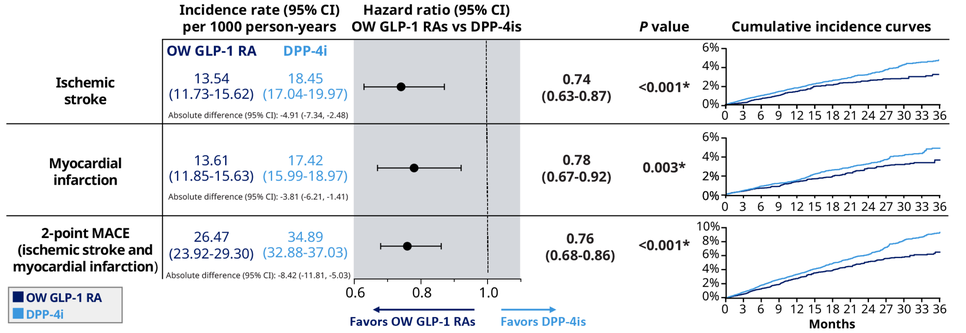
- The index date (between January 1, 2018, and June 30, 2021) was defined as the prescription date of the index drug (OW GLP-1 RA or DPP-4i). The baseline period was 1 year prior to the index date. The follow-up period was defined as the interval between the index date and end of follow-up and needed to be ≥3 months
- Patients were followed until the earliest of death; end of the study (September 30, 2021); new initiation of an SGLT-2 inhibitor, DPP-4i (among patients in the GLP-1 RA group) or GLP-1 RA (among patients in the DPP-4i group); lapse of continuous enrollment; or discontinuation of the index drug for >60 days
- Exclusion criteria: baseline GLP-1 RA or DPP-4i use, missing demographic information (age or sex), or pregnancy or T1D at any time during the baseline or follow-up periods
- Inclusion criteria: ≥18 years old on the index date, ≥2 separate diagnoses of T2D on different days during the study period, history of ASCVD (between 2001 and the index date), ≥1 prescription for the index drug (OW GLP-1 RA or DPP-4i), persistent use of the index drug (for ≥90 days with ≤60-day gaps), and continuous enrollment during the baseline and follow-up periods

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
Index year, n (%)			
2018	5970 (23.6)	9759 (24.6)	0.023
2019	7192 (28.4)	11,251 (28.4)	0.002
2020	7225 (28.6)	11,172 (28.2)	0.009
2021	4900 (19.4)	7501 (18.9)	0.009
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

- Ischemic stroke and MI events were identified as a primary diagnosis of inpatient claims using ICD-10 CM codes. One inpatient visit for ischemic stroke or MI was considered one stroke or MI event. 2-point MACE was defined as the composite of ischemic stroke and MI
- To reduce the observed selection bias between the two groups, IPTW using stabilized average treatment effect weights was used to balance baseline characteristics

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



Results

- Before weighting, the study included 26,430 OW GLP-1 RA users and 39,858 DPP-4i users (**Figure 1**). 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)

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]

Conclusions

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

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