Sodium-glucose cotransporter-2 inhibitor initiation and the short-term risk of hospitalized acute kidney injury

Study Protocol

Version 1 (April 27, 2018)

This study is administered and coordinated by investigators at the University of North Carolina at Chapel Hill. The principal investigator of the study is Magdalene Assimon, PharmD, PhD, a Post-Doctoral Fellow at the University of North Carolina Kidney Center.

Note: We declare that we have no knowledge, through advance exploratory analyses, of the likely ultimate findings of the study at the time that this protocol is submitted.

BACKGROUND AND RATIONALE

Type 2 diabetes mellitus (T2DM) is a major public health problem in the United States (U.S.). Since 1980, the number adults diagnosed with T2DM has dramatically increased, from 5.5 million to 30.2 million Americans in 2015.[1] Contemporary estimates indicate that over 12% of the U.S. population ≥ 18 years of age is diabetic.[1] While a healthy diet and regular exercise are cornerstones of T2DM management, treatment with anti-diabetic medications is often necessary to help individuals achieve glycemic control. In response to the rising prevalence T2DM, several novel anti-diabetic medications have been developed over the last 10 years.

Sodium glucose co-transporter 2 (SGLT2) inhibitors, including canagliflozin, dapagliflozin, empagliflozin and ertugliflozin, are the newest class of anti-diabetic medications approved for the treatment of T2DM by the U.S. Food and Drug Administration (FDA). The SGLT2 protein is a low-affinity, high capacity glucose transporter located in the proximal tubule of the kidney that mediates reabsorption of ~90% of the filtered glucose load. SGLT2 inhibitors work by blocking the SGLT2 transporter protein, which prevents the reabsorption of filtered glucose by the kidneys. Thus, SGLT2 inhibitors promote renal glucose excretion, thereby lowering elevated blood glucose levels in patients with T2DM. SGLT2 inhibitors are effective anti-diabetic agents. On average, these medications reduce hemoglobin A1C by 0.4% to 1.1%.[2] Because of their unique mechanism of action, SGLT2 inhibitors have a range of effects that may translate to clinical benefits beyond glycemic control.

Mechanistic studies indicate that SGLT2 inhibitors may slow of progression of kidney function decline, independent of their glucose lowering effects. SGLT2 inhibitor-induced natriuresis activates tubulo-glomerular feedback via increased macula densa sodium delivery, which leads to afferent arteriole vasoconstriction and a subsequent reduction in intraglomerular pressure. This reduction in intraglomerular pressure results in long-term renal protection (similar to renin-angiotensin-aldosterone system (RAAS) inhibition).[3] In fact, recently published clinical trial data supports the notion that SGLT2 inhibitors may be renal-protective. In a pre-specified analysis of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial, treatment with empagliflozin (vs. placebo) slowed progression of kidney function decline over a median follow-up of 3.1 years.[4] Similar benefits were observed with the SGLT2 inhibitor canagliflozin in a *post hoc* analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) program.[5] Despite their long-term renal benefits, the osmotic diuretic and naturetic effects of SGLT2 inhibitors can lead to an acute reduction in glomerular filtration rate (approximately 5 ml/min/1.73m^2), raising concerts that SGLT2 inhibitors may increase the risk of acute kidney injury (AKI).

From March 2013 to October 2015, the U.S. Food and Drug Administration (FDA) received 101 confirmable reports of AKI associated with SGLT2 inhibitor therapy; 96 patients required hospitalization and 15 patient required dialysis.[6] Half of the reported AKI cases occurred within one month of starting SGLT2 inhibitor therapy.[6] In response to this series of post-marketing safety reports, the FDA enhanced the renal-related warnings on the package inserts of all SGLT2 inhibitor medications in June 2016. However, subsequent studies evaluating the SGLT2 inhibitor-AKI association, have yielded inconsistent results.

Using data from the FDA adverse event report system (FAERS) Perlman *et al.* found that SGLT2 inhibitors, relative to other T2DM medications, were more often reported as the primary causative agent in acute renal failure cases reported to the FDA from January 2013 through September 2016.[7] In contrast, a pre-specified analysis of the EMPA-REG OUTCOME study, found that the incidence rate of adverse events consistent with acute renal failure (including AKI) across the 48 month follow-up period was lower among study participants treated with empagliflozin (n = 4,687) compared to those treated with placebo (n = 2,333).[4] Similar findings were observed in a recent epidemiologic study. Using electronic healthcare record data from the Mount Sinai chronic kidney disease (CKD) registry (n = 744) and Geisinger Health System (n = 2,414), Nadkarni *et al*. found that SGLT2 inhibitor new-use (vs. never-use) as associated with a lower risk of AKI over a 15-month follow-up period.[8] However, several major study design flaws, such as conditioning future exposure information to define baseline cohort membership, may have biased results.[9]

To further our understanding of the kidney-related risk-benefit profiles of SGLT2 inhibitors in the T2DM population, well-designed pharmacoepidemiologic studies are urgently needed. The proposed project will leverage the Truven Health MarketScan® research database to evaluate the association between SGLT2 inhibitor initiation and the risk of hospitalized AKI among commercially insured beneficiaries from the U.S.

SPECIFIC AIMS

Aim 1: To describe the temporal trends of SGLT2 inhibitor use after the FDA approval of canagliflozin (the first SGLT2 inhibitor available in the U.S.) in cohort of commercially insured beneficiaries with T2DM.

Hypothesis: After the FDA approval of canagliflozin (March 29, 2013), the monthly rate of SGLT2 inhibitor utilization will increase across historical calendar time.

Aim 2: To evaluate the association between SGLT2 inhibitor vs. sulfonylurea initiation and the short-term risk (30- 60- 90- and 180-day) of hospitalized AKI in cohort of commercially insured beneficiaries from the U.S., overall and within clinically relevant subgroups.

Hypothesis: SGLT2 inhibitor vs. sulfonylurea initiators will have a higher short-term risk of hospitalized AKI. This risk will be particularly elevated in vulnerable subgroups at high-risk for AKI.

DATA SOURCE

MarketScan® Commercial Claims and Encounters Database, 2013-2016.

STUDY POPULATION, DESIGN AND ANALYTIC APPROACH – AIM 1 (SGLT2 INHIBITOR PATTERNS OF USE)

Study Design

We will conduct a retrospective patterns of use study to describe the population-level use of SGLT2 inhibitors among individuals with T2DM from April 2013 thru December 2016 on a monthly basis.

Study Population

For each respective study month, the base population for Aim 1 analyses will consist of beneficiaries in the MarketScan® commercial claims database individuals who:

1) Are age 18 – 64 years.

2) Have commercial medical & prescription insurance (primary payer).

3) Have T2DM.

Inclusion Criteria:

In each monthly cohort we will ***include*** individuals:

1) With both continuous medical and prescription insurance (primary payer) during the 365-days prior to each study month of interest ***and*** during the study month of interest.

2) ≥ 1 inpatient or outpatient claim for T2DM in the 365-days prior to the study month of interest.

- *Type 2 Diabetes*
  - ICD-9 code(s): 250.x0, 250.x2
  - ICD-10 code(s): E11.xxxx

Exclusion Criteria:

In each monthly cohort we will ***exclude*** individuals:

1) < 18 years of age at the start of the study month of interest.

2) > 64 years of age at the start if the study month of interest.

3) With the following conditions (identified during the baseline period):

- *Stage 4 chronic kidney disease (CKD), Stage 5 CKD, or end-stage renal disease (ESRD).*
  - ICD-9 diagnosis code(s): 585.4–585.6
  - ICD-10 diagnosis code(s): N18.4–N18.6
- *CKD stage unspecified or stage unknown.*[10]
  - ICD-9 diagnosis code(s):
    - Patient has ***no claims*** for the following: 585.1–585.6
    - But ***has claims for*** at least one of the following: 016.0, 095.4, 189.0, 180.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403, 404, 440.1, 442.1, 477.3, 572.4, 581–583, 585.9, 586–588, 591, 642.1, 646.2, 753.12–753.19, 753.2, 794.4
  - ICD-10 diagnosis code(s):
    - Patient has ***no claims*** for the following: N18.1–N18.6
    - But ***has claims for*** at least one of the following: A18.11, A52.75, B52.0, C64, C68.9, D30.0, D41.0–D41.2, D59.3, E08.2, E09.2, E10.2, E11.2, E13.2, E74.8, I12, I13.0–I13.2, K76.7, M10.3, M32.14, M32.15, N01–N08, N11, N13.1–N13.3, N14, N15.0, N15.8, N15.9, N16, N18.8, N18.9, N19, N25, N26.1, N26.9, O10.2, O10.3, O12, O26.83, O90.89, Q61.02, Q61.1–Q61.8, Q62.0–Q62.3, R94.4

Analytic Approach

From April 2013 thru December 2016, we will calculate the monthly proportions (95% confidence intervals [CIs]) of individuals with ≥ 1 SGLT2 inhibitor (canagliflozin, dapagliflozin, empagliflozin) prescription fill per 100,000 eligible beneficiaries. The SGLT2 inhibitor ertugliflozin will not be evaluated in our analyses since it was FDA approved after the study period (December 19, 2017). We will also calculate the monthly proportions (95% CIs) of individuals with ≥ 1 study medication fill for each of the aforementioned generic products (assessed separately) per 100,000 eligible beneficiaries. Since study months can be of different lengths (e.g. 28, 29, 30 and 31 days) we will consider calibrating all monthly estimates to an equivalent month length of 30 days in sensitivity analyses.

STUDY POPULATION, DESIGN AND ANALYTIC APPROACH – AIM 2 (SGLT2 inhibitor AND AKI)

Study Population

The base population for Aim 2 analyses will consist of beneficiaries in the MarketScan® Commercial Claims and Encounters Database individuals who:

1) Are age 18 – 64 years.

2) Have commercial medical & prescription insurance (primary payer).

3) Have ≥ 1 prescription dispensing claim for an SGLT2 inhibitor or sulfonylurea between April 1, 2013 (after the FDA approval date of the first SGLT2 inhibitor, canagliflozin) and December 30, 2016.

Inclusion criteria:

We will *include* individuals:

1) Initiated a SGLT2 inhibitor or a sulfonylurea between April 1, 2013 and December 30, 2015. Study medication initiation is defined below.

2) At least 365-days of continuous insurance enrollment (both medical & prescription coverage) prior to SGLT2 inhibitor or sulfonylurea initiation.

Exclusion criteria:

We will *exclude* individuals:

1) < 18 years of age on the index date.

2) > 64 years of age on the index date.

3) With the following conditions (identified during the baseline period):

- *Stage 4 CKD, Stage 5 CKD or ESRD.*
  - ICD-9 diagnosis code(s): 585.4–585.6
  - ICD-10 diagnosis code(s): N18.4–N18.6
- *CKD stage unspecified or stage unknown.*[10]
  - ICD-9 diagnosis code(s):
    - Patient has *no claims* for the following: 585.1–585.6
    - But *has claims for* at least one of the following: 016.0, 095.4, 189.0, 180.9, 223.0,

236.91, 250.4, 271.4, 274.1, 283.11, 403, 404, 440.1, 442.1, 477.3, 572.4, 581–583, 585.9, 586–588, 591, 642.1, 646.2, 753.12–753.19, 753.2, 794.4

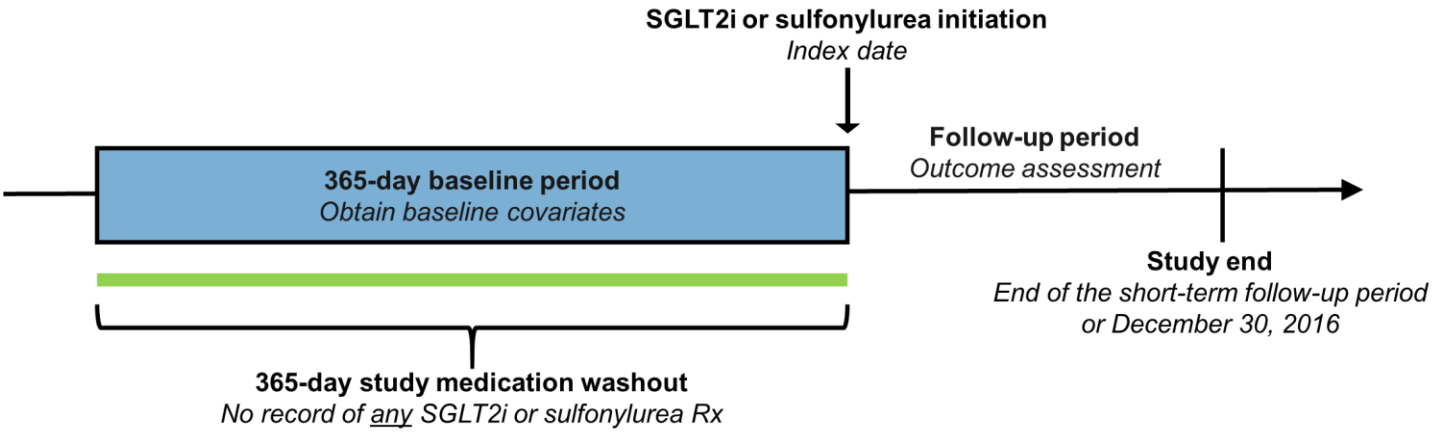
- ICD-10 diagnosis code(s):
  - Patient has *no claims* for the following: N18.1–N18.6
  - But *has claims for* at least one of the following: A18.11, A52.75, B52.0, C64, C68.9, D30.0, D41.0–D41.2, D59.3, E08.2, E09.2, E10.2, E10.65, E11.2, E13.2, E74.8, I12, I13.0–I13.2, K76.7, M10.3, M32.14, M32.15, N01–N08, N11, N13.1–N13.3, N14, N15.0, N15.8, N15.9, N16, N18.8, N18.9, N19, N25, N26.1, N26.9, O10.2, O10.3, O12, O26.83, O90.89, Q61.02, Q61.1–Q61.8, Q62.0–Q62.3, R94.4

- *Prior AKI*
  - ICD-9 diagnosis code(s): 584.x
  - ICD-10 diagnosis code(s): N17.x

Study Design

We will conduct a retrospective cohort study to evaluate the association between SGLT2 inhibitor vs. sulfonylurea initiation and the short-term risk of hospitalized AKI using a new-user design (**Figure 1**),[11]

Figure 1. *Study design schematic*



Exposures

We will use MarketScan® outpatient prescription claims data to identify all study exposures. The exposures of interest are the initiation (i.e. new-use) of an SGLT2 inhibitor or a sulfonylurea (**Table 1**). Sulfonylureas were chosen as the comparator medication because they are similarly used as a second-line treatment for T2DM but have no known association with AKI. The index date (initiation date or new-use date) will be defined as the date of first the SGLT2 inhibitor *or* sulfonylurea prescription fill after a 365-day washout period free of both SGLT2 inhibitor *and* sulfonylurea utilization.

Table 1. *Medications of interest*	
SGLT2 inhibitors	**Sulfonylureas**
Canagliflozin, dapagliflozin, empagliflozin	Glyburide, glipizide, glimepiride, acetohexamide, chlorpropamide, tolbutamide

The SGLT2 inhibitor ertugliflozin will not be evaluated in our analyses since it was FDA approved after the end of the study period (December 19, 2017).

Outcomes

We will use MarketScan® inpatient administrative claims data to identify all study outcomes. The primary outcomes of interest are 30-, 60-, 90- and 180-day hospitalized AKI. The claims-based definitions for hospitalized AKI that will be used in this study (**Table 2**) have been previously validated.[12]

Table 2. *Claims-based definitions for hospitalized AKI*		
Outcome	**Specification**	**Data file(s)**
Hospitalized AKI	Claim for an inpatient hospital admission with: **1)** An AKI ICD-9 or ICD-10 discharge diagnosis code located in ***any*** billing position ICD-9 diagnosis codes: 584.x ICD-10 diagnosis codes: N17.x	MarketScan® Inpatient claims
Hospitalized AKI-D	Claim for an inpatient hospital admission with: **1)** An AKI ICD-9 or ICD-10 discharge diagnosis code located in ***any*** billing position (specified above) ***PLUS*** **2)** An AKI ICD-9 or ICD-10 code for dialysis (at least 1 of the following in ***any*** billing position) ICD-9 diagnosis codes: V45.11 or V56[a] ICD-10 diagnosis codes: Z99.2, Z49[b], Z45.2 ICD-9 procedure codes: 39.95 or 54.98	MarketScan® Inpatient claims

[a] Specified 3-digit ICD-9 diagnosis codes include all existing 4th and 5th digit diagnosis codes. Specified 4-digit ICD-9 diagnosis codes include all existing 5th digit diagnosis codes.

[b] Specified 3-digit ICD-10 diagnosis codes include all existing 4th thru 7th digit diagnosis codes. Specified 4-digit ICD-10 diagnosis codes include all existing 5th thru 7th digit diagnosis codes.

Among individuals with a hospitalized AKI event during follow-up, we will describe the following:

- The proportion of hospitalized AKI cases that required dialysis. The definition of hospitalized AKI requiring dialysis (AKI-D) is specified in **Table 2**.
- The hospital discharge disposition (e.g. home/self-care, died) of all individuals who had an AKI

hospitalization. Information on discharge disposition will be obtained from the DSTATUS variable in the MarketScan® Inpatient claims file).

- The proportion of hospitalized AKI cases discharged alive that had a 30-day hospital re-admission .

Covariates

We will use MarketScan® inpatient, outpatient and prescription claims data to identify baseline covariates of interest (**Supplemental Tables S1 and S2**). Baseline covariates will include potential confounders and variables known to be strong risk factors for the outcome, AKI.[13] Covariates will be identified in the 365-day baseline period. Covariates of interest include:

1) Patient demographics.

2) Comorbid conditions.

- A baseline comorbid condition will be considered present if an applicable ICD-9/ICD-10 discharge code (located in any position) was associated with ≥ 1 inpatient claim or ≥ 1 outpatient claim during the 365-day baseline period.

3) Concomitant prescription medication use.

- Use of a medication of interest during the last 30 days of the baseline period (determined by the prescription fill date and the corresponding days supply).

4) Indicators of health care utilization.

Censoring Events

Censoring events will include: 1) discontinuation of the index study medication (defined below); 2) switching to/augmenting therapy with a non-index study medication (defined below); 3) loss of insurance coverage; 4) completed 30-, 60-, 90- or 180-days of follow-up (depending on the length of follow-up period being assessed); and 5) study end (December 31, 2016).

- We will define the ***discontinuation*** date as: the date when the index study medication is exhausted for greater than 30-days (i.e. the grace period) during follow-up period without a subsequent dispensing of a medication within the same medication class.

- We will define the ***switching/augmentation*** date as: the date of the 1st prescription fill for a non-index study medication during the follow-up period. For example, SGLT2 inhibitor initiators be censored if they fill a prescription for a sulfonylurea during follow-up.
  - *Note:* patients will only be at risk for a switching/augmentation event during times of continuous index medication use.

Subgroups

In secondary analyses we will assess the association of SGLT2 inhibitor vs. sulfonylurea initiation and the short-term risk of AKI within clinically relevant subgroups. Subgroups of interest include individuals:

- Across the age spectrum (e.g. 18–34, 35–44, 45–54, 55–64 years).

- By sex (males and females).
- *With* and *without* a history of:
    - CKD (stages 1–3).
    - Chronic liver disease.
    - Dysrhythmia.
    - Ischemic heart disease.
    - Heart failure.
    - Hypertension.
    - Obesity.
- *With* and *without* a recent history of gastrointestinal losses (diarrhea and vomiting).
- Who *were* and *were not* utilizing medications that influence renal hemodynamics including (the medications classes listed below will be analyzed individually and as composite groupings):
    - Diuretics.
    - RAAS inhibitors.
        - Angiotensin-converting enzyme (ACE) inhibitors.
        - Angiotensin II receptor blockers (ARBs)
        - Direct renin (DR) inhibitors.
    - Prescription non-steroidal anti-inflammatory drugs (NSAIDs).
- Who *did* vs. *did not* have a recent imaging or cardiac procedure where iodinated contrast was administered.

Analytic Approach

All analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). We will describe baseline characteristics across SGLT2 inhibitor and sulfonylurea initiators as count (%) for categorical variables and mean ± standard deviation for continuous variables. Baseline covariate distributions will be compared across treatment groups using standardized differences. A standardized difference > 0.1 represents meaningful imbalance between treatment groups.[14]

Individuals will be followed forward in historical time from the day immediately following the index date to the first occurrence of a study outcome or censoring event (specified previously). In primary analyses, we will use an on-treatment approach to evaluate the association between SGLT2 inhibitor vs. sulfonylurea initiation and the short-term risk of hospitalized AKI in the full study cohort. In secondary analyses we will: 1) evaluate the association between SGLT2 inhibitor vs. sulfonylurea initiation and the short-term risk of hospitalized AKI within clinically relevant subgroups (specified previously); and 2) evaluate the association between new-use of each SGLT2 inhibitor generic product (canagliflozin, dapagliflozin and empagliflozin [assessed separately]) vs. new-use of a sulfonylurea and the short-term risk of hospitalized AKI. Study outcomes will be assessed at 30-, 60- 90- and 180-days after study medication initiation.

Cox proportional hazards models will be used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) at each respective time point of interest (30-, 60- 90- and 180-days after new-use). In addition, Kaplan-Meier methods will be used to estimate risk differences (RDs) at each respective time point of interest (30-, 60-90- and 180-days after new-use). The 95% CIs for RDs will be obtained using a non-parametric bootstrap based on 250 resamples. Across all analyses, inverse probability of treatment (IPT) weighting will be used for confounding control. We will use separate multivariable logistic regression models to calculate the predicted probability (i.e. propensity score) of receiving SGLT2 inhibitor versus a sulfonylurea as a function of baseline covariates. Propensity scores will be used to generate IPT weights. A weight of (1 / propensity score) will be assigned to SGLT2 inhibitor initiators and a weight of (1 / [1 − propensity score]) will be assigned to and sulfonylurea initiators. Such weighting creates pseudo-populations of SGLT2 inhibitor and sulfonylurea initiators with covariate distributions similar to the full study cohort. Thus, our IPT weighted analysis will estimate the population average treatment effect.

Sensitivity Analyses

To examine the robustness of our results we plan to perform several sensitivity analyses.

1) First, to ensure that the study medications of interest are being used as second-line therapies for the treatment of Type 2 diabetes, we will restrict the study cohort to individuals who are concomitant metformin users. All primary analyses will be repeated.

2) Second, since medications for the treatment of type 2 diabetes are most often initiated in the outpatient setting, we will restrict the study cohort to individuals who were not hospitalized in the 30 days prior to study medication initiation. All primary analyses will be repeated.

3) Third, since prescribers typically assess the tolerability of new diabetes medications in the 4 to 6 weeks following medication initiation, we will restrict our analysis to index medications that have a days supply of 30 days or less. All primary analyses will be repeated.

4) Fourth, will we will utilize more restrictive outcome definitions for AKI. We will define AKI only considering ICD-9/ICD-10 discharge diagnosis codes in the ***primary (first)*** billing position only. All primary analyses will be repeated.

5) Fifth, we will use dialysis CPT codes, in addition the aforementioned dialysis-related ICD-9/ICD-10 diagnosis and procedure codes, when identifying hospitalized AKI events requiring dialysis. All primary analyses will be repeated.

- CPT codes for dialysis include: 90935, 90937, 90945, 90947, 90999

6) Sixth, we will consider additional acute kidney-related outcomes that have been associated with SGLT2 inhibitor use such as hospitalized ketoacidosis.[15] Applicable ICD-9/ICD-10 codes are outlined below.

- ICD-9 codes for ketoacidosis include: 250.1x
- ICD-10 codes for ketoacidosis include: E10.1xxx, E11.1xxx

7) Seventh, we will apply less stringent CKD exclusion criteria. We will only exclude ***all*** individuals with a history of ESRD. Applicable ICD-9/ICD-10 codes are outlined below. All primary analyses will be repeated.

- ICD-9 codes for ESRD include: 585.6
- ICD-10 codes for CKD include: N18.6,

8) Eighth, we will apply more stringent CKD exclusion criteria. We will exclude ***all*** individuals with a history of CKD, regardless of stage. Applicable ICD-9/ICD-10 codes are outlined below. All primary analyses will be repeated.

- ICD-9 codes for CKD include: 585, 016.0, 095.4, 189.0, 180.9, 223.0, 236.91, 250.4, 271.4, 274.1, 283.11, 403, 404, 440.1, 442.1, 477.3, 572.4, 581–583, 586–588, 591, 642.1, 646.2, 753.12–753.19, 753.2, 794.4
- ICD-10 codes for CKD include: N18, A18.11, A52.75, B52.0, C64, C68.9, D30.0, D41.0–D41.2, D59.3, E08.2, E09.2, E10.2, E11.2, E13.2, E74.8, I12, I13.0–I13.2, K76.7, M10.3, M32.14, M32.15, N01–N08, N11, N13.1–N13.3, N14, N15.0, N15.8, N15.9, N16, N19, N25, N26.1, N26.9, O10.2, O10.3, O12, O26.83, O90.89, Q61.02,Q61.1–Q61.8, Q62.0–Q62.3, R94.4

9) Ninth, we will consider shorter grace periods of 7 and 14 days to define index therapy discontinuation in our on-treatment analyses. All primary analyses will be repeated.

10) Tenth, we will analyze the study data using an intent-to-treat approach (ignoring index medication discontinuation and treatment switching/augmentation that occurs during follow-up). All primary analyses will be repeated.

11) Eleventh, we will utilize alternative propensity score methods to analyze the study data including: propensity score matching and standardized mortality ratio (SMR) weighting. All primary analyses will be repeated.

12) Twelfth, if the uptake of SGLT2 inhibitor initiation is rapid over the study period, we will consider instrumental variable and trend-in-trend analyses as additional analytic approaches.

13) Thirteenth, we will alter our study design and consider alternative washout period and baseline period lengths. All primary analyses will be repeated. We will consider a:

- Washout period of 180-days and a baseline period of 180-days (similar to the Fralick *et al*. study evaluating the association between SGLT2 inhibitor initiation and diabetic ketoacidosis).[15] Covariates will be ascertained in the 180-day baseline period. Patients will need to have continuous medical and prescription insurance in the 180-days prior to study medication initiation.
- Washout period of 180-days and a baseline period of 365 days. Covariates will be ascertained in the 365-day baseline period. Patients will need to have continuous medical and prescription insurance in the 365-days prior to study medication initiation.
- Other washout/baseline period combinations may also be considered.

14) Fourteenth, we will end study follow-up on September 30, 2015 prior to the implementation of ICD-10 on October 1, 2015. All primary analyses will be repeated.

15) Fifteenth, we restrict our study cohort to individuals with a baseline diagnosis of Type 2 diabetes. All primary analyses will be repeated.

- We will exclude individuals with ≥1 billed inpatient or outpatient ICD-9/ICD-10 discharge diagnosis code for Type 1 diabetes during the baseline period.
    - ICD-9 code(s): 250.x0, 250.x2
    - ICD-10 code(s): E11.xxxx

16) Sixteenth, we exclude patients with a history of Type 1 diabetes using two separate approaches outlined below. All primary analyses will be repeated.

- We will exclude individuals with ≥1 billed inpatient or outpatient ICD-9/ICD-10 discharge diagnosis code for Type 1 diabetes during the baseline period.
    - ICD-9 diagnosis code(s): 250.x1, 250.x3
    - ICD-10 diagnosis code(s):: E10.xxxx
- We will exclude individuals who filled a prescription for rapid-acting insulin (insulin lispro, insulin aspart, insulin glulisine), a surrogate for Type 1 diabetes, during the baseline period.

17) Seventeenth, we will exclude individuals with gestational diabetes. Applicable ICD-9/ICD-10 codes are outlined below. All primary analyses will be repeated.

- ICD-9 diagnosis code(s): 648.8x
- ICD-10 diagnosis code(s): O24.4xxx

18) Eighteenth, we will consider alternative second-line anti-diabetic agents as potential active comparator medications. All primary analyses will be repeated.

19) Finally, we will restrict the study cohort to new-users with an index date prior to June 14, 2016 (the date of the most recent FDA drug safety communication that strengthened kidney-related warnings on SGLT2 inhibitor package inserts). All primary analyses will be repeated.

Replication Study

If our findings are clinically significant in the MarketScan® population, we will conduct a replication study using data from a 20% random sample of the Medicare Fee-for-Service Database 2013-2016 using an identical study design and analytic approach. The source population for the replication study will consist of all elderly (≥ 66 years of age) Medicare beneficiaries (Part A, B and D coverage) with at least 1 prescription claim for a SGLT2 inhibitor or sulfonylurea between April 1, 2013 (after the FDA approval date of the first SGLT2 inhibitor, canagliflozin) and December 30, 2016. Study inclusion/exclusion criteria will be unchanged. All primary, secondary and sensitivity analyses will be repeated.

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APPENDIX

Supplemental Table S1. *Baseline covariates*

Demographic characteristics		
Covariate	**Definition**	**Data source**
Age	Patient age at index date *Variable:* AGE Continuous	MarketScan® Enrollment File
Sex	Patient sex *Variable:* SEX Categories 1 = male (ref.) 2 = female	MarketScan® Enrollment File
Region	Patient's geographic region of residence *Variable:* REGION Categories 1 = Northeast (ref.) 2 = North Central 3 = South 4 = West 5 = Unknown	MarketScan® Enrollment File
Year of index fill	Year of index date Categories 2013 (ref.) 2014 2015 2016 (include when data are available)	MarketScan® Prescription Claims
Calendar quarter of index fill	Calendar quarter of index fill Categories Q1 = January, February, March (ref.) Q2 = April, May, June Q3 = July, August, September Q4 = October, November, December	MarketScan® Prescription Claims
Comorbid conditions[a,b]		
Covariate	**Definition**	**Data source**
Diabetic neuropathy	History of diabetic neuropathy? ICD-9 diagnosis code(s): 250.6 ICD-10 diagnosis code(s): E10.4, E11.4 Categories	MarketScan® Inpatient and Outpatient Claims

	No (ref.) Yes	
Diabetic retinopathy	History of diabetic retinopathy? ICD-9 diagnosis code(s): 250.5 ICD-10 diagnosis code(s): E10.3, E11.3 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Diabetic hyperosmolarity	History of diabetic hyperosmolarity? ICD-9 diagnosis code(s): 250.2 ICD-10 diagnosis code(s): E11.0 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Diabetic ketoacidosis	History of diabetic hyperosmolarity? ICD-9 diagnosis code(s): 250.1 ICD-10 diagnosis code(s): E10.1, E11.1 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
CKD stage 1, 2 or 3	History of CKD (stage 1, 2 or 3)? ICD-9 diagnosis code(s): 585.1, 585.2, 585.3 ICD-10 diagnosis code(s): N18.1, N18.2, N18.3 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Proteinuria	History of proteinuria? ICD-9 diagnosis code(s): 791.0 ICD-10 diagnosis code(s): R80 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Glycosuria	History of glycosuria?	MarketScan® Inpatient and Outpatient Claims

	ICD-9 diagnosis code(s): 791.5 ICD-10 diagnosis code(s): R81 Categories No (ref.) Yes	
Atherosclerosis	History of atherosclerosis ICD-9 diagnosis code(s): 440 ICD-10 diagnosis code(s): I70 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Cancer	History of cancer? ICD-9 diagnosis code(s): 149–209 ICD-10 diagnosis code(s): C00–C96, C7A Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Chronic obstructive pulmonary disease (COPD) / asthma	History of COPD/asthma? ICD-9 diagnosis code(s): 491–494, 496 ICD-10 diagnosis code(s): J41–J47 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Conduction disorder	History of a conduction disorder? ICD-9 diagnosis code(s): 426 ICD-10 diagnosis code(s): I44–I45 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Dysrhythmia	History of a cardiac dysrhythmia? ICD-9 diagnosis code(s): 427 ICD-10 diagnosis code(s): I46–I49 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims

Hyperlipidemia	History of dyslipidemia? ICD-9 diagnosis code(s): 272.0–272.2, 272.4 ICD-10 diagnosis code(s): E78.0–E78.2, E78.4, E78.5 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Ischemic heart disease	History of ischemic heart disease? ICD-9 diagnosis code(s): 410–414 ICD-10 diagnosis code(s): I20–I25 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Heart failure	History of heart failure? ICD-9 diagnosis code(s): 398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 428 ICD-10 diagnosis code(s): I09.81, I11.0, I13.0, I50 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Hypertension	History of hypertension? ICD-9 diagnosis code(s): 401– 405 ICD-10 diagnosis code(s): I10–I16 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Liver disease (chronic)	History of chronic liver disease or cirrhosis? ICD-9 diagnosis code(s): 571 ICD-10 diagnosis code(s): K70–K76 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Overweight or obese	History of being overweight or obese? ICD-9 diagnosis code(s): 278.0	MarketScan® Inpatient and Outpatient Claims

	ICD-10 diagnosis code(s): E66 Categories No (ref.) Yes	
Peripheral vascular disease	History of peripheral vascular disease? ICD-9 diagnosis code(s): 250.7, 440.2, 440.3, 440.4, 440.8, 440.9, 443.1, 443.22, 443.81, 443.89, 443.9, 444.22, 444.81, 445.02 ICD-10 diagnosis code(s): E10.51, E10.52, E11.51, E11.52, I70.2, I70.3, I70.4, I70.5, I70.6, I70.7, I70.8, I70.9, I73.1, I73.89, I73.9, I74.3, I74.5, I75.02, I77.72 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Stroke	History of stroke? ICD-9 diagnosis code(s): 430–438 ICD-10 diagnosis code(s): I60–I69 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Alcohol abuse	History of alcohol abuse? ICD-9 diagnosis code(s): 303, 305.0 ICD-10 diagnosis code(s): F10 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Smoking	History of tobacco use? ICD-9 diagnosis code(s): 305.1, V15.82 ICD-10 diagnosis code(s): F17, Z87.891 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Non-compliance	History of non-compliance? ICD-9 diagnosis code(s): V15.81	MarketScan® Inpatient and Outpatient Claims

	ICD-10 diagnosis code(s): Z91.19 Categories No (ref.) Yes	
Recent cardiac surgery or procedure	Had cardiovascular surgery or a cardiovascular procedure in the 30 days prior to the index date? CPT procedure code(s): 33010, 33011, 33015, 33020, 33025, 33030, 33031, 33050, 33120, 33130, 33140, 33141, 33202, 33203, 33206, 33207, 33208, 33210, 33211, 33212, 33213, 33214, 33215, 33216, 33217, 33218, 33220, 33221, 33222, 33223, 33224, 33225, 33226, 33227, 33228, 33229, 33230, 33231, 33233, 33234, 33235, 33236, 33237, 33238, 33240, 33241, 33243, 33244, 33249, 33250, 33251, 33254, 33255, 33256, 33257, 33258, 33259, 33261, 33262, 33263, 33264, 33265, 33266, 33270, 33271, 33272, 33273, 33282, 33284, 33300, 33305, 33310, 33315, 33320, 33321, 33322, 33330, 33335, 33340, 33361, 33362, 33363, 33364, 33365, 33366, 33367, 33368, 33369, 33390, 33391, 33404, 33405, 33406, 33410, 33411, 33412, 33413, 33414, 33415, 33416, 33417, 33418, 33419, 33420, 33422, 33425, 33426, 33427, 33430, 33460, 33463, 33464, 33465, 33468, 33470, 33471, 33474, 33475, 33476, 33477, 33478, 33496, 33500, 33501, 33502, 33503, 33504, 33505, 33506, 33507, 33508, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536, 33542, 33545, 33548, 33572, 33600, 33602, 33606, 33608, 33610, 33611, 33612, 33615, 33617, 33619, 33620, 33621, 33622, 33641, 33645, 33647, 33660, 33665, 33670, 33675, 33676, 33677, 33681, 33684, 33688, 33690, 33692, 33694, 33697, 33702, 33710, 33720, 33722, 33724, 33726, 33730, 33732, 33735, 33736, 33737, 33750, 33755, 33762, 33764, 33766, 33767, 33768, 33770, 33771, 33774, 33775, 33776, 33777, 33778, 33779, 33780, 33781, 33782, 33783, 33786, 33788, 33800, 33802, 33803, 33813, 33814, 33820, 33822, 33824, 33840, 33845, 33851, 33852, 33853, 33860, 33863, 33864, 33870, 33875, 33877, 33880, 33881, 33883, 33884, 33886, 33889, 33891, 33910, 33915, 33916, 33917, 33920, 33922, 33924,	MarketScan® Inpatient Claims

	33925, 33926, 33927, 33928, 33929, 33930, 33933, 33935, 33940, 33944, 33945, 33946, 33947, 33948, 33949, 33951, 33952, 33953, 33954, 33955, 33956, 33957, 33958, 33959, 33962, 33963, 33964, 33965, 33966, 33967, 33968, 33969, 33970, 33971, 33973, 33974, 33975, 33976, 33977, 33978, 33979, 33980, 33981, 33982, 33983, 33984, 33985, 33986, 33987, 33988, 33989, 33990, 33991, 33992, 33993, 33999 Categories No (ref.) Yes	
Recent history of a gastrointestinal losses (diarrhea or vomiting)	Had a healthcare encounter for diarrhea or vomiting in the 30 days prior to the index date? ICD-9 diagnosis code(s): 001–009, 558, 078.82, 787.91, 787.01, 787.03, 787.04 ICD-10 diagnosis code(s): A00–A09, K52, R19.7, R11.1, R11.2 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Recent history of a major bleeding event	Hospitalization for a major bleeding event in the 30 days prior to the index date? ICD-9 diagnosis code(s): 285.1, 423.0, 431, 459.0, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.0, 578.1, 578.9, 599.71, 719.1, 784.7, 786.3, 998.11 ICD-10 diagnosis code(s): D62, I31.2, I61, R58, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K55.21, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K62.5, K92.0, K92.1, K92.2, R31.0, M25.0, R04.0, R04.2, R04.8, R04.9, D78.01, D78.02, D78.21, D78.22, E36.01, E36.02, E89.810, E89.811, G97.31, G97.32, G97.51, G97.52, H59.111, H59.112, H59.113, H59.119, H59.121,	MarketScan® Inpatient Claims

	H59.122, H59.123, H59.129, H59.311, H59.312, H59.313, H59.319, H59.321, H59.322, H59.323, H59.329, H95.21, H95.22, H95.41, H95.42, I97.410, I97.411, I97.418, I97.42, I97.610, I97.611, I97.618, I97.620, J95.61, J95.62, J95.830, J95.831, K91.61, K91.62, K91.840, K91.841, L76.01, L76.02, L76.21, L76.22, M96.810, M96.811, M96.830, M96.831, N99.61, N99.62, N99.820, N99.821 Categories No (ref.) Yes	
Recent procedure where radiocontrast was administered	Patient had and imaging or cardiac procedure in the 30 days prior to the index date where radiocontrast was administered? CPT codes: 0042T, 36221, 36222, 36223, 36224, 36225, 36226, 36228, 36251, 36252, 36253, 36254, 37227, 70460, 70470, 70481, 70482, 70487, 70488, 70491, 70492, 70496, 70498, 71260, 71270, 71275, 72126, 72127, 72129, 72130, 72132, 72133, 72191, 72193, 72194, 72198, 73201, 73202, 73206, 73701, 73702, 73706, 74160, 74170, 74174, 74175, 74177, 74178, 75572, 75573, 75574, 75635, 75650, 75658, 75660, 75662, 75665, 75671, 75676, 75680, 75685, 75705, 75710, 75711, 75712, 75716, 75726, 75731, 75733, 75736, 75741, 75742, 75743, 75744, 75745, 75746, 75756, 75774, 75791, 75894, 75896, 75898, 75952, 75953, 75954, 75955, 75956, 75957, 78445, 93454, 93455, 93456, 93457, 93458, 93459, 93460, 93461, 93563, 93564, 93565, 93566, 93567, 93568, 93571, 93572 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims
Recent history of hypovolemia	Patient had health care encounter for volume depletion in the 30 days prior to the index date? ICD-9 procedure code(s): 276.5 ICD-10 procedure code(s): E86 Categories No (ref.) Yes	MarketScan® Inpatient and Outpatient Claims

Medication utilization		
Covariate	**Definition**	**Data source**
Number of unique prescription medications	Number of unique prescription medications available (i.e. different generic products) used during the last 30-days of the baseline period? Continuous	MarketScan® Prescription Claims
Number of unique diabetes medications	Number of unique diabetes medications medications available (i.e. different generic products) used during the last 30-days of the baseline period? Continuous	MarketScan® Prescription Claims
ACE inhibitor	Utilization of an ACE inhibitor during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
ARB	Utilization of an ARB during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
DR inhibitor	Utilization of an DR inhibitor during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
RAAS antagonist	Utilization of ≥1 RAAS antagonist medication (ACE inhibitor, ARB or DR inhibitor) during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Thiazide/ thiazide-like diuretic	Utilization of a thiazide or thiazide-like diuretic during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Loop diuretic	Utilization of a loop diuretic during the last 30-days of the baseline period?	MarketScan® Prescription Claims

	Categories No (ref.) Yes	
Potassium sparing diuretic	Utilization of a potassium sparing diuretic during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Carbonic anhydrase inhibitor	Utilization of a carbonic anhydrase inhibitor (diuretics only) during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Diuretic	Utilization of ≥1 diuretic medication (thiazide, loop, or potassium sparing diuretic) on the last day of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
NSAID	Utilization of a prescription NSAID during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Metformin	Utilization of a prescription metformin during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Dipeptidyl peptidase-4 inhibitor (DPP4i)	Utilization of a DPP4i during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Thiazolidinedione (TZD)	Utilization of a TZD during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims

Glucagon-like peptide analog (GLP-1)	Utilization of a GLP-1 during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Meglitinide	Utilization of a meglitinide during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Alpha-glucosidase inhibitor	Utilization of an alpha-glucosidase inhibitor during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Amylin analogue	Utilization of an amylin analogue during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Insulin	Utilization of insulin during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Beta blocker	Utilization of a beta blocker during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Calcium channel blocker	Utilization of calcium channel blocker during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Alpha blocker	Utilization of an alpha blocker during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims

Central alpha agonist	Utilization of a central alpha agonist during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Vasodilator	Utilization of a vasodilator during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Statin	Utilization of a statin during the last 30-days of the baseline period? Categories No (ref.) Yes	MarketScan® Prescription Claims
Health care utilization		
Covariate	**Definition**	**Data source**
Recent outpatient visit to an endocrinologist	Outpatient visit to an endocrinologist in the in the 30 days before the index date (based upon TSVCDAT)? STDPLAC = 11 (Office) *AND* STDPROV = 270 (Endocrinology & Metabolism) Categories No (ref.) Yes	MarketScan® Outpatient Claims
Recent outpatient visit to an primary care/family physician	Outpatient visit to a primary care/family physician in the 30 days before the index date (based upon TSVCDAT)? STDPLAC = 11 (Office) *AND* STDPROV = 204 (Internal Medicine [NEC]) or 240 (Family Practice) Categories No (ref.) Yes	MarketScan® Outpatient Claims
Recent inpatient hospital admission	Individual was hospitalized during the in the 30 days prior to the index date (based upon DISDATE)? Categories No (ref.)	MarketScan® Inpatient Claims

	Yes	
Recent emergency department visit	Individual had an ER visit during the in the 30 days prior to the index date (based upon DISDATE)? Categories No (ref.) Yes	MarketScan® Inpatient Claims
Number of baseline hospitalizations	Number of hospital discharges occurring in the 365-day baseline period (based upon DISDATE) Continuous Categories 0 1 ≥ 2	MarketScan® Inpatient Claims
Number of baseline emergency department visits	Number of emergency department visits occurring in the 365-day baseline period (based upon TSVCDAT) STDPLAC = 23 (Emergency Room – Hospital) Continuous Categories 0 1 ≥ 2	MarketScan® Outpatient Claims

Baseline characteristics will be assessed in the 365 days before study medication initiation unless otherwise stated. A baseline comorbid conditions will be considered present if an applicable ICD-9/ICD-10 discharge code (located in any position) was associated with ≥ 1 inpatient claim or ≥ 1 outpatient claim during the 365-day baseline period.

[a] Specified 3-digit ICD-9 diagnosis codes include all existing 4th and 5th digit diagnosis codes. Specified 4-digit ICD-9 diagnosis codes include all existing 5th digit diagnosis codes.

[b] Specified 3-digit ICD-10 diagnosis codes include all existing 4th, 5th, 6th and 7th digit diagnosis codes. Specified 4-digit ICD-10 diagnosis codes include all existing 5th, 6th and 7th digit diagnosis codes. Specified 5-digit ICD-10 diagnosis codes include all existing 6th and 7th digit diagnosis codes.

Supplemental Table S2. *List of generic names of baseline medication classes of interest*

Medication class	Generic name(s)
ACE inhibitor	Benazepril, captopril, cilazapril, enalapril, fosinopril, imidapril, lisinopril, moexipril, monopril, perindopril, quinapril, ramipril, tensoril, trandolapril, zofenopril
ARB	Valsartan, telmisartan, losartan, irbesartan, azilsartan, olmesartan, valsartan, candesartan, eprosartan,
DR inhibitor	Aliskiren
RAAS antagonist	Includes all: ACE inhibitors, ARBs and DR inhibitors
Thiazide/thiazide-like diuretic	HCTZ, hydrochlorothiazide, chlorothiazide, chlorthalidone, indapamide, methyclothiazide, metolazone
Loop diuretic	Furosemide, bumetanide, ethacrynic acid, torsemide
Potassium sparing diuretic	Amiloride, triamterene, spironolactone, eplerenone
Carbonic anhydrase inhibitor **Exclude ophthalmic dosage forms	Acetazolamide, dorzolamide, methazolamide
Diuretic	Includes all: thiazide, loop and potassium sparing diuretics
NSAIDs	Aspirin, diflunisal, salicylic acid, salsalate, ibuprofen, dexibuprofen, naproxen, fenoprofen, ketoprofen, dexketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, tolmetin, sulindac, etodolac, ketorolac, diclofenac, aceclofenac, nabumetone, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, phenylbutazone, mefenamic, meclofenamic, flufenamic, tolfenamic, celecoxibsund
Metformin	Metformin
DPP4i	Sitagliptin, saxagliptin, linagliptin, alogliptin
TZD	Pioglitazone, rosiglitazone
GLP1	Exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide
Meglitinide	Nateglinide
Alpha-glucosidase inhibitor	Acarbose, miglitol, voglibose
Amylin analogue	Pramlintide, repaglinide
Insulin **Exclude insulin needles/syringes	Insulin, insulin lispro, insulin aspart, insulin glulisine, insulin beef regular, insulin pork regular, insulin human regular, insulin isophane, insulin glargine, insulin detemir, insulin degludec, insulin beef, insulin pork, insulin human
Beta blocker **Exclude ophthalmic dosage forms	Acebutolol, atenolol, betaxolol, bisoprolol, bucindolol, carteolol, carvedilol celiprolol, metoprolol, labetalol, nadolol, nebivolol, oxprenolol, penbutolol pindolol, propranolol, sotalol, timolol
Calcium channel blocker	Amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, cilnidipine, clevidipine, diltiazem, efonidipine, isradipine, nicardipine, nifedipine, verapamil, felodipine, lacidipine, lercanidipine, manidipine, nisoldipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, pranidipine, gallopamil, fendiline

Alpha blocker	Alfuzosin, prazosin, doxasozin, terazosin, silodosin
Central alpha agonist	Clonidine, methyldopa, guanabenz, guanfacine
Vasodilator	Hydralazine, minoxidil
Statin	Atorvastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin