Exploring the Associations Between Newer Glucose-Lowering Drugs Use and Cognitive Function Decline in Adults With Diabetes: A Target Trial Emulation

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Introduction

Type 2 diabetes (T2D) increases the risk of cognitive function decline (CFD). Data suggests that two newer glucose-lowering drugs (i.e., glucagon-like peptide-1 receptor agonist (GLP-1RA), sodium-glucose transport protein 2 inhibitors (SGLT2i)) may have cognitive benefits. However, real-world evidence about the effect is either limited or conflicting.

Objective

We aimed to investigate the associations between the two newer GLD and CFD among adults with T2D.

Methods

- Study design: retrospective cohort study, following a target trial emulation framework
- Data source: All of US Electronic health records (01/01/2005-07/01/2022)
- Population: Adults with T2D identified by the SUPREME-DM algorithm, age >= 45 years
- Exposure: (1) dipeptidyl peptidase 4 inhibitors (DPP4i) new users, (2) SGLT2i new users, and (3) GLP-1RA new users RxNorm codes were used to identify the medication exposure.
- Comparator: SGLT2i and GLP-1RA new users were compared to DPP4i new users respectively
- Outcome: cognitive function decline (CFD), including mild cognitive impairment and Alzheimer's disease and related dementias, measured by ICD codes and survey
- Follow-up: follow the patients until 1) onset of disease outcome, 2) death, 3) disenrollment from the HER, 4) end of study, 5) switch to other drug, which ever comes first
- Statistical method: The two comparison pairs were matched with a 1:1 propensity score (PS) based on age, sex, socioeconomic status, comorbidities (e.g., obesity, cardiovascular disease), labs (e.g., A1c) and vitals (e.g., BMI). In matched cohort, hazard ratio (HRs) with 95% CI was estimated by using Cox proportional hazard model

Fig 1. Outcomes in 1:1 PS-Matched Cohorts for GLP-1RAs Versus DPP4is

	GLP-1RA vs. DPP4i	
	GLP-1RA	DPP4i
Unmatched cohort		
No. of events/no. of patients at risk	140/6527	1006/16352
Follow-up, years	2.53	5.50
Matched cohort		
No. of events/no. of patients at risk	140/6527	313/6527
Follow-up, years	2.53	5.00
Incidence rate (per 1000 person-years)	8.48	9.59
Rate difference	- 1.11	Ref: 0
Adjusted HR (95% CI)	**0.77(0.63, 0.94)**	Ref: 1

Figure 1. Kaplan-Meier curve for GLP-1RAs Versus DPP4is cohort

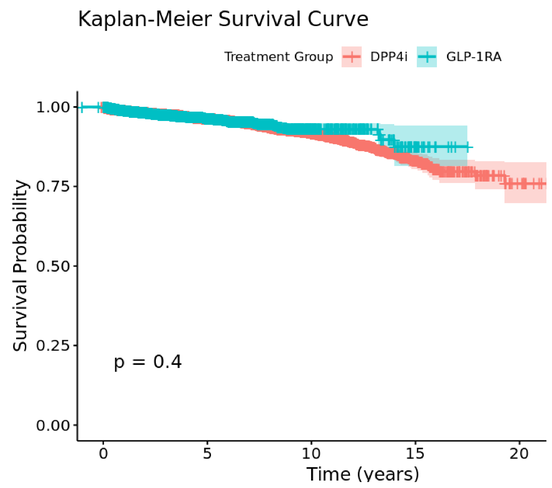
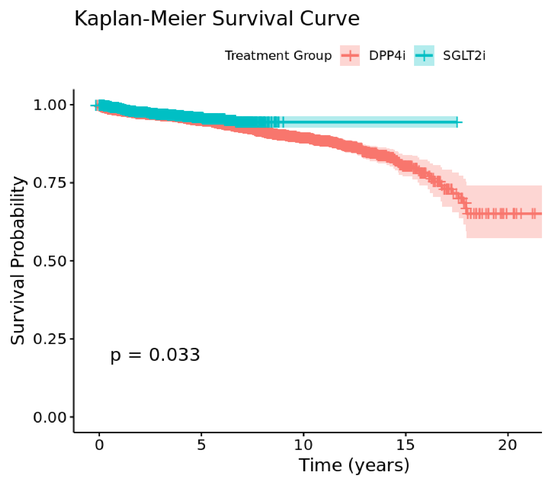


Table 2. Outcomes in 1:1 PS-Matched Cohorts for SGLT2is Versus DPP4is

	SGLT2i vs. DPP4i	
	SGLT2i	DPP4i
Unmatched cohort		
No. of events/no. of patients at risk	89/4905	1006/16352
Follow-up, years	1.86	5.50
Matched cohort		
No. of events/no. of patients at risk	89/4905	277/4905
Follow-up, years	1.86	4.49
Incidence rate (per 1000 person-years)	9.76	12.58
Rate difference	2.82	
Adjusted HR (95% CI)	**0.67(0.52, 0.87)**	Ref: 1

Note: HR: hazard ratio; CI: confidence interval

Figure 2. Kaplan-Meier curve for SGLT2is Versus DPP4is cohort



Results

- 6,527 individuals were included in the GLP-1RA v.s. DPP4i matched cohort, the CFD incidence was 8.48 and 9.59 per 1000 person-years, respectively (p <.01).
- 4,905 individuals were included in the SGLT2i v.s. DPP4i matched cohort, the CFD incidence was 9.76 and 12.58 per 1000 person-years respectively (p <.01).
- In the Cox model, the GLP-1RA group was associated with a significantly lower risk of incident CFD (HR 0.77 [95% CI 0.63-0.94]) than the DPP4i group. The SGLT2i group was associated with a significantly lower risk of incident CFD (HR 0.67 [95% CI 0.52-0.87]) than the DPP4i group.

Conclusions

- Compared to DPP4 inhibitors, SGLT2i and GLP-1RAs were associated with a significantly lower risk of indecent CFD in real-world populations with T2D.

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