nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data management activities were conducted using SAS 9.04 (SAS Institute Inc., Cary, NC)
Data analysis	We are unable to share code used for analyses because it includes OptumLabs variable and table names. These are third party data owned by OptumLabs and are subject to restrictions on sharing as a condition of access. The medication names, ICD codes, CPT codes used for analyses are all included in Supplemental Materials to ensure reproducibility of the work

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

This study was conducted using de-identified data from OptumLabs Data Warehouse and linked 100% sample of Medicare fee-for-service claims. These data are third party data owned by OptumLabs and contain sensitive patient information; therefore, the data is only available upon request. Interested researchers engaged

in HIPAA compliant research may contact connected@optum.com for data access requests. The data use requires researchers to pay for rights to use and access the data. These data are subject to restrictions on sharing as a condition of access.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Patient sex was ascertained from OptumLabs Data Warehouse and Medicare enrollment files. These data were not collected by the research team.
Reporting on race, ethnicity, or other socially relevant groupings	Patient race and ethnicity was ascertained from OptumLabs Data Warehouse and Medicare enrollment files. These data were not collected by the research team.
Population characteristics	The study cohort was comprised of individuals with private, Medicare Advantage, and Medicare fee-for-service ('traditional Medicare") insurance coverage included in OptumLabs Data Warehouse and linked 100% sample of Medicare parts A, B, and D. We identified adults aged ≥21 years who had filled a new prescription for a GLP-1RA, SGLT2i, DPP-4i, or sulfonylurea between 1/1/2014-12/31/2021. The date of the first fill was used as the index date for each patient, but patients were required to have a second fill of the study drug class to confirm its use and 12 months of enrollment prior to the index date to ascertain baseline covariates. We allowed a 30-day gap between the last day covered by a preceding prescription and the new prescription to count as continued use. Patients could enter the cohort only once, the first time they met the eligibility criteria for a medication class. Patients with missing sex, year of birth, or region were excluded (<1%). Exclusion criteria (applied to the baseline 12-month period) were: fill for any study drug or glinide (excluded due to its similarity to sulfonylurea) during the baseline period; any second study drug during days 0-30 after index date; insulin use; type 1 diabetes (defined by presence of any type 1 diabetes ICD-9/10 codes during the baseline period); pregnancy; and metastatic cancer. We then restricted the study population to patients at moderate CVD risk, defined as an estimated 1-5% annualized predicted risk of experiencing a MACE event. The final (weighted) study population included 82,438 patients in the DPP-4i group (mean age 65.8 [SD, 8.4], 75.0% non-Hispanic White, 50.9% male, 79.0% on metformin), 44,255 patients in the GLP-1RA group (mean age 65.5 [SD, 8.3], 75.9% non-Hispanic White, 51.1% male, 79.3% on metformin), 46,473 patients in the SGLT2i group (mean age 65.5 [SD, 8.4], 75.6% non-Hispanic White, 50.6% male, 79.0% on metformin), and 207,186 patients in the sulfonylurea group (mean age 65.7 [SD, 8.4], 74.8% non-Hispanic White, 51.0% male, 78.9% on metformin). Baseline patient characteristics are detailed in Table 1.
Recruitment	N/A
Ethics oversight	Mayo Clinic IRB deemed study exempt as it relies on de-identified patient data

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	All patients meeting eligibility criteria within OptumLabs Data Warehouse and Medicare fee-for-service claims were included
Data exclusions	No data were excluded. Patients not meeting eligibility criteria defined in the manuscript were excluded.
Replication	All analyses were run in duplicate to verify findings. Replication efforts were successful.
Randomization	There was no prospective randomization because this is a retrospective observational study. Propensity scores and inverse probability of treatment weighting were used to emulate randomization.
Blinding	There was no blinding because this is a retrospective observational study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT05214573
Study protocol	Available on NCT05214573
Data collection	Secondary analysis of data from OptumLabs Data Warehouse and Medicare parts A, B, and D
Outcomes	The primary outcome was time to MACE, defined as the composite of hospitalization for non-fatal acute myocardial infarction (MI) or non-fatal stroke or all-cause mortality, whichever occurred first. Secondary outcomes were time to expanded MACE, defined as the composite of MACE, HHF, and revascularization procedure, and the time to individual components of expanded MACE. Diagnosis codes used to ascertain all baseline covariates and outcomes are detailed in the Supplement included with the manuscript