Janssen Research & Development*

Study Protocol for Retrospective Observational Studies with Secondary Data

Comparison of Canagliflozin vs. Alternative Antihyperglycemic Treatments on Risk of Heart Failure Hospitalization and Amputation for Patients with Type 2 Diabetes Mellitus and the Subpopulation with Established Cardiovascular Disease

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AMENDMENT 5

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2. AMENDMENTS AND UPDATES

Amendment Number	Date	Section of study protocol	Reason
1	10/2/2017	8.2, 8.3, and all relevant sections	Updated based on advice/information request from FDA dated 12 September 2017 and 27 September 2017.
2	1/16/2017	Revised 8.2, 8.3, 8.4, 9, 10.1, 10.3; added Appendix 1	Updated based on advice/information request from FDA dated 14 December 2017
3	1/31/2018	n/a	Administrative Correction- the protocol Amendment INT-2 had the incorrect body of the protocol. Amendment INT-3 provided the correction.
4	2/13/2018	Revised 10.1, 10.2, 10.3	Based on FDA advice dated 8 February 2018 and 13 February 2018 teleconference, added a 'modified intent-to-treat' time-at-risk definition and revised the description regarding the analysis for clinical characterization for all exposure cohorts.
5	3/28/2018	Revised 10.1, 10.3	Based on FDA advice 20 March 2018, added clarification about the role of censoring before and after exposure initiation, added sensitivity analyses to evaluate robustness of censoring assumptions.

3. LIST OF ABBREVIATIONS

abbreviation	description of abbreviated term
AHA	antihyperglycemic agents
CAD	coronary artery disease
CDM	Common Data Model
COBRA	Consolidated Omnibus Budget Reconciliation Act
CV	cardiovascular
DM	diabetes mellitus
DPP-4(i)	dipeptidyl peptidase-4 (inhibitors)
EPS	exposure propensity score
GLP-1(a)	glucagon-like peptide-1 (agonists)
ICD-9	International classification of disease, version 9
IRB	Institutional Review Board
ITT	intent-to-treat
LADA	latent autoimmune diabetes in adults
OMOP	Observational Medical Outcomes Partnership
PVD	peripheral vascular disease
RLRM	regularized logistic regression model
SGLT2i	sodium-glucose co-transporter 2 inhibitors
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TZDs	thiazolidinediones
US	United States

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5. ABSTRACT

Recent studies have suggested that SGLT2 inhibitors may reduce the risk of cardiovascular events, relative to placebo, and SGLT2i drugs may lower risk of hospitalization for heart failure and all-cause mortality relative to other glucose lowering drugs. However, there are limited head-to-head comparisons that provide a real-world perspective of the safety and effectiveness of canagliflozin relative to other drugs in the SGLT2i class or alternative therapies. This study aims to examine the comparative effects of canagliflozin vs. other alternative treatments for T2DM, overall and within the subpopulation of patients with established cardiovascular diseases, across 4 US administrative claims databases. We will study 2 health outcomes {1) hospitalization for heart failure, and 2) below knee lower extremity amputation }, amongst new users of canagliflozin vs. new users of {1) empagliflozin, 2) dapagliflozin, 3) empagliflozin or dapagliflozin, 4) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 5) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs } and amongst new users of empagliflozin or dapagliflozin vs. new users of {1) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 2) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs } for patients with T2DM, overall and in the subpopulation with established cardiovascular diseases. We will perform clinical characterization to descriptively summarize and compare the exposure populations, and perform population-level effect estimation analyses for comparative effectiveness and safety.

6. RATIONALE AND BACKGROUND

Diabetes mellitus (DM), a chronic condition, is associated with significant morbidity and mortality. As the United States (US) population ages, the incidence and prevalence as well as its financial and social impact will continue to rise. Based on data from the National Diabetes Statistics Report (2014),[1] it was estimated that the overall prevalence of DM in the US population was 9.3% (29.1 million) in 2012, and reached an astonishing rate of 25.9% (11.8 million) among those 65 years and older. Patients with type 2 diabetes mellitus (T2DM) often have a high prevalence of several other comorbidities including hypertension, obesity, hyperlipidemia, coronary artery disease (CAD), peripheral vascular disease (PVD), and renal dysfunctions.

Patients with T2DM have many treatment options to manage their disease, including metformin, sodium-glucose co-transporter 2 inhibitors (SGLT2i), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonist, thiazolidinediones (TZD), sulfonylureas (SU), insulin or other antihyperglycemic agents (AHA). Canagliflozin is one of the drugs in the SGLT2i class. Clinical trials have suggested canagliflozin may reduce the risk of major adverse cardiovascular events, relative to placebo. These findings are largely consistent with results from a placebo-controlled clinical trial for empagliflozin, another drug in the SGLT2i class [2]. However, there have been no studies that have provided a direct comparison among the drugs in the SGLT2i class to determine if the safety and effectiveness profile of each drug follow a common class effect. An observational database study was conducted to compare all SGLT2i drugs with other glucose-lowering drugs for hospitalization of heart failure and all-cause mortality, and showed lower risk of both outcomes associated with SGLT2i [3]. The study did not provide molecule-

specific effect estimates, nor did it provide real-world evidence about any of the other adverse outcomes that have been observed in SGLT2i trials, such as amputation.

This study aims to examine the comparative effects of canagliflozin vs. other SGLT2 inhibitors and other alternative treatments for T2DM, overall and within the subpopulation of patients with established cardiovascular diseases, across 4 US administrative claims databases.

7. STUDY OBJECTIVES

7.1. Primary Objective(s):

- To estimate the incidence of health outcomes {1) hospitalization for heart failure, 2) below knee lower extremity amputation }, in patients diagnosed with type 2 diabetes mellitus (T2DM) who are newly exposed to 1) canagliflozin, 2) empagliflozin, 3) dapagliflozin, 4) empagliflozin or dapagliflozin, 5) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 6) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs, for the period from start of exposure through the end of exposure (treatment discontinuation for at least 30 days).

- To estimate the incidence of health outcomes {1) hospitalization for heart failure, 2) below knee lower extremity amputation }, in patients diagnosed with T2DM **and with established cardiovascular disease** who are newly exposed to 1) canagliflozin, 2) empagliflozin, 3) dapagliflozin, 4) empagliflozin or dapagliflozin, 5) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 6) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs, for the period from start of exposure through the end of exposure (treatment discontinuation for at least 30 days).

- To compare the hazards of outcomes {1) hospitalization for heart failure, 2) below knee lower extremity amputation } in the target cohort { patients diagnosed with T2DM who newly exposed to canagliflozin } versus each comparator cohort { patients diagnosed with T2DM who are newly exposed to 1) empagliflozin, 2) dapagliflozin, 3) empagliflozin or dapagliflozin, 4) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 5) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs } during the 'on treatment' period from start of exposure through the end of exposure (treatment discontinuation for at least 30 days) and the 'intent-to-treat' period from start of exposure through end of continuous observation.

- To compare the hazards of outcomes {1) hospitalization for heart failure, 2) below knee lower extremity amputation } in the target cohort { patients diagnosed with T2DM who newly exposed to canagliflozin } in the target cohort { patients diagnosed with T2DM **and with established cardiovascular disease** who are newly exposed to canagliflozin } versus each comparator cohort { patients diagnosed with T2DM **and with established cardiovascular disease** who newly exposed to 1) empagliflozin, 2) dapagliflozin, 3) empagliflozin or dapagliflozin, 4) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 5) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs }

during the 'on treatment' period from start of exposure through the end of exposure (treatment discontinuation for at least 30 days) and the 'intent-to-treat' period from start of exposure through end of continuous observation.

- To compare the hazards of outcomes {1) hospitalization for heart failure, 2) below knee lower extremity amputation } in the target cohort { patients diagnosed with T2DM who newly exposed to empagliflozin or dapagliflozin } versus each comparator cohort {patients diagnosed with T2DM who are newly exposed to 1) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 2) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs } during the 'on treatment' period from start of exposure through the end of exposure (treatment discontinuation for at least 30 days) and the 'intent-to-treat' period from start of exposure through end of continuous observation.

- To compare the hazards of outcomes {1) hospitalization for heart failure, 2) below knee lower extremity amputation } in the target cohort { patients diagnosed with T2DM **and with established cardiovascular disease** who newly exposed to empagliflozin or dapagliflozin } versus each comparator cohort { patients diagnosed with T2DM **and with established cardiovascular disease** who are newly exposed to 1) any DPP-4 inhibitor, GLP-1 agonist or other select AHA, 2) any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin or other select AHAs } during the 'on treatment' period from start of exposure through the end of exposure (treatment discontinuation for at least 30 days) and the 'intent-to-treat' period from start of exposure through end of continuous observation.

8. RESEARCH METHODS

8.1. Study Design and Setting

This study will involve clinical characterization and population-level effect estimation. The clinical characterization analysis will provide descriptive summary statistics about baseline characteristics for each of the exposure cohorts of interest. The population-level effect estimation analysis will follow a retrospective, observational, comparative cohort design. We define 'retrospective' to mean the study will be conducted using data already collected prior to the start of the study. We define 'observational' to mean there is no intervention or treatment assignment imposed by the study. We define 'cohort' to mean a set of patients satisfying one or more inclusion criteria for a duration of time. We define 'comparative cohort design' to mean the formal comparison between two cohorts, a target cohort and comparator cohort, for the risk of an outcome during a defined time period after cohort entry [4]. The design will be conducted in four administrative claims databases in the US, as described in section 8.2. The specific exposure cohorts are described in section 8.3. The time-at-risk definitions are described in section 10.1. The statistical analysis plan for population-level effect estimation is described in section 10.3.

8.2. Data Source(s)

This study will be conducted in four observational health databases:

1. Truven Health MarketScan™ Commercial Claims and Encounters Database (CCAE)

2. Truven Health MarketScan™ Medicare Supplemental and Coordination of Benefits Database (MDCR)

3. Truven Health MarketScan™ Multi-state Medicaid Database (MDCD)

4. OptumInsight's de-identified Clinformatics™ Datamart, Extended – Date of Death (Optum)

Each database is described below:

1. Truven Health MarketScan™ Commercial Claims and Encounters Database (CCAE)

   CCAE is a medical and drug insurance claims database of unique de-identified patients that include active employees, early retirees, COBRA continuers, and their dependents insured by employer-sponsored plans. The database contains inpatient admission records, outpatient services, prescription drugs, populations, eligibility status, and costs of services.

   As of 13 February 2018 (data lock on version CDM_Truven_CCAE_v656), the latest available version of CCAE contains more than 136 million patients with observations from January 2000 through July 2017. The major data elements contained within this database that will be used within this analysis include: outpatient pharmacy dispensing claims – which provide dispensing date, National Drug Code (NDC) to identify the prescription product, days supply, and quantity; inpatient and outpatient medical claims – which provide service date, procedure codes (coded in CPT-4, HCPCS, ICD-9-CM or ICD-10-PCS), and diagnosis codes (coded in ICD-9-CM or ICD-10-CM); and enrollment records – which provide the dates of insurance eligibility, as well as year of birth and sex. The database does contain selected laboratory test results (those sent to a contracted third-party laboratory service provider) for a non-random sample of the population, but this data will not be used within these analyses. As an administrative claims database, records may exist for each reimbursement transaction, such that it is possible for the database to document multiple drugs, diagnoses, and procedures during inpatient and outpatient medical services for a given person over time, during the enrollment period. Claims submitted using the CMS-1500 form are limited to 12 diagnoses per claim. A person may experience discontinuation in their eligibility within the same database and the same database may contain observations during multiple discontinuous periods of time for a given individual.

   The following limitations of Truven CCAE should be noted:

   - The commercially insured patients represent a higher socioeconomic status than the overall US population.
   - Data are based on financial claims filed for reimbursement; disease coding may reflect financial incentives for reimbursement rather than clinically and systematically verified definitions.

- Prescriptions are those filled at outpatient pharmacies, not those prescribed or administered within inpatient services. The extent to which prescribed records went unfulfilled is not known. It is also not known whether medications were actually taken as directed, although repeated dispensing of the same drug would suggest that this is the case.
- There is a data lag; Truven only sends records that are 100% paid, which can take about 6 months after year end.

2. Truven Health MarketScan™ Medicare Supplemental and Coordination of Benefits Database (MDCR)

   MDCR is an administrative health claims database for Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans (predominantly fee-for-service plans). Only plans where both the Medicare-paid amounts and the employer-paid amounts were available and evident on the claims were selected for this database. MDCR captures person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug. It also includes results for outpatient lab tests processed by large national lab vendors.

   As of 13 February 2018 (data lock on version CDM_Truven_MDCR_v657), the latest available version of MDCR contains more than 9.8 million patients with observations from January 2000 through July 2017. The major data elements contained within this database that will be used within this analysis include: outpatient pharmacy dispensing claims – which provide dispensing date, National Drug Code (NDC) to identify the prescription product, days supply, and quantity; inpatient and outpatient medical claims – which provide service date, procedure codes (coded in CPT-4, HCPCS, ICD-9-CM or ICD-10-PCS), and diagnosis codes (coded in ICD-9-CM or ICD-10-CM); and enrollment records – which provide the dates of insurance eligibility, as well as year of birth and sex. The database does contain selected laboratory test results (those sent to a contracted third-party laboratory service provider) for a non-random sample of the population, but this data will not be used within these analyses. As an administrative claims database, records may exist for each reimbursement transaction, such that it is possible for the database to document multiple drugs, diagnoses, and procedures during inpatient and outpatient medical services for a given person over time, during the enrollment period. Claims submitted using the CMS-1500 form are limited to 12 diagnoses per claim. A person may experience discontinuation in their eligibility and the database may contain observations during multiple discontinuous periods of time for a given individual.

   The following limitations of MDCR should be noted:

   - The commercially insured patients represent a higher socioeconomic status than the overall Medicare population.
   - Exact birth date is not available, only year of birth.

- Data based on financial claims filed for reimbursement, disease coding may reflect financial incentives for reimbursement rather than clinically and systematically verified definitions.

- Prescriptions are those filled, not those prescribed. We do not know the universe of prescribed records that went unfulfilled.

- There is data lag, MarketScan only sends records that are 100% paid, which can take about 6 months after year end.

3. Truven Health MarketScan™ Multi-state Medicaid Database (MDCD)

   MDCD contains the pooled healthcare experience of Medicaid enrollees from multiple states. MDCD includes medical claims from inpatient and outpatient services and prescription drug claims, as well as information on enrollment, long-term care, and other medical care.

   As of 13 February 2018 (data lock on version CDM_Truven_MDCD_v635), the latest available version of MDCD contains more than 25.5 million patients with observations from February 2006 through December 2016. The major data elements contained within this database that will be used within this analysis include: outpatient pharmacy dispensing claims – which provide dispensing date, National Drug Code (NDC) to identify the prescription product, days supply, and quantity; inpatient and outpatient medical claims – which provide service date, procedure codes (coded in CPT-4, HCPCS, ICD-9-CM or ICD-10-PCS), and diagnosis codes (coded in ICD-9-CM or ICD-10-CM); and enrollment records – which provide the dates of insurance eligibility, as well as year of birth and sex. The database does not contain any laboratory test results. As an administrative claims database, records may exist for each reimbursement transaction, such that it is possible for the database to document multiple drugs, diagnoses, and procedures during inpatient and outpatient medical services for a given person over time, during the enrollment period. Claims submitted using the CMS-1500 form are limited to 12 diagnoses per claim. A person may experience discontinuation in their eligibility and the database may contain observations during multiple discontinuous periods of time for a given individual.

   The following limitations of MDCD should be noted:

   - No state information is available.

   - Exact birth date is not available, only year of birth.

   - Lab tests processed by large national lab vendors are not available for MDCD patients.

   - Members eligible for Medicare may have incomplete data.

- Data based on financial claims filed for reimbursement, disease coding may reflect financial incentives for reimbursement rather than clinically and systematically verified definitions.

- Prescriptions are those filled, not those prescribed. We do not know the universe of prescribed records that went unfulfilled.

4. OptumInsight's de-identified Clinformatics™ Datamart, Extended – Date of Death (Optum)

   Optum is an administrative health claims database for members of United Healthcare, who are fully insured in commercial plans or in administrative services only (ASOs) and commercial Medicare. For each group, only members with both medical and prescription drug coverage are included. Optum captures person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug, and includes results for outpatient lab tests processed by large national lab vendors (about 30% of the population).

   As of 13 February 2018 (data lock on version CDM_Optum_Extended_DoD_v654), the latest available version of Optum contains more than 80 million patients with observations from June 2000 through June 2017. The major data elements contained within this database that will be used within this analysis include: outpatient pharmacy dispensing claims – which provide dispensing date, National Drug Code (NDC) to identify the prescription product, days supply, and quantity; inpatient and outpatient medical claims – which provide service date, procedure codes (coded in CPT-4, HCPCS, ICD-9-CM or ICD-10-PCS), and diagnosis codes (coded in ICD-9-CM or ICD-10-CM); and enrollment records – which provide the dates of insurance eligibility, as well as year of birth and sex. The database does contain selected laboratory test results (those sent to a contracted third-party laboratory service provider) for a non-random sample of the population, but this data will not be used within these analyses. As an administrative claims database, records may exist for each reimbursement transaction, such that it is possible for the database to document multiple drugs, diagnoses, and procedures during inpatient and outpatient medical services for a given person over time, during the enrollment period. Claims submitted using the CMS-1500 form are limited to 12 diagnoses per claim. A person may experience discontinuation in their eligibility and the database may contain observations during multiple discontinuous periods of time for a given individual.

   The following limitations of Optum should be noted:

   - Family enrollment, capitated plan information and exact birth date are not available

   - All claims are limited to first 5 diagnostic codes.

- Data based on financial claims filed for reimbursement, disease coding may reflect financial incentives for reimbursement rather than clinically and systematically verified definitions.

- Prescriptions are those filled, not those prescribed. We do not know the universe of prescribed records that went unfulfilled.

All four databases have been standardized into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM),[a] which includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts and enables consistent application of analyses across multiple disparate data sources [5, 6]. Complete specifications for the extract, transform, and load (ETL) process for each database is available at: https://github.com/OHDSI/ETL-CDMBuilder.

The standardized vocabularies within OMOP CDM enable disparate source codes to be mapped into a common referent standard for each clinical domain, such as conditions, drugs, and procedures. As an example of particular relevance for this analysis, the standard vocabulary for conditions is SNOMED-CT and source vocabularies that have been mapped into SNOMED-CT include both ICD-9-CM and ICD-10-CM. In the US, with the transition of diagnosis recording from ICD-9-CM to ICD-10-CM occurring in October2015, the use of OMOP standardized vocabularies is quite valuable because it means a common definition for exposures, outcomes, and covariates can be applied to all data, both pre- and post-October 2015 using SNOMED concepts instead of ICD-9-CM or ICD-10-CM codes. The source codes that map to all standard concepts are provided in Annex 1, and the full OMOP standard vocabulary is available for download at: http://athena.ohdsi.org/.

All analyses will be performed independently within each of these four databases to produce four source-specific results for each analysis. No patient-level data will be pooled across the databases for any analysis, in part to avoid the potential risk of 'double-counting' cases for duplicate patients, i.e., the databases will be kept separate to produce database-specific effect estimates (although we will potentially combine database-specific results meta-analytically). The extent of overlap between patients in these databases is unknown, and because all databases have been de-identified, it is not possible or allowable to attempt to link patients across databases. CCAE represents a privately-insured population of employees and their dependents, making it unlikely they would also qualify for a state Medicaid program, as represented in MDCD. A small proportion of patients do transition from CCAE to MDCR when they retire from their employee and purchase supplemental Medicare insurance, but in these cases, the patients would not be duplicated at the same period of time, but rather their person-time would be split between the two databases. It would be similarly unlikely that a person opting to purchase supplemental Medicare insurance qualifies for state Medicaid benefits. Persons with data in any of the Truven datasets may potentially be captured in Optum if the employer or state

[a] https://github.com/OHDSI/CommonDataModel

programs contained in Truven are administered by plans within the Optum catchment, but employers and plans are de-identified so the extent of overlap cannot be determined.

8.3. Study Populations

12 exposure cohorts will be constructed to allow for clinical characterization, and population-level effect estimation. The list of titles for these 12 exposure cohorts is provided here, and the complete specification of each exposure cohort is detailed in Appendix 1.

1. new users of canagliflozin
2. new users of canagliflozin with established cardiovascular disease
3. new users of empagliflozin
4. new users of empagliflozin with established cardiovascular disease
5. new users of dapagliflozin
6. new users of dapagliflozin with established cardiovascular disease
7. new users of empagliflozin or dapagliflozin
8. new users of empagliflozin or dapagliflozin with established cardiovascular disease
9. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
10. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease
11. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
12. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease

Additionally, sensitivity analyses will be performed on subgroups of the exposure cohorts, based on prior use of non-metformin AHA and prior use of comparator cohort-defining drugs. The subgroups can broadly be considered in three types: a) Prevalent new users refer to patients who are new users of the cohort-defining drugs and were exposed to AHA during the 365 days prior to the index date of cohort defining drug; b) Incident new users refer to patients who are new users of the cohort-defining drugs and were not exposed to any non-metformin AHA during the 365 days prior to the index date of cohort defining drug; and c) Incident new users of the cohort-defining drugs refer to patients who are new users of the cohort-defining drugs (for both the target and the comparison cohort in each pair-wise comparison). For completeness, these cohorts required to perform these sensitivity analyses are enumerated below:

13. new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
14. new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
15. new users of canagliflozin with no prior exposure to empagliflozin
16. new users of canagliflozin with no prior exposure to dapagliflozin
17. new users of canagliflozin with no prior exposure to empagliflozin or dapagliflozin
18. new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA

19. new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
20. new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
21. new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
22. new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin
23. new users of canagliflozin with established cardiovascular disease and no prior exposure to dapagliflozin
24. new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin
25. new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
26. new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
27. new users of empagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
28. new users of empagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
29. new users of empagliflozin with no prior exposure to canagliflozin
30. new users of empagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
31. new users of empagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
32. new users of empagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
33. new users of dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
34. new users of dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
35. new users of dapagliflozin with no prior exposure to canagliflozin
36. new users of dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
37. new users of dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
38. new users of dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
39. new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
40. new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
41. new users of empagliflozin or dapagliflozin with no prior exposure to canagliflozin

42. new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
43. new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
44. new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
45. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
46. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
47. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
48. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
49. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
50. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
51. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to canagliflozin
52. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to empagliflozin or dapagliflozin
53. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
54. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
55. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin
56. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin
57. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
58. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA

59. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to canagliflozin
60. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to empagliflozin or dapagliflozin
61. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
62. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
63. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin
64. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin

Generally, each cohort has an index cohort entry event of an initial drug exposure and satisfies the following inclusion criteria:

- First exposure to the particular drug(s) in database (index date)
- Exposure start is between 1 April 2013 and 15 May 2017.
- At least 365 days of continuous observation time prior to index
- At least 1 condition occurrence of ‘Type II diabetes’ any time in the prior continuous observation time (which is at least 365 days long) before or on the index date (first exposure to the particular drug(s) in database)
- Exactly 0 condition occurrences of ‘Type I diabetes’ any time in the prior continuous observation time (which is at least 365 days long) before or on the index date (first exposure to the particular drug(s) in database)
- Exactly 0 condition occurrences of ‘Secondary diabetes’ any time in the prior continuous observation time (which is at least 365 days long) before or on the index date (first exposure to the particular drug(s) in database)

Note, there is no patient age restriction, and there is no restriction on the healthcare setting(s) of the study population for the exposure cohorts.

Each cohort with ‘established cardiovascular disease’ additionally satisfies the following inclusion criteria:

- at least 1 occurrence of ‘conditions indicating established cardiovascular disease’ on or any time in the prior continuous observation time (which is at least 365 days long) prior to the index date (defined as diagnosis codes classified as ‘arteriosclerotic vascular disease’, ‘cerebrovascular disease’, ‘late effects of cerebrovascular disease’, ‘myocardial infarction’, ‘angina pectoris’, ‘precerebral arterial occlusion’, ‘chronic

ischemic heart disease', 'acute ischemic heart disease', 'intracranial hemorrhage', 'subdural hemorrhage', 'cerebral hemorrhage', subarachnoid hemorrhage', 'coronary occlusion', 'cerebral artery occlusion', 'peripheral vascular disease', or 'peripheral circulatory disorder associated with diabetes mellitus'), or

- at least 1 occurrence of 'procedures indicated established cardiovascular disease' on or any time in the prior continuous observation time (which is at least 365 days long) prior to the index date (defined by all procedure codes classified as 'operative procedure on coronary artery' or 'operative procedure on artery of extremity', and mainly comprised of 'percutaneous transluminal coronary angioplasty', 'coronary artery bypass graft', or 'revascularization').

Each cohort has cohort exit criteria based on the end of the period of persistent exposure to the cohort-defining drug, using a 30-day persistence gap window. Additionally, cohort exit is censored if a drug era start for a non-metformin AHA other than the cohort-defining drug(s) is observed after cohort entry.

Section 9 highlights the prevalence of prior antidiabetic treatments within each cohort.

Throughout the document, when a drug class is referenced, the specific ingredients that are included in the drug class are as follows:

- DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin
- GLP-1 agonists: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide
- TZDs: pioglitazone, rosiglitazone, troglitazone
- Sulfonylureas: glipizide, glyburide, glimepiride, chlorpropamide, tolazamide, tolbutamide, acetohexamide
- Other select AHAs: acarbose, bromocriptine, miglitol, nateglinide, repaglinide

Note, metformin is not included in any cohort definition, as it is often prescribed as first line of therapy, and therefore not expected to be meaningfully comparable with canagliflozin exposure. Metformin-containing combination products are included in all cohort definitions.

For all exposure cohorts, we derive 'drug eras' as periods of persistent exposure to a particular active ingredient or set of ingredients. 'Drug eras' are derived from verbatim drug exposure records, including outpatient pharmacy dispensing claims records. From an outpatient pharmacy dispensing claims record, we define the drug exposure start date = dispensing date, and define the exposure end date = dispensing date + days supply. 'Drug eras' consolidate drug exposure records of a particular ingredient for a given patient by combining together records where the drug exposure end date of one record is within a 'persistence window' of the drug exposure start date of a subsequent record. A 'persistence window' of 30 days means that a person will be assumed to be persistently exposed to a drug so long as two successive dispensings have no more than a 30-day gap between the end date of the first and the start date of the second. A 'surveillance window' may be appended to the end date of each period of persistent exposure. A 'surveillance window' of 30 days means that a person who completed a drug regimen will continue to be followed for 30 days after the last exposure end date. As an example, if a person

had an initial prescription dispensing for canagliflozin on 1Jan2015, which came with 30 days supply, and a second prescription for canagliflozin on 15Feb2015, also with 30 days supply, the data would be processed as follows: the first exposure record would be assigned start date = 1Jan2015 and end date = 31Jan2015 (1Jan2015 + 30d). the second exposure record would be assigned start date = 15Feb2015, end date = 17Mar2015 (15Feb2015+30d). Because the two exposures were less than 30 days apart (15Feb2015 – 31Jan2015 = 16 days), these two exposure records would be consolidated into one drug era record, with start date = 1Jan2015 and end date = 17Mar2015. With an additional 'surveillance window' of 30 days, this drug era record would be expanded to have start date = 1Jan2015 and end date = 17Apr2015 (17Mar2015 + 30d). The drug era logic used here does not account for stockpiling if subsequent prescriptions overlap in time, nor does it account for dose tailoring, since the period of exposure is defined at the ingredient level.

The human-readable textual description of each exposure cohort definition is listed in Appendix 1, and the listing of concepts and associated source codes for each conceptset in italics in provided in Annex 1. The complete specification for each cohort definition, including human-readable textual description, listing of all included concepts and associated source codes, and computer-executable SQL, has been generated using the OHDSI open-source analytics tool [7], ATLAS. Annex 2 contains the JSON files that can be used to import any of these cohort definitions into any ATLAS installation. In the exposure cohort definitions detailed in Appendix 1, please note that when referring to exposure, the "event" is the initial exposure and is not based in any way on the occurrence of outcome events.

8.3.1. Target Cohorts

Four of the exposure cohorts (E) described in section 8.3 will be used as target cohorts:

1. E1: new users of canagliflozin
2. E2: new users of canagliflozin with established cardiovascular disease
3. E7: new users of empagliflozin or dapagliflozin
4. E8: new users of empagliflozin or dapagliflozin with established cardiovascular disease

In addition, for the sensitivity analyses of subgroups of interest, 22 exposure cohorts (E) described in section 8.3 will be used as target cohorts:

5. E13: new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
6. E14: new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
7. E15: new users of canagliflozin with no prior exposure to empagliflozin
8. E16: new users of canagliflozin with no prior exposure to dapagliflozin
9. E17: new users of canagliflozin with no prior exposure to empagliflozin or dapagliflozin
10. E18: new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
11. E19: new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA

12. E20: new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
13. E21: new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
14. E22: new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin
15. E23: new users of canagliflozin with established cardiovascular disease and no prior exposure to dapagliflozin
16. E24: new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin
17. E25: new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
18. E26: new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
19. E39: new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
20. E40: new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
21. E42: new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
22. E43: new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
23. E44: new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
24. E45: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
25. E47: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
26. E48: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA

8.3.2. Comparator Cohorts

10 of the exposure cohorts (E) described in section 8.3 will be used as comparator cohorts:

1. E3: new users of empagliflozin
2. E4: new users of empagliflozin with established cardiovascular disease
3. E5: new users of dapagliflozin
4. E6: new users of dapagliflozin with established cardiovascular disease
5. E7: new users of empagliflozin or dapagliflozin
6. E8: new users of empagliflozin or dapagliflozin with established cardiovascular disease
7. E9: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
8. E10: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease
9. E11: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA

10. E12: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease

In addition, for the sensitivity analyses of subgroups of interest, 38 exposure cohorts (E) described in section 8.3 will be used as comparator cohorts:

11. E27: new users of empagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
12. E28: new users of empagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
13. E29: new users of empagliflozin with no prior exposure to canagliflozin
14. E30: new users of empagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
15. E31: new users of empagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
16. E32: new users of empagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
17. E33: new users of dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
18. E34: new users of dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
19. E35: new users of dapagliflozin with no prior exposure to canagliflozin
20. E36: new users of dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
21. E37: new users of dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
22. E38: new users of dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
23. E39: new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
24. E40: new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
25. E41: new users of empagliflozin or dapagliflozin with no prior exposure to canagliflozin
26. E42: new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
27. E43: new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
28. E44: new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
29. E45: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure

30. E46: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
31. E47: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
32. E48: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
33. E49: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
34. E50: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
35. E51: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to canagliflozin
36. E52: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to empagliflozin or dapagliflozin
37. E53: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
38. E54: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
39. E55: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin
40. E56: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin
41. E57: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
42. E58: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
43. E59: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to canagliflozin
44. E60: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to empagliflozin or dapagliflozin
45. E61: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA

46. E62: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
47. E63: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin
48. E64: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin

For the primary analyses, 14 target cohort (T)-comparator cohort (C) comparisons will be made for population-level effect estimation:

1. T1: new users of canagliflozin, vs. C1: new users of empagliflozin
2. T1: new users of canagliflozin, vs. C3: new users of dapagliflozin
3. T1: new users of canagliflozin, vs. C5: new users of empagliflozin or dapagliflozin
4. T1: new users of canagliflozin, vs. C7: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
5. T1: new users of canagliflozin, vs. C9: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
6. T2: new users of canagliflozin with established cardiovascular disease, vs. C2: new users of empagliflozin with established cardiovascular disease
7. T2: new users of canagliflozin with established cardiovascular disease, vs. C4: new users of dapagliflozin with established cardiovascular disease
8. T2: new users of canagliflozin with established cardiovascular disease, vs. C6: new users of empagliflozin or dapagliflozin with established cardiovascular disease
9. T2: new users of canagliflozin with established cardiovascular disease, vs. C8: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease
10. T2: new users of canagliflozin with established cardiovascular disease, vs. C10: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease
11. T3: new users of empagliflozin or dapagliflozin, vs. C7: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
12. T3: new users of empagliflozin or dapagliflozin, vs. C9: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
13. T4: new users of empagliflozin or dapagliflozin with established cardiovascular disease, vs. C8: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease
14. T4: new users of empagliflozin or dapagliflozin with established cardiovascular disease, vs. C10: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease

Exposure cohorts E7 and E8 will be the comparator cohorts (C5 and C6) in comparisons #3 and #8; and the target cohorts (T3 and T4) in comparisons #11, #12, #13, and #14.

In addition, for the sensitivity analyses of subgroups of interest, 42 target cohort (T)-comparator cohort (C) comparisons will be made for population-level effect estimation:

Sensitivity analyses for comparison 1:

15. T5: new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C11: new users of empagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
16. T6: new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C12: new users of empagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
17. T7: new users of canagliflozin with no prior exposure to empagliflozin vs. C13: new users of empagliflozin with no prior exposure to canagliflozin

Sensitivity analyses for comparison 2:

18. T5: new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C17: new users of dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
19. T6: new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C18: new users of dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
20. T8: new users of canagliflozin with no prior exposure to dapagliflozin vs. C19: new users of dapagliflozin with no prior exposure to canagliflozin

Sensitivity analyses for comparison 3:

21. T5: new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C23: new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
22. T6: new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C24: new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
23. T9: new users of canagliflozin with no prior exposure to empagliflozin or dapagliflozin vs. C25: new users of empagliflozin or dapagliflozin with no prior exposure to canagliflozin

Sensitivity analyses for comparison 4:

24. T5: new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C33: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with at least 1 prior non-metformin AHA exposure

in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA

25. T6: new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C34: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
26. T10: new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA vs. C35: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to canagliflozin

Sensitivity analyses for comparison 5:

27. T5: new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C41: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
28. T6: new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C42: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
29. T11: new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA vs. C43: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to canagliflozin

Sensitivity analyses for comparison 6:

30. T12: new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C14: new users of empagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
31. T13: new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C15: new users of empagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
32. T14: new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin vs. C16: new users of empagliflozin with established cardiovascular disease and no prior exposure to canagliflozin

Sensitivity analyses for comparison 7:

33. T12: new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C20: new users of dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure

34. T13: new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C21: new users of dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
35. T15: new users of canagliflozin with established cardiovascular disease and no prior exposure to dapagliflozin vs. C22: new users of dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin

Sensitivity analyses for comparison 8:

36. T12: new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C28: new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
37. T13: new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C29: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
38. T16: new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin vs. C30: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin

Sensitivity analyses for comparison 9:

39. T12: new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C37: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
40. T13: new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C38: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
41. T17: new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA vs. C39: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin

Sensitivity analyses for comparison 10:

42. T12: new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs.

C45: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA

43. T13: new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure vs. C46: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
44. T18: new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA vs. C47: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin

Sensitivity analyses for comparison 11:

45. T19: new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C33: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
46. T20: new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C34: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
47. T21: new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA vs. C36: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to empagliflozin or dapagliflozin

Sensitivity analyses for comparison 12:

48. T19: new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C41: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
49. T20: new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C42: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA

50. T22: new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA vs. C44: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to empagliflozin or dapagliflozin

Sensitivity analyses for comparison 13:

51. T23: new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C37: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
52. T24: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C38: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
53. T25: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA vs. C40: new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin

Sensitivity analyses for comparison 14:

54. T23: new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C45: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
55. T24: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure vs. C46: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
56. T26: new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA vs. C48: new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin

For each treatment group, the generalizability of the 'established cardiovascular disease' subpopulation will be assessed by descriptive comparisons with the 'overall' cohort. For example, 'new users of canagliflozin with established cardiovascular disease' will be compared with 'new users of canagliflozin' to determine what baseline covariates differentiate the populations.

8.4. Outcomes of Interest

Two outcomes cohorts will be constructed to allow for clinical characterization and population-level effect estimation. The human-readable textual description of each cohort definition is listed below, and the listing of concepts and associated source codes for each conceptset in italics is provided in Annex 1. The complete specification for each cohort definition, including human-readable textual description, listing of all included concepts and associated source codes, and computer-executable SQL, has been generated using the OHDSI open-source analytics tool, ATLAS. The hyperlinks below are available internally within JNJ; Annex 2 contains the JSON files that can be used to import any of these cohort definitions into any ATLAS installation. In the following outcome cohort definitions in section 8.4, please note that here, "event" is used to refer to an outcome event, without consideration of exposure status.

1. Hospitalizations for heart failure (primary inpatient diagnosis):

   Non-technical summary: All hospital admissions with a primary diagnosis of 'heart failure'.

   Complete specification:

   Initial Event Cohort
   People having any of the following:

   - a visit occurrence of Inpatient Visit[2]
     - occurrence start is between 2013-04-01 and 2017-05-15 (inclusive)

       Having all of the following criteria:

       - at least 1 occurrences of a condition occurrence of *heart failure*
         - condition type is any of: Inpatient detail - primary, Inpatient header - primary, Primary Condition, Carrier claim detail - 1st position, Carrier claim header - 1st position, Inpatient detail - 1st position, Inpatient header - 1st position, Outpatient detail - 1st position, Outpatient header - 1st position

       starting between 0 days Before and 0 days After event index date

   with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: all events per person.

   Limit qualifying cohort to: all events per person.
   Date Offset Exit Criteria
   This cohort definition end date will be the index event's end date plus 0 days

Cohort Collapse Strategy:
Collapse cohort by era with a gap size of 0 days.

2. Below Knee Lower Extremity Amputation events:

   Non-technical summary: All new below-knee lower extremity amputation procedures, excluding recent (within 30 day) revisions.

   Complete specification:

   Initial Event Cohort
   People having any of the following:

   - a procedure of *below-knee amputations*
     - occurrence start is between 2013-04-01 and 2017-05-15 (inclusive)

   with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: all events per person.

   For people matching the Primary Events, include:
   Having all of the following criteria:

   - exactly 0 occurrences of a procedure of *below-knee amputations*

     starting between 30 days Before and 1 days Before event index date

   Limit cohort of initial events to: all events per person.
   Limit qualifying cohort to: all events per person.
   Date Offset Exit Criteria
   This cohort definition end date will be the index event's start date plus 0 days
   Cohort Collapse Strategy:
   Collapse cohort by era with a gap size of 0 days.

8.4.1. Negative Control Outcomes

Negative control outcomes, outcomes known not to be causally associated with any of the exposure cohorts [8], and are to be used for empirical calibration [9]. The same analysis performed for each target-comparator-outcome combination will also be performed for each negative control outcome. Because of the *a priori* assertion of no effect, we assume the true relative risk for each negative control outcome is 1, and the distance between RR=1 and the observed effect estimate will be classified as error. The sample of negative controls will therefore be used to construct an empirical distribution of the error distribution, which will be used to calibrate the p-values from the unknown outcomes of interest. Analyses performed for negative control outcomes should not be considered formal hypothesis tests, and should not be included in any multiplicity adjustment. The negative control outcomes used in this study in the table below. These negative control outcomes were selected on the basis of being unlisted as potential effects on the product labels of any cohort-defining drugs, not having an observed statistical association from disproportionality analysis of FAERS, and having no identified published literature linking the outcome to any of the exposures of interest. The *a priori* assumption that these outcomes have no causal relation with the exposure is inherently

untestable. The use of a large sample of negative controls also helps to mitigate the risk that any particular negative control has a non-null effect that would bias the error distribution estimate. Negative control outcomes may have a myriad of sources of systematic error, including measurement error due to outcome misclassification for coding imprecision, and unobserved confounding with the exposures of interest; the role of empirical calibration is to use the estimated systematic error from the negative control sample as a proxy for the potential residual bias that may exist for the unknown outcome of interest.

concept_id	concept_name
376707	Acute conjunctivitis
433753	Alcohol abuse
257007	Allergic rhinitis
442077	Anxiety disorder
436665	Bipolar disorder
380094	Carpal tunnel syndrome
255573	Chronic obstructive lung disease
257012	Chronic sinusitis
443617	Conduct disorder
134438	Contact dermatitis
78619	Contusion of knee
378752	Corneal opacity
137063	Corns and callus
133228	Dental caries
134681	Diffuse spasm of esophagus
432251	Disease caused by parasite
378161	Disorder of ear
139057	Disorder of oral soft tissues
31057	Disorder of pharynx
138225	Disorder of sebaceous gland
440329	Herpes zoster without complication
441788	Human papilloma virus infection
140673	Hypothyroidism
374375	Impacted cerumen
139099	Ingrowing nail
436962	Insomnia
201322	Internal hemorrhoids without complication
132466	Lumbar sprain
255891	Lupus erythematosus
444100	Mood disorder
440374	Obsessive-compulsive disorder
380733	Otalgia
372328	Otitis media
4002650	Plantar fasciitis
373478	Presbyopia
436073	Psychotic disorder

concept_id	concept_name
438688	Sarcoidosis
432597	Schizoaffective schizophrenia
435783	Schizophrenia
372409	Sciatica
73562	Solitary sacroiliitis
133141	Tinea pedis
436070	Vitamin D deficiency
434008	White blood cell disorder

For each negative control outcome, events will be defined as follows:

Initial Event Cohort
People having any of the following:

- a condition occurrence of <*negative control outcome*>

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of <*negative control outcome*>

  starting between 90 days Before and 1 days Before event index date

Limit cohort of initial events to: **all events per person.**
Limit qualifying cohort to: **all events per person.**

Date Offset Exit Criteria
This cohort definition end date will be the index event's start date plus 0 days

8.5. Other Variables of Interest (Demographic Characteristics, Confounders, Effect Modifiers)

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates.

The types of baseline covariates used to fit the propensity score model will be:

- Demographics
  - Gender
  - Age group (5-year bands)
  - Index year
  - Index month
- Condition occurrence record for the concept or any its descendants observed during 365d on or prior to cohort index

- Drug exposure record for the concept or any its descendants observed during 365d on or prior to cohort index
- Procedure occurrence record for the concept or any its descendants observed during 365d on or prior to cohort index
- Measurement record for the verbatim concept observed during 365d on or prior to cohort index
- Charlson Index - Romano adaptation, using conditions all time on or prior to cohort index
- Number of distinct conditions observed in 365d on or prior to cohort index (defined as unique SNOMED condition concepts)
- Number of distinct drugs observed in 365d on or prior to cohort index (defined as unique RxNorm ingredient concepts)
- Number of distinct procedures observed in 365d on or prior to cohort index (defined as unique CPT4/HCPCS/ICD9P/ICD10P concepts)
- Number of distinct observations observed in 365d on or prior to cohort index
- Number of distinct measurements observed in 365d on or prior to cohort index (defined as unique LOINC concepts)
- Number of visits observed in 365d on or prior to cohort index
- Number of inpatient visits observed in 365d on or prior to cohort index
- Number of ER visits observed in 365d on or prior to cohort index
- Prior outcome history, observed during all time prior to or on the cohort index, for all study outcomes

Specific drug exposure concepts that define the target and comparator cohorts will be excluded from the propensity score model fitting, but will be used for clinical characterization. Other antidiabetic treatments not used to define the target cohort and comparator cohort will be used in the propensity score model to attempt to balance prior treatment utilization.

This large-scale empirical adjustment strategy should address expected confounders, including demographics, prior cardiovascular risk factors, comorbidities associated with mortality, and health service utilization behavior. The study will be subject to the limitation that some confounders may be unmeasured or inadequately represented in US claims data, including weight, smoking status, level of baseline glycemic control, and lifestyle behaviors, such as diet and exercise.

9. SAMPLE SIZE AND STUDY POWER

The sample size of the cohorts is listed below. These patient counts represent the initial population, prior to statistical adjustment, so provide an upper bound of exposure available for each analysis.

cohort_definition_name	CCAE	MDCD	MDCR	Optum
new users of canagliflozin	78,541	7,497	11,678	45,321
new users of canagliflozin with established cardiovascular disease	19,440	2,554	6,319	14,802
new users of empagliflozin				

cohort_definition_name	CCAE	MDCD	MDCR	Optum
	35,586	549	2,956	14,372
new users of empagliflozin with established cardiovascular disease	9,415	187	1,649	5,138
new users of dapagliflozin	48,226	1,104	2,958	10,098
new users of dapagliflozin with established cardiovascular disease	11,193	401	1,513	2,964
new users of empagliflozin or dapagliflozin	80,409	1,630	5,717	23,297
new users of empagliflozin or dapagliflozin with established cardiovascular disease	19,696	578	3,055	7,727
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	173,694	23,613	38,679	112,161
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease	40,238	8,283	22,835	44,997
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	223,202	43,407	45,333	152,011
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease	40,238	8,283	22,835	44,997
new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure	60851	6121	9935	35390
new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure	17690	1376	1743	9931
new users of canagliflozin with no prior exposure to empagliflozin	77869	7465	11617	44930
new users of canagliflozin with no prior exposure to dapagliflozin	75520	7394	11411	43276
new users of canagliflozin with no prior exposure to empagliflozin or dapagliflozin	74912	7364	11352	42920
new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	31043	3625	3959	19814
new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	14599	1178	1358	8243
new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure	15684	2183	5429	12136
new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure	3756	371	890	2666

cohort_definition_name	CCAE	MDCD	MDCR	Optum
new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin	19266	2546	6286	14653
new users of canagliflozin with established cardiovascular disease and no prior exposure to dapagliflozin	18745	2508	6172	14203
new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin	18585	2500	6141	14071
new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	6982	1140	2073	5971
new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	2902	283	654	2048
new users of empagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure	27747	448	2490	11212
new users of empagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure	7839	101	466	3160
new users of empagliflozin with no prior exposure to canagliflozin	27578	461	2444	12757
new users of empagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure	7648	156	1402	4204
new users of empagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure	1767	31	247	934
new users of empagliflozin with established cardiovascular disease and no prior exposure to canagliflozin	7257	149	1362	4552
new users of dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure	36273	928	2481	7872
new users of dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure	11953	176	477	2226
new users of dapagliflozin with no prior exposure to canagliflozin	39024	979	2568	9311
new users of dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure	8834	353	1277	2438

cohort_definition_name	CCAE	MDCD	MDCR	Optum
new users of dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure	2359	48	236	526
new users of dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin	8943	362	1328	2716
new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure	60688	1354	4775	17931
new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure	19721	276	942	5366
new users of empagliflozin or dapagliflozin with no prior exposure to canagliflozin	64430	1426	4877	21097
new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	34395	704	2031	10179
new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	18006	251	824	4595
new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure	15586	499	2573	6271
new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure	4110	79	482	1456
new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin	15629	505	2612	6959
new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	7523	229	1020	3101
new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	3499	70	394	1177
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	79176	13334	21033	58955

cohort_definition_name	CCAE	MDCD	MDCR	Optum
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	94518	10279	17646	53206
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to canagliflozin	165243	22789	37738	107577
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to empagliflozin or dapagliflozin	167004	23459	38334	110192
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	19748	4906	12625	25772
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	20490	3377	10210	19225
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin	38202	8035	22337	43525
new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin	38679	8228	22670	44383
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	8347	450	612	3577
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	214855	42957	44721	148434
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to canagliflozin	217985	42994	44848	149231
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to empagliflozin or dapagliflozin	218808	43335	45119	150820
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1	19748	4906	12625	25772

cohort_definition_name	CCAE	MDCD	MDCR	Optum
agonist, TZD, SU, insulin, or other select AHA				
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	20490	3377	10210	19225
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin	38202	8035	22337	43525
new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin	38679	8228	22670	44383

The table below presents the total number of events and sample sizes needed to detect a relative increase in risk of below-knee amputation in the target cohort, for a range of potential values of baseline risk in the comparator cohort. As expected, as the baseline event rate decreases, the required sample size increases, although the total number of events needed to detect a certain level of risk (e.g., hazard ratio) remains the same. For example, in order to detect a relative risk of 1.5 for below-knee amputation, with a targeted type I error rate (alpha) of 0.05 (2-sided) and a type II error rate (beta) of 0.20 (power=80%), 191 amputation events from both treatment groups combined would be needed. This would require a matched sample size of approximately 78,610 patients (with 1:1 matching between the target and comparator cohort, each cohort would be 39,305 patients), assuming the event rate of 1.5 per 1,000 person years in the comparison group, the maximum duration of follow-up was 3 years and an annual drop-out rate of 15%. Note that these calculations reflect a general principle; the actual power to detect a certain level of risk would be changing at the time of each analysis, since the baseline event rate, number of events, and duration of maximum follow-up would change accordingly.

1-Sided Alpha	Power	Relative Risk increase	Incidence Rate of Control Group (per 1000 PYs)	Total Number of Events Needed*	Estimated Number of Patients Across Both Cohorts (1:1 matching)*	Estimated Number of Patients Across Both Cohorts (1:1 matching)**
0.025	80%	50% (RR=1.5)	1.0	191	90752	117844
			1.5	191	60544	78610
			3.5	191	26021	33772
		75% (RR=1.75)	1.0	101	43635	56660

1-Sided Alpha	Power	Relative Risk increase	Incidence Rate of Control Group (per 1000 PYs)	Total Number of Events Needed*	Estimated Number of Patients Across Both Cohorts (1:1 matching)*	Estimated Number of Patients Across Both Cohorts (1:1 matching)**
			1.5	101	29114	37799
			3.5	101	12518	16244
		100% (RR=2.0)	1.0	66	26144	33946
			1.5	66	17445	22648
			3.5	66	7504	9737
	90%	50% (RR=1.5)	1.0	256	121636	157948
			1.5	256	81148	105362
			3.5	256	34877	45264
		75% (RR=1.75)	1.0	135	58324	75734
			1.5	135	38914	50524
			3.5	135	16732	21713
		100% (RR=2.0)	1.0	88	34858	45261
			1.5	88	23260	30198
			3.5	88	10005	12982

*Assuming 3 years of enrollment and 3.25 years of maximum duration of follow up adjusting for 15% annual drop-out rate.
**Assuming maximum duration of 3 years

To further summarize the exposure cohorts, the table below provides the prevalence of prior antidiabetic treatments within each exposure cohort from the CCAE database. This table provides a sense of the proportion of patients that may be excluded for any particular target cohort-comparator cohort analysis in which patients belonging to both cohorts are excluded. Also, the table summarizes where there is potential imbalance between cohorts, which would require sufficient adjustment to reduce the risk of residual bias.

Prior T2DM treatment	**new users of canagliflozin**	**new users of canagliflozin with established cardiovascular disease**	**new users of empagliflozin**	**new users of empagliflozin with established cardiovascular disease**	**new users of dapagliflozin**	**new users of dapagliflozin with established cardiovascular disease**	**new users of empagliflozin or dapagliflozin**	**new users of empagliflozin or dapagliflozin with established cardiovascular disease**	**new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA**	**new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease**	**new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA**	**new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease**
Acarbose	1%	1%	1%	1%	1%	1%	1%	1%				
canagliflozin			23%	23%	19%	20%	20%	21%	5%	5%	2%	5%
dapagliflozin	4%	4%	7%	7%					3%	3%	1%	3%
dulaglutide	1%	1%	5%	5%	3%	3%	3%	4%				
empagliflozin	1%	1%			2%	2%			1%	1%	1%	1%
exenatide	13%	15%	11%	14%	11%	13%	11%	13%				
glimepiride	25%	28%	23%	26%	22%	25%	22%	25%	14%	16%		16%
Glipizide	20%	22%	19%	22%	18%	20%	18%	21%	16%	18%		18%
Glyburide	13%	15%	11%	12%	11%	13%	11%	13%	9%	11%		11%
insulin detemir	8%	9%	8%	10%	7%	9%	8%	9%	4%	5%		5%

Prior T2DM treatment	new users of canagliflozin	new users of canagliflozin with established cardiovascular disease	new users of empagliflozin	new users of empagliflozin with established cardiovascular disease	new users of dapagliflozin	new users of dapagliflozin with established cardiovascular disease	new users of empagliflozin or dapagliflozin	new users of empagliflozin or dapagliflozin with established cardiovascular disease	new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA	new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease	new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA	new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease
Insulin Glargine	16%	20%	17%	21%	15%	18%	15%	19%	10%	12%		12%
Insulin Lispro	5%	7%	5%	7%	4%	6%	4%	6%	3%	4%		4%
Insulin, Aspart, Human	7%	10%	8%	11%	7%	9%	7%	10%	4%	6%		6%
Insulin, Glulisine, Human	1%	1%	1%	1%	1%	1%	1%	1%	0%	1%		1%
Linagliptin	5%	6%	7%	8%	5%	6%	6%	6%				
liraglutide	17%	19%	16%	18%	15%	17%	15%	17%				
Metformin	89%	90%	89%	90%	88%	90%	89%	90%	81%	81%	69%	81%
miglitol	0%	0%	0%	0%	0%	0%	0%	0%				
nateglinide	1%	2%	1%	2%	1%	2%	1%	2%				
pioglitazone	20%	23%	17%	20%	17%	20%	17%	20%	10%	11%		11%
Regular Insulin, Human	2%	3%	2%	2%	2%	2%	2%	2%	1%	2%		2%
repaglinide	1%	2%	1%	2%	1%	2%	1%	2%				
rosiglitazone	4%	7%	3%	5%	3%	5%	3%	5%	1%	2%		2%
saxagliptin	10%	11%	9%	10%	10%	11%	9%	11%				
sitagliptin	35%	39%	33%	37%	32%	36%	32%	36%				

For the descriptive analyses as part of clinical characterization, these cohorts should provide sufficient sample to adequately summarize and compare baseline characteristics within the cohorts.

For population-level effect estimation, where our aim is to produce an unbiased estimate of the average treatment effect, the precision we will achieve will vary by the incidence rate of each outcome. Because our focus is to estimate the magnitude of the effect, it is acceptable to be underpowered for the analyses, recognizing that this will manifest as wider confidence intervals that account for the random sampling error inherent to the analysis. Smaller sample size for specific comparisons may limit the internal study validity of estimates. Small samples may also limit the ability to fit adequate propensity models and thus limit our ability to control confounding. Meta-analysis across sources may offer increased precision for a composite estimate and, because of the differences in populations represented by the various data sources, will provide additional understanding of the study's external validity. Similarity of estimated associations across data sources will support broad applicability of findings. Heterogeneity of findings across data sources may indicate that associations between exposure and outcome vary according to patient characteristics. The consistency of study results will be quantified using the I^2 statistic. If the degree of heterogeneity is acceptable (I^2 <40%), random-effects meta-analysis will be performed using the Hartung-Knapp-Sidik-Jonkman method. No multiplicity adjustment will be performed.

10. DATA ANALYSIS PLAN

10.1. Calculation of time-at-risk

We will apply six time-at-risk definitions:

1) The primary time-at-risk will be defined as the 'on treatment' period, defined as the time from 1 day after exposure cohort start date (based on the date of first exposure to the cohort-defining drug(s)) to 0 days from exposure cohort end date, where exposure cohort end date was defined as the persistent period of exposure, allowing for 30 day gap between successive exposures until the final exposure record, representing the date the subject expected to finish the supply of the last drug dispensing per the prescription information. The exposure cohort end date may be censored by the start of a drug era for a non-metformin AHA other than the cohort defining drug(s).
2) A secondary time-at-risk definition will be an 'intent-to-treat' (ITT) period, defined as the time from 1 day after exposure cohort start date (based on the date of first exposure to the cohort-defining drug(s)) to all days from exposure cohort start date, which will be the end of the patient's observation period for which the exposure cohort start date occurred.
3) An additional sensitivity analysis will be performed using an 'on treatment with delayed induction and delayed lag' period, defined as the time from 60 days after the exposure cohort start date to 60 days after the exposure cohort end date, where exposure cohort end date was similarly defined as in 1) above.
4) A second sensitivity analysis will be performed using a 'modified intent-to-treat' period, defined as the time from 1 day after exposure cohort start date (based on the date of first exposure to the cohort-defining drug(s)) until the end of the patient's observation period

for which the exposure cohort start date occurred for those persons who only qualify for the target or comparator cohort, and from 1 day after exposure start date of the first cohort entry until the date of the second cohort entry for those persons who qualify for both the target and comparator cohorts.

5) A third sensitivity analysis will be performed using a 'on treatment with no censoring at switch' period, defined as the time from 1 day after exposure cohort start date (based on the date of first exposure to the cohort-defining drug(s)) to 0 days from exposure cohort end date, where exposure cohort end date was defined as the persistent period of exposure, allowing for 30 day gap between successive exposures until the final exposure record, representing the date the subject expected to finish the supply of the last drug dispensing per the prescription information. The exposure cohort end date is not censored by the start of a drug era for a non-metformin AHA other than the cohort defining drug(s), meaning the patient is at risk during the entire time they are exposed to the cohort-defining drug even if they augment therapy with another treatment.
6) A fourth sensitivity analysis will be performed using a 'on treatment with delayed induction and delayed lag and no censoring at switch' period, defined as the time from 60 days after the exposure cohort start date to 60 days after the exposure cohort end date, where exposure cohort end date was similarly defined as in 5) above, whereby cohort end date represents the discontinuation of the target defining drug(s) without regard to if another non-metformin AHA in initiated during the period of exposure.

For all analyses, a qualifying person from an exposure cohort will contribute time-at-risk from the time-at-risk start date until some censoring event occurs. For the 'on treatment' and 'intent-to-treat' analyses, time-at-risk start date is defined as the date of first exposure to the particular drug(s) in the database, where the exposure start is between 1April2013 and 15May2017; for the 'on treatment with delayed induction and delayed lag', the time-at-risk start date is defined as 60 days after the date of first exposure to the particular drug(s) in the database. For the 'on treatment' period, the censoring event is the earliest of: 1) exposure cohort end date, as defined by the end of persistent period of exposure censored at the time of a drug era start for a non-metformin AHA other than the cohort-defining drug, and 2) observation period end date (which is defined by end of continuous insurance eligibility or death). For the 'intent-to-treat' period, the censoring event is the observation period end date. For the 'on treatment with delayed induction and delayed lag' period, the censoring event is the earliest of: 1) 60 days after the exposure cohort end date, and 2) observation period end date. For the 'modified intent-to-treat' period, the censoring event is the earliest of 1) the observation period end date, and 2) the start of the cohort entry for the second of the target and comparator cohorts for those patients qualifying for both cohorts. For the 'on treatment with no censoring at switch' period, the censoring event is the earliest of: 1) exposure cohort end date, as defined by the end of persistent period of exposure, and 2) observation period end date (which is defined by end of continuous insurance eligibility or death). For the 'on treatment with delayed induction and delayed lag and no censoring at switch' period, the censoring event is the earliest of: 1) 60 days after the exposure cohort end date, defined by discontinuation of exposure to the cohort defining drug(s), and 2) observation period end date. In all circumstances, a patient is not censored by experiencing hospitalization for other reasons.

10.2. Patient Characteristics Summary

Cohort characterization: this type of descriptive analyses is intended to provide a characterization of the baseline covariates. Baseline variables include demographics (age, gender, index year), as well as conditions, drugs, procedures, and measurements observed during the 365d on or prior to exposure, as listed in section 8.5. Cohort characterization will be performed on all 64 exposure cohorts, as listed in section 8.3 (the 12 exposure cohorts used in the primary analyses plus the 52 exposure cohorts created for purposes of the sensitivity analyses).

Cohort comparison: this type of descriptive analysis provides an explicit head-to-head comparison between two cohorts of baseline covariates, using standardized difference as a metric to compare individual factors. Covariates with standardized difference > 10% will be highlighted as potential imbalanced confounding factors. Cohort comparison will be performed for all 56 target-comparator comparisons, as listed in section 8.3.2 (the 14 target-comparator comparisons used in the primary analysis plus the 42 target-comparator comparisons used in sensitivity analyses).

Incidence will be computed for both outcomes across all 64 exposure cohorts, as listed in section 8.3. The number of persons and person-years-at-risk for each exposure-outcome-database combination will be provided, along with the number of events during the time-at-risk periods. Incidence proportions and incidence rates will be computed. Incidence summary will be stratified by gender.

All clinical characterization analyses involve direct observation of the experience of patients, which can provide context about the real-world patterns of utilization in different populations, but cannot be used for causal inference or to draw comparative conclusions about the effects of any treatment.

10.3. Model Specification

Population-level effect estimation

Population-level effect estimation: this type of analysis attempts to provide an unbiased estimate of the average treatment effect of an exposure on an outcome. These questions using a comparative cohort design take the following form:

We will compare <insert target cohort here> with <insert comparator cohort here> for the <insert metric from statistical model here> of <insert outcome here> in the <insert time-at-risk period here>.

For each of the 14 comparisons listed in section 8.3.2, we will perform an estimation analysis on all 2 outcomes listed in section 8.4. Therefore, the number of primary analyses per database will be (7 overall comparisons + 7 ‘established CV disease’ subpopulation comparisons) * 2 outcomes = 28 target-comparator-outcome combinations. Additionally, there are 42 sensitivity analysis comparisons * 2 outcomes = 84 sensitivity target-comparator-outcome combinations. In total, we will examine 28+84 = 112 target-comparator-outcome combinations in each database.

For each target-comparator combination, we will use a collection of negative control outcomes, as listed in section 8.4, as a diagnostic tool to quantify residual bias and empirically calibrate statistics generated during the analysis.

Each analysis will be performed against all 4 databases, as listed in section 8.2.

In this study, we compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model.

Patients with an observed with an outcome prior to index exposure will be handled in two ways:

- Time-to-first-ever-event analysis: This analysis will estimate hazards of first occurrence of outcome amongst patients with no history of the outcome. Patients with the outcome, observed prior to target or comparator cohort entry will be excluded from consideration.
- Time-to-first-post-index-event analysis: This analysis will estimate hazards of an occurrence of outcome amongst all exposed patients, independent of prior outcome history. Patients with no history of the outcome will be followed during the time-at-risk until observed a first occurrence of event; patients with a prior history of the outcome will be followed during the time-at-risk until observing the first recurrent event that occurs after the exposure index date.

For both cohorts, we impose a requirement that patients must have at least 1 day of continuous observation after the time-at-risk start, 1 day from the cohort start date. We also impose a requirement that study time is restricted to the calendar time between 1 April 2013 and 15 May 2017. The overall study population could be considered to be patients who entered either the target cohort or comparator cohort. Patients who qualify for the target cohort and then subsequently qualify for the comparator cohort will contribute time-at-risk to the target cohort until they are censored by entry into the comparator cohort, at which time they will contribute time-at-risk to the comparator cohort. Patients who qualify for the comparator cohort and then subsequently qualify for the target cohort will contribute time-at-risk to the comparator cohort until they are censored by entry into the target cohort, at which time they will contribute time-at-risk to the target cohort.

The time-to-event of outcome among patients in the target and comparator cohorts is determined by calculating the number of days from the start of the time-at-risk window, 1 day from cohort start date, until the earliest event among 1) occurrence of the outcome post-index before 0 days from cohort end date, 2) the end of the time-at-risk window, 0 days from cohort end date, and 3) the end of the observation period that spans the time-at-risk start.

Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. In this study, the propensity score is estimated for each patient, using the predicted probability from a regularized logistic regression model, fit with a Laplace prior (LASSO) and the regularization hyperparameter selected by optimizing the likelihood in a 10-fold cross validation, using a starting variance of 0.01 and a tolerance of 2e-7.

Covariates to be used in the propensity score model are listed in section 8.5, as was applied in prior studies [10]. Use of regularized regression addresses the collinearity that exists between covariates in the propensity score model.

All covariates that occur in fewer than 10 persons between the target and comparator cohorts combined will be excluded prior to model fitting.

The target cohort and comparator cohorts will be matched using variable ratio matching on the propensity, with a maximum ratio of 100 and using a caliper of 0.2 times the standard deviation of the propensity score distribution. Propensity score stratification using 10 strata will also be used to construct matched sets. The final outcome model will apply a Cox proportional hazard model conditioned on the matched sets.

Output and Evaluation

Covariate balance will be summarized in tabular form by showing the mean value for all baseline covariates in the target and comparator cohort, with the associated standardized mean difference computed for each covariate.

Once the propensity score model is fit, we will plot the propensity score distribution of the target and comparator cohorts to evaluate the comparability of the two cohorts. The plot will be scaled to the preference score, normalizing for any imbalance in cohort size. The area under the Receiver Operating Characteristic (ROC) curve (AUC) will be reported. The covariates selected within the propensity score model, with associated coefficients will also be reported.

A plot showing the propensity score distributions for both cohorts before and after matching will be provided. Covariate balance will be evaluated by plotting the standardized mean difference of each covariate before propensity score stratification against the standardized mean difference for each covariate after propensity score stratification.

An attrition diagram will be provided to detail the loss of patients from the original target cohort and comparator cohort to the subpopulations that remain after all design considerations have been applied.

The final outcome model, a conditional Cox proportional hazards model, will be summarized by providing the hazards ratio and associated 95% confidence interval. The number of persons, amount of time-at-risk, and number of outcomes in each cohort will also be reported.

In total, (7 overall comparisons + 7 ‘established CV disease’ subpopulation comparisons + 42 sensitivity comparisons) * 2 outcomes (hospitalization for heart failure and below-knee lower extremity amputation) * 6 time-at-risk windows (‘on treatment’, ‘intent-to-treat’, ‘on treatment with delayed induction and delayed lag’, ‘modified intent-to-treat’, ‘on treatment with no censoring at switch’, ‘on treatment with delayed induction and delayed lag and no censoring at switch’) * 2 propensity score adjustment strategies (variable ratio matching and stratification) * 2 outcome models (time-to-first-ever vs. time-to-first-post-exposure) * 4 databases =

10,752 target-comparator-outcome-analysis-database studies will be performed (subject to first passing the study diagnostics).

For each target-comparator-outcome-analysis combination, heterogeneity of the hazards ratios will be estimated across the 4 databases, using I^2 as a metric [11]. If there is sufficient homogeneity across sources (I^2<40%), [12], source-specific estimates will be pooled through random effect meta-analysis using the Hartung-Knapp-Sidik-Jonkman method. Source-specific and composite estimates will be presented in a forest plot.

Evidence Evaluation

For population-level effect estimation analyses:

Within each target-comparator-outcome-database combination, we will execute diagnostics to determine if the analysis can be appropriately conducted. The diagnostics will include:

- Cohort characterization for target and comparator
- Propensity score distribution
- Covariate balance before and after PS matching
- Estimation for negative controls, to assess residual error

Negative control outcomes will be used to evaluate the potential impact of residual systematic error in the study design, and to facilitate empirical calibration of the p-value for the outcomes of interest. Negative control outcomes are concepts known not to be associated with either the target or comparator group, such that we can assume the true relative risk should equal 1. For each negative control outcome, the study design described above will be implemented and the effect estimate will be recorded. The distribution of effect estimates across all negative control outcomes will be used to fit an empirical null distribution which models the observed residual systematic error. The empirical null distribution will then be applied to the target outcome of interest to calibrate the p-value. Empirical calibration serves as an important diagnostic tool to evaluate if the residual systematic error is sufficient to cast doubt on the accuracy of the unknown effect estimate. The calibration effect plot and calibration probability plots will be generated for review. We will report the traditional p-value and empirically calibrated p-value for each negative control, as well as the outcomes of interest.

All analyses will be performed within the Janssen Epidemiology Analytics team. A lead programmer will develop and execute the source code. A second programmer will review the code and execute to confirm the results generated. Analysis source code will be provided as part of the final output generated.

11. STRENGTHS AND LIMITATIONS OF THE RESEARCH METHODS

Strengths:

- The 4 databases provide complementary perspectives about treatment utilization and effects within the US population.

- Cohort studies allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date designation but patients new to one drug or drug class can be prevalent users of other select AHAs.
- Propensity score adjustment allows balancing on a large number of baseline potential confounders.
- The use of a set of negative control outcomes allows for estimation of residual bias inherent to the study design and data.

Limitations:

- Misclassification among different types of diabetes is possible as a result of misdiagnosis and/or inaccurate coding. For example, (i) latent autoimmune diabetes in adults (LADA; an autoimmune form of T1DM presenting in adulthood) is often initially misdiagnosed and treated with oral AHAs [13].
- The definition for T2DM relies on ICD-9/10 codes taken at face value, and some patients with bona fide autoimmune diabetes may still remain, despite our best attempt to exclude them. For example, it is possible that some patients with T1DM who are older than 40 years of age are correctly recognized as T1DM by their treating healthcare providers, yet their insurance claims captured during entire enrollment history never use codes for T1DM.

  Patients with T2DM who were not managed by any AHAs will not be included. Some of these patients may be newly diagnosed with T2DM and managed by diet and exercise (which is not usually captured by insurance claims), some may have pre-diabetes or may have diagnostic testing to rule out T2DM, and some may not have prescription drug coverage. These patients are considered not comparable to patients with established T2DM, and not clinically relevant in terms of choosing different therapeutic alternatives (ie, the clinical question about which drug to choose instead of whether to take AHAs or not).
- Outcome misclassification is possible for all outcomes. "Hospitalization for heart failure" is an outcome that has been previously used in multiple prior publications, including to study the comparative effects of SGLT2 inhibitors vs. non-SGLT2 antihyperglycemic agents (see Kosiborod Circulation 2017, http://circ.ahajournals.org/content/early/2017/05/16/CIRCULATIONAHA.117.029190), and identifying cases in claims data has been consistently shown to have adequate positive predictive value (see "Mini-Sentinel Systematic Evaluation of Health Outcome of Interest Definitions For Studies Using Administrative Data: Congestive Heart Failure" https://www.sentinelinitiative.org/sites/default/files/SurveillanceTools/ValidationsAndLiterature/MS_HOI_CHFReport_0.pdf). "Below knee lower extremity amputation" is an outcome defined by a procedure, which is unambiguous in definition. Because procedure codes are directly used for reimbursement purposes, unlike diagnosis codes which are only used indirectly to justify the procedures, they are generally regarded as having high validity in administrative claims systems. It is unlikely that an insured person would obtain an amputation procedure outside the scope of their insurance plan and a clinician providing this service is unlikely not to seek reimbursement given the time and resources involved, so sensitivity should be high within these defined populations. It is also unlikely a person would have a procedure code for completed amputation surgery without having the procedure performed, so the specificity of the outcome definition is expected to

be high as well. The Truven MarketScan databases contain de-identified patient-level data without the ability to re-connect with the patient or retrieve medical charts for source record verification. Therefore, there is a risk of unexpected measurement error that cannot be eliminated."

- Causality between drug exposure and any given event cannot be drawn for individual cases.
- Socioeconomic variables (such as race/ethnicity, education, income), behavioral variables (such as diet, alcohol consumption, eating disorders) are not available or may not be completely captured from these databases, which will lower the validity for outcome identification, risk factor/confounding adjustment, or causal interpretation.
- Free drug samples are not captured in insurance claims databases, which may result in misclassification of some exposure as non-exposure, prevalent drug use as new use (potentially missing incident events or incident events following exposure misclassified as historical events). Although some Health Maintenance Organizations (HMOs) forbid direct access to sales representatives and therefore may not have the free-sample issue, sensitivity analyses are not done due to limited sample size and changing of insurance over time.
- Adjustment by propensity score may not completely remove confounding bias [14].

12. PROTECTION OF HUMAN SUBJECTS

The use of the Truven MarketScan databases and the Optum Extended DoD database were reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE REACTIONS

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports. The study results will be assessed for medically important results.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The protocol will be registered at www.clinicaltrials.gov after finalization. Results will be reported to the registration location within 12 months of completion. Additionally, results will be submitted for peer-reviewed publication.

15. REFERENCES

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16. APPENDIX 1: EXPOSURE COHORT DEFINITIONS

1. [501] E1. new users of canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

2. [501] E2. new users of canagliflozin with established cardiovascular disease
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

3. [501] E3. new users of empagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug exposure of *dapagliflozin*
- a drug era of *canagliflozin*

4. [501] E4. new users of empagliflozin with established cardiovascular disease
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *dapagliflozin*
- a drug era of *canagliflozin*

5. [501] E5. new users of dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

6. [501] E6. new users of dapagliflozin with established cardiovascular disease
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

7. [501] E7. new users of empagliflozin or dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

8. [501] E8. new users of empagliflozin or dapagliflozin with established cardiovascular disease
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

9. [501] E9. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

10. [501] E10. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

11. [501] E11. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

12. [501] E12. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

13. [501] E13. new users of canagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

14. [501] E14. new users of canagliflozin with no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

15. [501] E15. new users of canagliflozin with no prior exposure to empagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

16. [501] E16. new users of canagliflozin with no prior exposure to dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *dapagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

17. [501] E17. new users of canagliflozin with no prior exposure to empagliflozin or dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin or dapagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

18. [501] E18. new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

19. [501] E19. new users of canagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

20. [501] E20. new users of canagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
  - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
  - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

21. [501] E21. new users of canagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first canagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

22. [501] E22. new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

23. [501] E23. new users of canagliflozin with established cardiovascular disease and no prior exposure to dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *dapagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

24. [501] E24. new users of canagliflozin with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin or dapagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

25. [501] E25. new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
  - for the first time in the person's history
  - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
  - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
  - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

26. [501] E26. new users of canagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *canagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin or dapagliflozin*

27. [501] E27. new users of empagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug exposure of *dapagliflozin*
- a drug era of *canagliflozin*

28. [501] E28. new users of empagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug exposure of *dapagliflozin*
- a drug era of *canagliflozin*

29. [501] E29. new users of empagliflozin with no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug exposure of *dapagliflozin*
- a drug era of *canagliflozin*

30. [501] E30. new users of empagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *dapagliflozin*
- a drug era of *canagliflozin*

31. [501] E31. new users of empagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *dapagliflozin*
- a drug era of *canagliflozin*

32. [501] E32. new users of empagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *canagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *dapagliflozin*
- a drug era of *canagliflozin*

33. [501] E33. new users of dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

34. [501] E34. new users of dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

35. [501] E35. new users of dapagliflozin with no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

36. [501] E36. new users of dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

37. [501] E37. new users of dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

38. [501] E38. new users of dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *empagliflozin*
- a drug era of *canagliflozin*

39. [501] E39. new users of empagliflozin or dapagliflozin with at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

40. [501] E40. new users of empagliflozin or dapagliflozin with no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

41. [501] E41. new users of empagliflozin or dapagliflozin with no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

42. [501] E42. new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

43. [501] E43. new users of empagliflozin or dapagliflozin with no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

44. [501] E44. new users of empagliflozin or dapagliflozin with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

45. [501] E45. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first empagliflozin or dapagliflozin exposure
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

46. [501] E46. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

47. [501] E47. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

48. [501] E48. new users of empagliflozin or dapagliflozin with established cardiovascular disease and no prior exposure to any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of *empagliflozin or dapagliflozin*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of *empagliflozin or dapagliflozin*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
- a drug era of *canagliflozin*

49. [501] E49. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

50. [501] E50. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

51. [501] E51. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

52. [501] E52. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with no prior exposure to empagliflozin or dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin or dapagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

53. [501] E53. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4, GLP-1, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

54. [501] E54. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4, GLP-1, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

55. [501] E55. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

56. [501] E56. new users of any DPP-4 inhibitor, GLP-1 agonist, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin or dapagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*
- a drug era of *TZD, SU, or insulin*

57. [501] E57. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with at least 1 prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4, GLP-1, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

58. [501] E58. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4, GLP-1, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

59. [501] E59. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

60. [501] E60. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with no prior exposure to empagliflozin or dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin or dapagliflozin*

  starting between all days Before and 1 days Before event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

61. [501] E61. new users of any DPP-4, GLP-1, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4, GLP-1, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and at least 1 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

62. [501] E62. new users of any DPP-4, GLP-1, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior non-metformin AHA exposure in 365 days prior to first exposure of any DPP-4, GLP-1, TZD, SU, insulin, or other select AHA
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *non-metformin AHA*

  starting between 365 days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

63. [501] E63. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to canagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *canagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

64. [501] E64. new users of any DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA with established cardiovascular disease and no prior exposure to empagliflozin or dapagliflozin
Initial Event Cohort
People having any of the following:

- a drug exposure of any *DPP-4 inhibitor, GLP-1 agonist, or other select AHA*
    - for the first time in the person's history
    - occurrence start is between 2013-4-1 and 2017-05-15 (inclusive)

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

For people matching the Primary Events, include:
Having all of the following criteria:

- exactly 0 occurrences of a condition occurrence of *Secondary Diabetes* starting between all days Before and 0 days After event index date
- and at least 1 occurrences of a condition occurrence of *Type II Diabetes* starting between all days Before and 0 days After event index date
- and exactly 0 occurrences of a condition occurrence of *Type I Diabetes* starting between all days Before and 0 days After event index date

- and exactly 0 occurrences of a drug exposure of *empagliflozin or dapagliflozin*

  starting between all days Before and 1 days Before event index date

- And having any of the following criteria:
    - at least 1 occurrences of a condition occurrence of *conditions indicating established cardiovascular disease starting* between all days Before and 0 days After event index date
    - or at least 1 occurrences of a procedure of *procedures indicating established cardiovascular disease starting* between all days Before and 0 days After event index date

Custom Drug Era Exit Criteria
This strategy creates a drug era from the codes found in the specified concept set. If the index event is found within an era, the cohort end date will use the era's end date. Otherwise, it will use the observation period end date that contains the index event.
Use the era end date of any *DPP-4 inhibitor, GLP-1 agonist, TZD, SU, insulin, or other select AHA*

- allowing 30 days between exposures
- adding 0 days after exposure end

Censoring Events:
Exit Cohort based on the following:

- a drug era of *empagliflozin or dapagliflozin*
- a drug era of *canagliflozin*

17. ANNEX. LIST OF STAND-ALONE DOCUMENTS

1. concept_sets' folder contains the files for Annex 1: list of variables and codesets
2. cohort_definition_expressions' folder contains the files for Annex 2: files containing the JSON syntax