GLUCAGON-LIKE PEPTIDE 1 RECEPTOR AGONISTS AND OBSTRUCTIVE SLEEP APNEA RISK USING MEDICARE DATA 2007 - 2019

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000000965

Study ID

1000000965

DARWIN EU® study

No

Study countries

United States

Study description

We will implement an active-comparator, new user (ACNU) retrospective cohort study design to identify new users of GLP-1RA and new users of SGLT-2 inhibitors after a washout period of 12 months without any dispensed prescriptions for the two drug classes compared. This emulates a head-to-head trial comparing patients assigned to treatment with GLP-1RA versus SGLT-2 inhibitors. By enrolling only new users and following subjects from the start of treatment, time-varying hazards, including lag times, can be assessed, and described, while preserving the temporality of covariate assessment. The rationale behind choosing an active comparator (a guideline treatment alternative for GLP-1 agonists) is to minimize the impact of confounding by indication and other unmeasured patient characteristics (such as healthy initiator bias or frailty).

Aim 1: To estimate the comparative effect of GLP-1RA versus sodium-glucose co-transporter-2 (SGLT-2) inhibitors on the incidence of OSA in older adults with type 2 diabetes.

Aim 2: To investigate whether comorbid OSA at baseline modifies the comparative effect of GLP-1RA (vs. SGLT-2 inhibitors) on the incidence of adapted major adverse cardiovascular events (MACE) defined as stroke, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or all-cause mortality in older adults with type 2 diabetes.

Study status

Ongoing

Research institutions and networks

Institutions

University of North Carolina at Chapel Hill

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Institution

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 25/02/2026

Actual: 25/03/2026

Study start date

Planned: 25/03/2026

Actual: 25/03/2026

Data analysis start date
Planned: 25/03/2026

Actual: 25/03/2026

Date of final study report
Planned: 24/09/2027

Sources of funding

- No external funding

Study protocol

Dissertation Protocol_final_clean.pdf (847.92 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Active comparator, new user cohort study

Main study objective:

Aim 1: To estimate the comparative effect of GLP-1RA versus sodium-glucose co-transporter-2 (SGLT-2) inhibitors on the incidence of OSA in older adults with type 2 diabetes.

Aim 2: To investigate whether comorbid OSA at baseline modifies the comparative effect of GLP-1RA (vs. SGLT-2 inhibitors) on the incidence of adapted major adverse cardiovascular events (MACE) defined as stroke, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or all-cause mortality in older adults with type 2 diabetes.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

OZEMPIC

RYBELSUS

WEGOVY

VICTOZA

SAXENDA

TRULICITY

MOUNJARO

JARDIANCE

INVOKANA

STEGLATRO

Medicinal product name, other

FARXIGA

Study drug International non-proprietary name (INN) or common name

EXENATIDE

LIRAGLUTIDE

LIXISENATIDE

ALBIGLUTIDE

DULAGLUTIDE

SEMAGLUTIDE

DAPAGLIFLOZIN

CANAGLIFLOZIN

EMPAGLIFLOZIN

ERTUGLIFLOZIN

Anatomical Therapeutic Chemical (ATC) code

(A10BJ01) exenatide

exenatide

(A10BJ02) liraglutide

liraglutide

(A10BJ03) lixisenatide

lixisenatide

(A10BJ04) albiglutide

albiglutide

(A10BJ05) dulaglutide

dulaglutide

(A10BJ06) semaglutide

semaglutide

(A10BK01) dapagliflozin

dapagliflozin

(A10BK02) canagliflozin

canagliflozin

(A10BK03) empagliflozin

empagliflozin

(A10BK04) ertugliflozin

ertugliflozin

Medical condition to be studied

Type 2 diabetes mellitus

Sleep apnoea syndrome

Population studied

Short description of the study population

Medicare Fee-for-Service (FFS) Database (Parts A, B, and D) 2007-2019 (or additional years of data if available). This US federal database contains deidentified individual-level, longitudinal information on demographics, diagnoses, and procedures, and outpatient prescription dispensations recorded during billing of all health care encounters.

Age groups

- Elderly (≥ 65 years)
  - Adults (65 to < 75 years)
  - Adults (75 to < 85 years)
  - Adults (85 years and over)

Study design details

Setting

We will include an active comparator new user cohort where GLP-1 agonists are compared with SGLT-2 inhibitors. New users are defined as individuals who initiate the drugs of interest or their active comparator after a preceding washout period of at least 12 months without a prescription for the drug classes compared. Participants are allowed to have other anti-hyperglycemic drugs during the washout period except the drugs being compared. Study subjects are required to have 2 diagnosis codes for T2DM and at least 12 months of continuous part A, B, and D coverage before the first prescription date. Since SGLT2 inhibitors were approved in March 201348, the earliest possible first prescription date for this study will be January 1, 2014, allowing for adoption and uptake in clinical practice and mitigating channeling bias immediately after approval.

We will exclude all patients who do not refill the same drug class within the days supply and a grace period of 30 days after the first prescription. Requiring two prescriptions increases the probability that patients actually started therapy. We will describe the patients who do not meet the refill criterion to assess the potential selection imposed by requiring a refill. Patients with evidence of pre-existing OSA (diagnosis of OSA, prescriptions for modafinil and armodafinil, prior use of continuous positive airway pressure (CPAP) therapy, oral device) and adapted Major Adverse Cardiovascular Events (MACE) (see outcome section) within all the available lookback period prior to the first prescription or between the first and 2nd prescription will be excluded from the analysis for Aim 1 and Aim 2 respectively. For both Aims 1 and 2, we will also exclude patients with a history of bariatric surgery, stage 4 chronic kidney disease, end-stage renal disease or dialysis during the lookback period prior to the first prescription. Additionally, for Aim 1, we will exclude patients with any sleep disorder, tracheostomy and current hom

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Comparators

Exposure will be defined by at least two same drug class prescription dispensing claims of either GLP-1 agonists or SGLT-2 inhibitors (active comparator) for Aim 1 and at least one prescription dispensing claim of either GLP-1 agonists or SGLT-2 inhibitors for Aim 2 between January 1, 2014, and December 31, 2018, identified using Anatomical Therapeutic Chemical (ATC) classification codes and National Drug Codes (NDCs). We will identify an active comparator cohort where GLP-1 agonists are compared with SGLT-2 inhibitors.

Outcomes

Aim 1: incident obstructive sleep apnea (OSA). The American Academy of Sleep Medicine (AASM) guidelines recommend ordering sleep studies (in-lab polysomnography or technically adequate home sleep apnea tests) only when

there is clinical suspicion of moderate-to-severe OSA and note that repeat testing after a negative result is uncommon unless symptoms persist or the initial test was inconclusive. OSA will therefore be defined if there are both a polysomnography and least one diagnosis code for OSA (ICD-9 code 327.23 or ICD-10 code G47.33) within 60 days after the polysomnography (Healthcare Common Procedure Coding System 95808, 95810, 95811, G0398-G0400). Date of diagnosis will be assigned at the first OSA claim associated with polysomnography. However, because this algorithm was used for cohort definition and has not been validated in Medicare claims data, we will implement four other algorithms for defining OSA: 1) A polysomnography and at least one procedure code for OSA treatment (positive airway pressure (PAP) therapy or oral device) or diagnosis code for OSA within 60 days after the polysomnography. 2) A polysomnography and at least one diagnosis code for unspecified sleep apnea plus one procedure code for OSA treatment (positive airway pressure (PAP) therapy or oral device) within 60 days after the polysomnography. 3) At least two diagnosis codes of OSA within 60 days. 4) At least one procedure code for OSA treatment (positive airway pressure (PAP) therapy or oral device). The performance of all five algorithms will be assessed in a validation study using linked Medicare and EHR data.
Aim 2: adapted MACE, a composite of myocardial infarction (MI), stroke, coronary artery bypass grafting (CABG), percutaneous transluminal coronary angioplasty (PTCA), and all-cause mortality. We use an adapted definition that substitutes all-cause mortality for cardiovascular death because Medicare claims data do not reliably distinguish cause-specific mortality.

Data analysis plan

Propensity Score (PS) methods will be used to control for measured confounders. Specifically, logistic regression will be utilized to estimate propensity scores - the probability of initiating GLP-1RA compared to SGLT-2 inhibitors, conditional on baseline covariates. Our primary aim is to estimate the

counterfactual scenario of what would have happened to the initiators of GLP-1RA if they had initiated SGLT-2 inhibitors instead. To achieve this goal, we will estimate the average treatment effect in the treated (ATT) by reweighting the comparator drug initiators by the propensity score odds (PS/(1-PS)) (Standardized Morbidity Ratio Weighting).56 The adequacy of covariate balance will be evaluated based on standardized absolute mean differences (SAMD), with a threshold of less than 0.1 indicating satisfactory balance.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

US fee-for-service Medicare

Data sources (types)

Administrative healthcare records (e.g., claims)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Unknown