STUDY PROTOCOL WITH STATISTICAL ANALYSIS PLAN

Official Title:
Associations of Early Add-On GLP-1 Receptor Agonist and SGLT2 Inhibitor Therapy With Mortality and Kidney Outcomes in Adults With Obesity and Type 2 Diabetes Across Cardiovascular-Kidney-Metabolic Stages 2-3: A Target-Trial Emulation

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Study Protocol with Statistical Analysis Plan

1. Background and Rationale

Obesity, type 2 diabetes, and cardiovascular-kidney-metabolic (CKM) syndrome frequently coexist and are associated with increased risks of mortality and adverse cardiorenal outcomes. GLP-1 receptor agonists and SGLT2 inhibitors are widely used in the management of type 2 diabetes and obesity and may provide cardiovascular and kidney benefits. However, the comparative effectiveness of early add-on treatment strategies after initiation of either class remains incompletely understood in routine clinical practice. This study uses a target-trial emulation framework and routinely collected electronic health record data from the TriNetX US Collaborative Network to compare early treatment intensification strategies and associated risks of mortality and major cardiorenal outcomes.

2. Study Objective

To compare the 36-month risks of all-cause mortality and major cardiorenal outcomes among adults with obesity, type 2 diabetes, and CKM stage 2-3 who initiated a GLP-1 receptor agonist or an SGLT2 inhibitor and subsequently followed different early treatment intensification strategies.

3. Data Source

The study data were obtained from the TriNetX US Collaborative Network.

4. Study Period / Follow-up End Date

Participants were followed through January 31, 2026.

5. Study Design

This study is a retrospective observational target-trial emulation using routinely collected electronic health record data from the TriNetX US Collaborative Network. Eligible adults with obesity, type 2 diabetes, and cardiovascular-kidney-metabolic stage 2-3 who initiated a GLP-1 receptor agonist or an SGLT2 inhibitor were

identified and compared according to early treatment intensification strategies within 90 days after treatment initiation.

6. Study Population

Adults aged 20 years or older with obesity, type 2 diabetes, and cardiovascular-kidney-metabolic stage 2-3 identified from the TriNetX US Collaborative Network who newly initiated a GLP-1 receptor agonist or an SGLT2 inhibitor during the study period.

7. Inclusion Criteria

1. Age ≥ 20 years at cohort entry
2. Obesity, defined as BMI ≥ 27 kg/m^2
3. Type 2 diabetes mellitus
4. CKM stage 2-3 before index treatment initiation
5. New initiation of a GLP-1 receptor agonist or an SGLT2 inhibitor during the study identification period
6. Sufficient baseline data for eligibility assessment, treatment assignment, covariate measurement, and outcome ascertainment

8. Exclusion Criteria

1. Prior use of relevant glucose-lowering drug classes within 6 months before cohort entry
2. Major cardiovascular disease or advanced kidney disease within 12 months before cohort entry
3. Major cardiovascular or renal events within 6 months before cohort entry
4. Any history of diabetes other than type 2 diabetes
5. HIV infection
6. Bariatric surgery
7. Solid-organ transplantation
8. Missing or insufficient data for eligibility, exposure, covariate, or outcome assessment

9. Exposure Groups

Participants were grouped into two base-therapy cohorts based on the first qualifying glucose-lowering prescription during the study period after the 6-month washout from GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, and sulfonylureas:

Cohort 1: GLP-1 RA Base Therapy Adults who initiated a GLP-1 receptor agonist as

base therapy. Within this cohort, participants were further classified by the first add-on treatment within 90 days into three mutually exclusive treatment strategies:

1a. GLP-1 RA with SGLT2 inhibitor add-on
1b. GLP-1 RA with DPP-4 inhibitor or sulfonylurea add-on
1c. GLP-1 RA only (no early add-on)

Cohort 2: SGLT2i Base Therapy Adults who initiated an SGLT2 inhibitor as base therapy. Within this cohort, participants were further classified by the first add-on treatment within 90 days into three mutually exclusive treatment strategies:

2a. SGLT2 inhibitor with GLP-1 receptor agonist add-on
2b. SGLT2 inhibitor with DPP-4 inhibitor or sulfonylurea add-on
2c. SGLT2 inhibitor only (no early add-on)

For add-on strategies, the index date (T_0) was defined as the date of add-on initiation within 90 days after initiation of base therapy. For the no early add-on strategy, the index date was defined as the 90-day landmark after initiation of base therapy. Because the index date was anchored to each participant's first qualifying base-therapy prescription, participants were uniquely assigned to a single base-therapy cohort and are mutually exclusive across the two cohorts.

Comparative effectiveness was assessed using four prespecified pairwise propensity score-matched comparisons: Comparison 1: 1a vs 1b (within the GLP-1 RA base-therapy cohort) Comparison 2: 1a vs 1c (within the GLP-1 RA base-therapy cohort) Comparison 3: 2a vs 2b (within the SGLT2i base-therapy cohort) Comparison 4: 2a vs 2c (within the SGLT2i base-therapy cohort)

10. Outcomes

10.1 Primary Outcome

All-cause mortality within 36 months.

10.2 Secondary Outcomes

1. Major adverse cardiovascular events (MACE), defined as cardiovascular arrest, myocardial infarction, or stroke
2. Major adverse kidney events (MAKE), defined as end-stage kidney disease, dialysis dependence or initiation, kidney failure, or death

11. Follow-up

Follow-up began on the assigned index date and continued until the earliest occurrence of the outcome of interest, death, last recorded encounter, or January 31,

2026.

12. Statistical Analysis Plan

12.1 General Approach

This study applied a target-trial emulation framework to compare early treatment intensification strategies using observational data. Comparative effectiveness was assessed over 36 months.

12.2 Propensity Score Methods

Multinomial propensity-score methods were used to address nonrandom treatment selection.

12.3 Matching

One-to-one nearest-neighbor matching without replacement was performed using a caliper of 0.2 times the standard deviation of the logit propensity score.

12.4 Covariates

Baseline covariates were included in treatment assignment modeling and covariate balance assessment. Covariate balance after matching was evaluated using standardized mean differences. Residual imbalance, if present, was further adjusted in the outcome models.

12.5 Main Outcome Models

Kaplan-Meier methods and Cox proportional hazards models were used to estimate comparative risks, hazard ratios, and 95% confidence intervals.

12.6 Estimands

Primary estimands included relative hazards and absolute risk differences at 36 months for the four prespecified pairwise propensity score-matched comparisons of early treatment intensification strategies described in Section 9.

12.7 Analysis Strategies

Both intention-to-treat and per-protocol analyses were performed.

- **Intention-to-treat analysis:** Participants were analyzed according to the initially assigned treatment strategy regardless of subsequent treatment changes.

- **Per-protocol analysis:** Participants were followed according to persistence with the assigned treatment strategy under protocol-defined treatment adherence criteria.

12.8 Subgroup Analyses

Prespecified subgroup analyses were conducted according to:

1. CKM stage
2. Obesity severity
3. Baseline kidney function
4. Baseline cardiovascular comorbidity

12.9 Sensitivity Analyses

Additional analyses included:

1. Six-month landmark analyses
2. Region-stratified analyses
3. Extended follow-up analyses
4. Formal interaction testing across demographic and clinical strata
5. E-value analyses for robustness to unmeasured confounding
6. Multiplicity control using the Benjamini-Hochberg method

13. Ethical Considerations

This study was approved by the Institutional Review Board of Chung Shan Medical University Hospital under approval number CS1-25149.

14. Data Privacy

The study used de-identified electronic health record data from the TriNetX US Collaborative Network. No directly identifiable personal information was included in the analytical dataset.

15. Limitations

As a retrospective observational study, this analysis may be subject to residual confounding, misclassification, and incomplete capture of exposures, outcomes, or covariates in routine clinical data. However, the target-trial emulation framework and propensity-score methods were used to improve comparability across treatment groups.