Comparative Safety of Second-line Antihyperglycemic Agents in Older Adults with Diabetes: Insights from the LEGEND-T2DM study

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Background

Second-line therapies for type 2 diabetes (T2DM) are recommended for managing uncontrolled glucose and diabetes related complications in patients for whom control targets are not achieved with first metformin therapy alone. The recent 2024 American College of Physicians guideline recommends the use of novel agents, including both sodium glucose cotransporter 2 inhibitor (SGLT2i) and glucagon like peptide-1 receptor agonist (GLP1RA), as second-line antihyperglycemic agents due to their cardiovascular benefits.(1) However, safety of these drugs has not been systematically investigated, particularly in older adults who are at a higher risk of experiencing adverse events due to multiple comorbidities and the various other medications prescribed to treat those conditions.(2, 3) Therefore, the aim of this study was to provide systematic evidence regarding the safety outcomes of these second-line pharmacological treatments in older adults with T2DM.

Methods

This study is part of the Large-scale Evidence Generation and Evaluation across a Network of Database for Type 2 Diabetes Mellitus (LEGEND-T2DM) study led by the Observational Health Data Sciences and Informatics (OHDSI) collaborative. A total of 19 databases from the US and international data partners were included, with all databases mapped to Observational Medical Outcome Partnership (OMOP) common data model version 5. The full LEGEND-T2DM protocol is available on online (https://ohdsi-studies.github.io/LegendT2dm/Protocol.html).

The study population included older adults (≥65 years) with T2DM who were prescribed second-line agents. Second-line agents were defined as dipeptidyl peptidase 4 inhibitor (DPP4i), sulfonylureas (SU), sodium glucose cotransporter 2 inhibitor (SGLT2i), and glucagon like peptide-1 receptor agonist (GLP1RA). The cohort were restricted to patients with 90 days of prior treatment with metformin as first-line treatment and without a long-term insulin use (≥30 days). We applied a new-user active comparator design with the index date defined as the date of the initial prescription of a second-line agent. Patients were followed until the initially prescribed second-line agent treatment was discontinued (on-treatment follow-up).

The primary outcomes were 21 patient-centric safety outcomes, categorized into glucose, electrolytes, and weight change (5 outcomes); gastrointestinal and musculoskeletal outcomes (6 outcomes); and cancer and other outcomes (10 outcomes).

Large-scale propensity score matching was used to mitigate confounding bias between the two second-line agent groups. Calibrated hazard ratios (HRs) were calculated using the Cox proportional hazard model and empirical calibration was performed using negative control outcomes. A random-effect meta-analysis was applied to calculate the pooled HR estimates, including only databases with more than 1,000 patients for each group and passed diagnostics.

Results

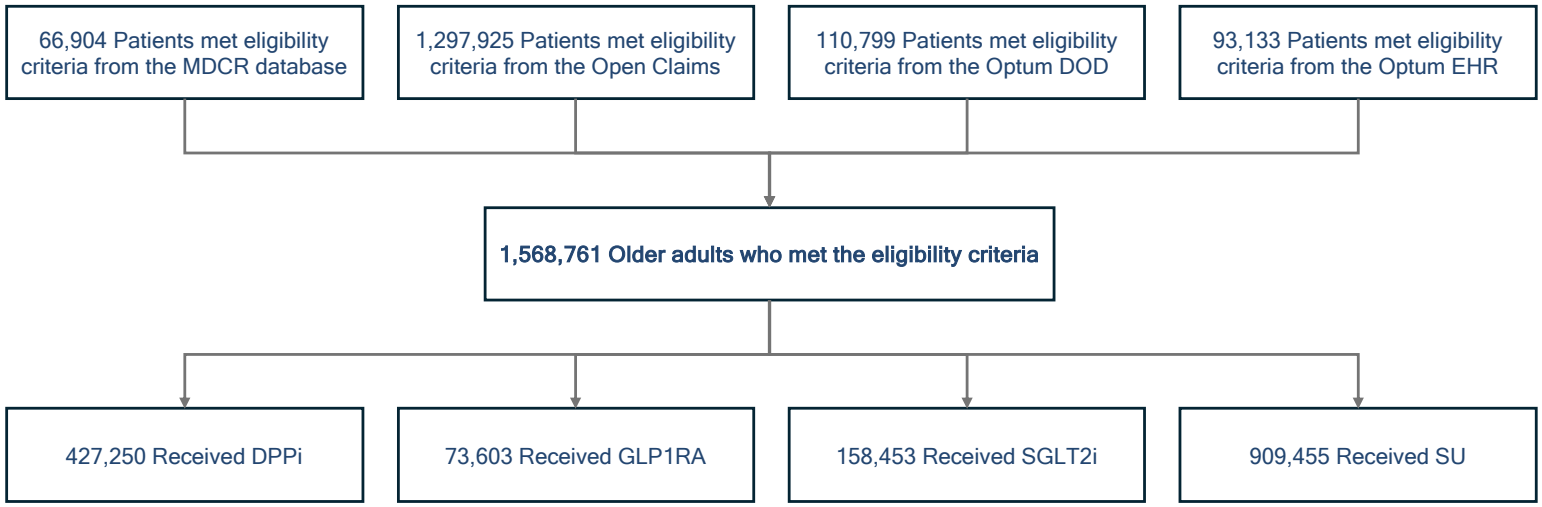
A total of 1,844,751 adults aged 65 or older, from 19 databases met the eligible criteria for the study. Among them, 504,789 (27.4%) patients started with a DPP4i, 76,336 (4.1%) with a GLP1RA, 177,504 (9.6%) with an SGLT2i group, and 1,086,122 (58.9%) with a SU. The meta-analysis was performed using the four US databases (Merative MarketScan Medicare Supplemental Database, Optum Clinformatics Extended Data Mart – Date of Death, Optum de-identified Electronic Health Record Dataset, and United States Open Claims) that met study diagnostics. The final meta-analyzed results included 427,250 patients for DPP4i, 73,603 for GLP1RA, 158,453 for SGLT2i, and 909,455 for SU from the four US databases that met the minimum number of patients in all study groups (**Figure 1**). The proportions of female adults in study groups were 53.0% for the DPP4i, 56.7% for GLP1RA, 44.6% for SGLT2i and 49.3% for SU groups.

After the propensity score matching, all covariates were balanced. **Table 1 and Table 2** showed the meta-analytic HRs across the four databases. Compared with the SGLT2i and GLP1RA groups, the DPP4i group had a significantly higher incidence of hyperkalemia (HR [95% CI] 1.51 [1.17-1.95] and 1.4 [1.03-2.13], respectively) and peripheral edema (HR 1.43 [1.13-1.82] and 1.39 [1.14-1.70], respectively). The DPP4i, GLP1RA, and SGLT2i groups had significantly lower risks of hypoglycemia and venous thromboembolism compared with the SU group (for hypoglycemia, HR [95% CI] 0.23 [0.19-0.28], 0.12 [0.16-0.26] and 0.19 [0.14-0.29], respectively; for venous thromboembolism, HR 0.89 [0.81-0.98], 0.78 [0.63-0.96] and 0.79 [0.64-0.97], respectively). The risk of GI-related outcomes (nausea and vomiting) was consistently higher in the GLP1RA group compared to other groups.

Conclusion

SGLT2 inhibitors and GLP1RA had a lower risk of adverse events compared with DPP4 inhibitors or SU as second-line treatment for older adults with T2DM. These findings support the use of SGLT2 inhibitors and GLP1RA not only for their effectiveness but also for their enhanced safety.

Figure 1. Number of patients extracted from each database and number of patients in the final cohort for each drug group.



MDCR: IBM MarketScan Medicare Supplemental Database, Optum Clinformatics Extended Data Mart – Date of Death, Optum de-identified Electronic Health Record Dataset, and United States Open Claims

Table 1. Meta-analysis results of safety outcomes related to hemodynamic, gastrointestinal and musculoskeletal diseases between antihyperglycemic agent groups in older adults with type 2 diabetes.

Outcomes	Target vs comparator (reference)					
	DPP4i vs GLP1RA	DPP4i vs SGLT2i	DPP4i vs SU	GLP1RA vs SGLT2i	GLP1RA vs SU	SGLT2i vs SU
Glucose, electrolytes, and weight change						
Hypoglycemia	1.25 (0.95-1.64)	1.24 (0.86-1.78)	0.23 (0.19-0.28)	1.10 (0.55-2.23)	0.12 (0.16-0.26)	0.19 (0.14-0.29)
Diabetic ketoacidosis	1.28 (0.80-2.04)	0.76 (0.53-1.09)	1.01 (0.82-1.23)	0.52 (0.33-0.83)	0.98 (0.64-1.50)	1.85 (1.37-2.49)
Abnormal weight gain	0.71 (0.41-1.22)	1.20 (0.85-1.69)	0.69 (0.53-0.90)	1.42 (0.63-3.21)	0.76 (0.57-1.02)	0.56 (0.43-0.74)
Hyperkalemia	1.48 (1.03-2.13)	1.51 (1.17-1.95)	1.04 (0.92-1.18)	0.92 (0.78-1.10)	0.64 (0.52-0.79)	0.74 (0.60-0.90)
Peripheral edema	1.39 (1.14-1.70)	1.43 (1.13-1.82)	0.93 (0.86-1.01)	1.01 (0.83-1.23)	0.69 (0.58-0.82)	0.66 (0.53-0.81)
Gastrointestinal and musculoskeletal						
Nausea	0.66 (0.51-0.84)	1.14 (0.87-1.49)	0.97 (0.89-1.06)	1.75 (1.41-2.16)	1.44 (1.13-1.84)	0.88 (0.72-1.06)
Vomiting	0.68 (0.54-0.86)	1.12 (0.84-1.48)	0.99 (0.91-1.08)	1.76 (1.56-1.98)	1.35 (1.09-1.66)	0.92 (0.71-1.18)
Diarrhea	0.92 (0.78-1.07)	1.12 (0.85-1.47)	0.95 (0.87-1.03)	1.31 (1.17-1.46)	1.02 (0.85-1.23)	0.82 (0.68-0.998)
Acute pancreatitis	1.09 (0.81-1.48)	1.32 (0.96-1.81)	1.01 (0.84-1.21)	1.15 (0.67-1.99)	0.98 (0.72-1.31)	0.81 (0.62-1.05)
Bone fracture	1.15 (0.97-1.35)	0.89 (0.64-1.24)	0.98 (0.90-1.07)	0.93 (0.82-1.06)	0.85 (0.68-1.05)	0.97 (0.77-1.22)
Joint pain	1.24 (1.01-1.52)	1.23 (0.95-1.60)	1.06 (0.96-1.17)	0.88 (0.73-1.07)	0.90 (0.64-1.26)	0.88 (0.71-1.09)

All the hazard ratios represented the risk in the target cohort to the comparator cohort (reference). *Glycemic controls were limited to specific databases due to data availability. Red shadow means significant high risk than reference and blue means significant low risk to reference.

Table 2. Meta-analysis results of cancer and other outcomes between antihyperglycemic agent groups in older adults with type 2 diabetes.

Outcomes	Target vs comparator (reference)					
	DPP4i vs GLP1RA	DPP4i vs SGLT2i	DPP4i vs SU	GLP1RA vs SGLT2i	GLP1RA vs SU	SGLT2i vs SU
Cancer and other outcomes						
Bladder cancer	0.93 (0.36-2.42)	1.31 (0.79-2.18)	0.89 (0.77-1.03)	1.16 (0.77-1.73)	0.73 (0.52-1.02)	0.75 (0.47-1.18)
Breast cancer	0.95 (0.74-1.22)	1.05 (0.65-1.69)	0.97 (0.86-1.10)	1.05 (0.81-1.35)	1.09 (0.85-1.39)	0.91 (0.59-1.40)
Renal cancer	1.15 (0.46-2.90)	1.93 (1.30-2.86)	1.01 (0.83-1.25)	1.94 (0.70-5.39)	0.99 (0.56-1.76)	0.52 (0.36-0.74)
Thyroid tumor	0.87 (0.59-1.28)	1.01 (0.69-1.49)	1.12 (0.85-1.48)	0.97 (0.63-1.49)	1.08 (0.72-1.61)	1.26 (0.65-2.43)
Genitourinary infection	1.09 (0.94-1.27)	1.10 (0.87-1.40)	1.01 (0.93-1.10)	0.98 (0.89-1.08)	0.90 (0.75-1.08)	0.931 (0.77-1.12)
Hypotension	1.02 (0.86-1.21)	1.03 (0.81-1.32)	1.09 (1.00-1.19)*	0.91 (0.72-1.14)	0.94 (0.77-1.14)	1.12 (0.91-1.37)
Photosensitivity	0.46 (0.28-0.77)	1.12 (0.67-1.89)	1.16 (0.96-1.41)	1.83 (0.92-3.67)	1.72 (1.07-2.78)	0.99 (0.63-1.57)
Lower extremity amputation	1.14 (0.59-2.23)	0.54 (0.33-0.86)	0.91 (0.73-1.15)	0.57 (0.27-1.18)	0.02 (0.00 -41751.12)	1.20 (0.83-1.71)
Venous thromboembolism	1.02 (0.80-1.30)	1.15 (0.88-1.49)	0.89 (0.81-0.98)	0.98 (0.81-1.18)	0.78 (0.63-0.96)	0.79 (0.64-0.97)

All the hazard ratios represented the risk in the target cohort to the comparator cohort (reference). *Glycemic controls were limited to specific databases due to data availability. Red shadow means significant high risk than reference and blue means significant low risk to reference.

Reference

1. Qaseem A, Obley AJ, Shamliyan T, Hicks LA, Harrod CS, Crandall CJ. Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: A Clinical Guideline From the American College of Physicians. Annals of Internal Medicine. 2024.
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2024 [Available from: https://www.cdc.gov/diabetes/php/data-research/?CDC_AAref_Val=https://www.cdc.gov/diabetes/data/statistics-report.
3. American Diabetes Association Professional Practice Committee. 13. Older Adults: Standards of Care in Diabetes—2024. Diabetes Care. 2023;47(Supplement_1):S244-S57.