Supplementary Material*

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Supplement. **Supplementary Materials**

* This supplementary material was provided by the authors to give readers further details on their article. The material was not copyedited.

Supplement

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Rationale for sensitivity analyses

Several sensitivity analyses were conducted to demonstrate the robustness of our findings.

i. From the analysis, we excluded the first time period, April 2013 through December 2014, immediately subsequent to the launch of SGLT-2i due to the lack of adequate equipoise between the treatment groups in the early phase of post-marketing (1). Specifically, differences in age and general health status between first-line SGLT-2i and metformin initiators were greater in the first time period compared with later time periods, with SGLT-2i initiators younger and generally healthier. Additionally, the first time block was more likely to include prior antidiabetic drug users, particularly for Medicare. This database started approximately one year before the beginning of the study cohort entry, thereby providing a relatively short look-back period for wash-out antidiabetic drug use.

ii. The study cohorts were restricted to individuals with continuous health insurance enrollment for at least two years before cohort entry to assess the impact of the probable inclusion of prior antidiabetic drug users. The choice of a two-year time frame was to further minimize chances of including prior antidiabetic drug users because individuals with T2D probably received antidiabetic drugs for two years.

iii. An intention-to-treat analysis was conducted to address potential informative censoring by carrying forward the initial exposure for 365 days without considering treatment discontinuation or the initiation of the comparator drug (2).

iv. We additionally censored individuals on initiation of the comparator drug to evaluate potential exposure misclassification because 16% of SGLT-2i initiators started prescribing metformin, whereas 2% of metformin initiators started prescribing SGLT-2i during the follow-up period (data not shown).

v. For a subset of the study population with baseline HbA_{1c} levels available, we re-estimated the PS further conditioning on HbA_{1c} levels to adjust for baseline glucose control.

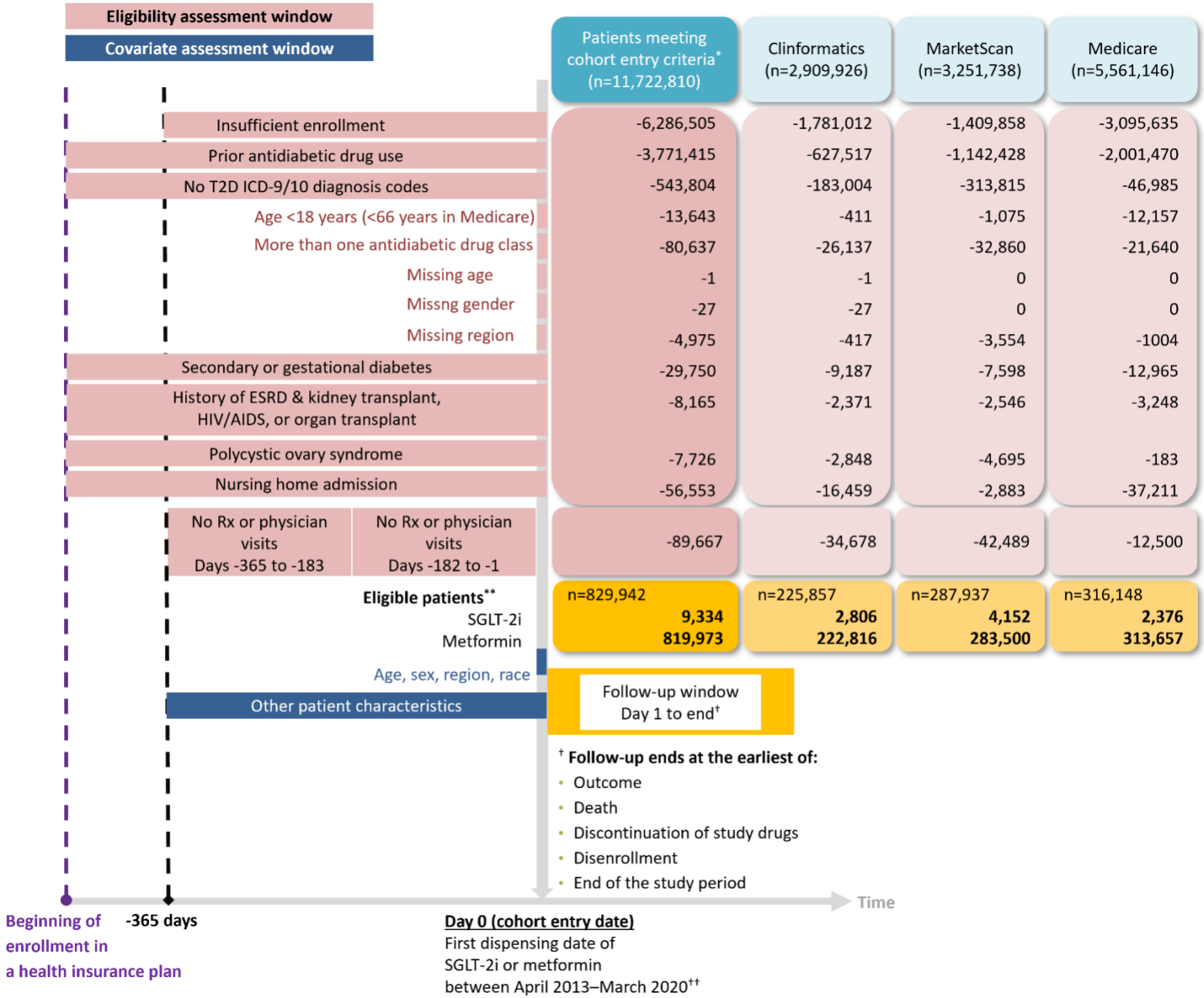
vi. We also quantified the bias associated with the imbalance in baseline HbA_{1c} levels across treatment groups after PS matching (3).

vii. We evaluated cardiovascular endpoints of first-line SGLT-2i and metformin against first-line DPP-4i, which cost higher than metformin without a known impact on the cardiovascular outcomes of interest based on recent evidence (4), to assess the impact of unmeasured socioeconomic status because a previous finding suggested that bias might toward a protective effect for antidiabetic drugs at a considerably higher cost if newer and expensive drugs were used more often in healthier patients with higher socioeconomic status (5).

viii. We re-estimated the propensity scores after replacing the 4 census regions (Northeast, Midwest, South, and West) of the primary analysis with 50 States and 1 federal district in the propensity score models to explore the presence of potential residual confounding because of geographic variation in clinical care. For this analysis, to accommodate many levels of the State variable, propensity scores were estimated without time block stratification because of the limited sample size. Instead, to address evolving channeling over time, such as changes in the prevalence of CVD, interaction terms between these characteristics and time blocks were included in the propensity score models. We included time blocks as a matching factor in addition to the PS and baseline CVD in the matching process to ensure balance in time blocks. Some levels of the State variable had either zero or very few individuals. To improve the stability of propensity score prediction, we combined these levels.

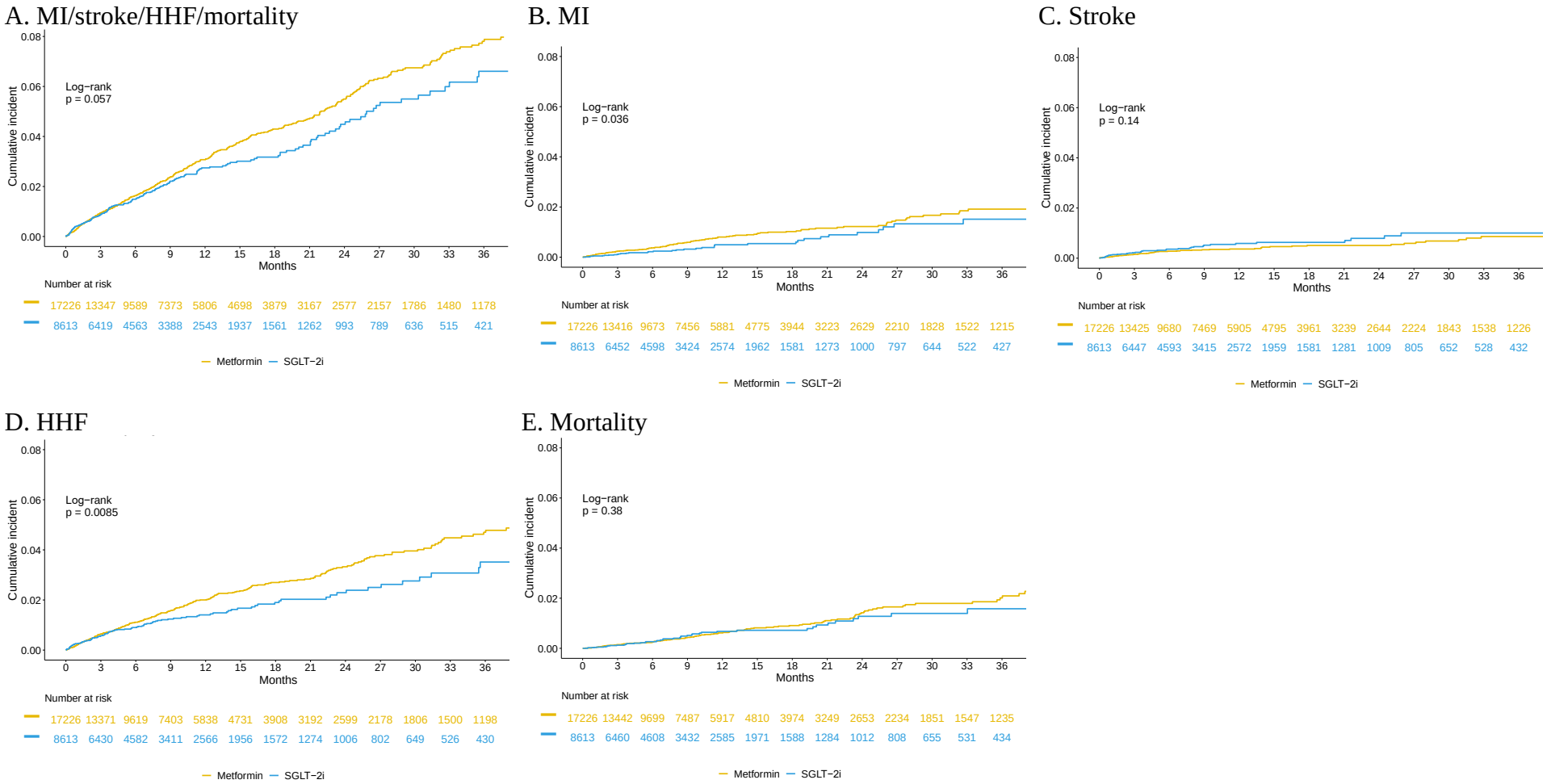
ix. We evaluated the effect of individual SGLT-2i versus metformin on the primary cardiovascular outcomes. Because of the limited sample size of each SGLT-2i and the varying degrees of use over time, within each database, we fitted a propensity score model for each drug without time block stratification but with interaction terms between some characteristics, which prevalence changed over time, and time blocks. We included time blocks as a matching factor in addition to the PS and baseline CVD in the matching process to ensure balance in time blocks. Nevertheless, these analyses were still statistically underpowered because of the limited sample size.

Supplement Figure 1. Study design diagram and flowchart of study cohort



T2D: type 2 diabetes; ESRD: end-stage renal disease; HIV/AIDS: human immunodeficiency virus/acquired immune deficiency syndrome; Rx: prescription.
* Cohort entry criteria: initiation of either SGLT-2i or metformin between April 1, 2013 and March 31, 2020 (December 31, 2018 for MarketScan and Medicare)
** Individuals who were censored on cohort entry were additionally excluded.

Supplement Figure 2. Kaplan-Meier curves of cumulative incidence for secondary cardiovascular outcomes, comparing SGLT-2i versus metformin after 1:2 propensity score matching.



MI/stroke/HHF/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, hospitalization for heart failure, or all-cause mortality; MI: hospitalization for myocardial infarction; Stroke: hospitalization for ischemic or hemorrhagic stroke; HHF: hospitalization for heart failure; Mortality: all-cause mortality.

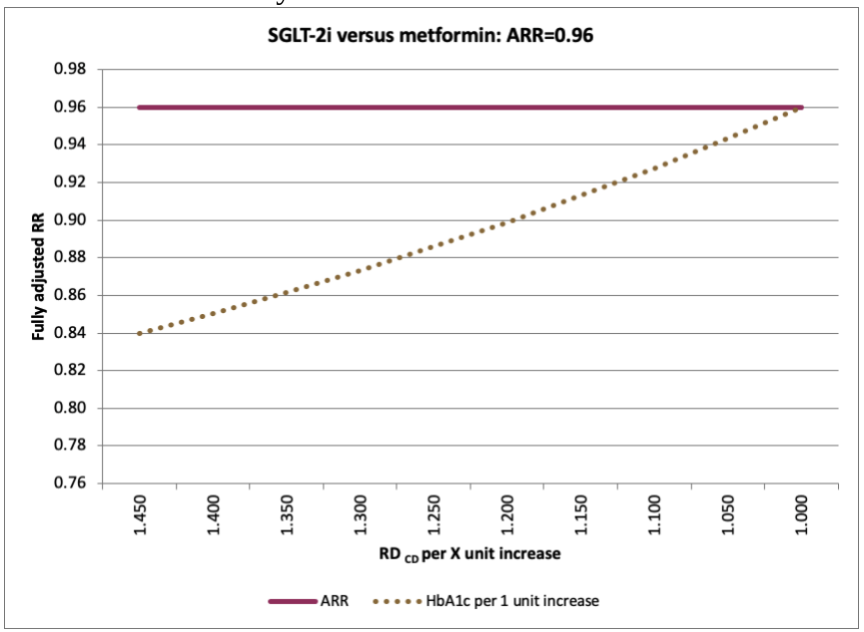
Supplement Figure 3. [Sensitivity analysis] Hazard ratios and incidence rate differences for primary outcomes, comparing SGLT-2i versus metformin after 1:2 propensity score matching.

Outcomes	Sensitivity analyses	HR (95% CI)	IRD/1,000 PY (95% CI)
Primary			
MI/stroke/mortality	Main	0.96 (0.77, 1.19)	-1.21 (-4.52, 2.11)
	ITT 365 days	0.95 (0.76, 1.19)	-0.96 (-4.66, 2.74)
	2-yr enrollment	0.92 (0.71, 1.19)	-1.57 (-5.65, 2.51)
	T1 exclusion	0.96 (0.75, 1.22)	-1.26 (-5.24, 2.72)
	Censor on alternative	0.96 (0.76, 1.20)	-1.00 (-4.53, 2.54)
	HbA1c restriction	1.10 (0.57, 2.15)	1.93 (-9.11, 12.98)
HHF/mortality	Main	0.80 (0.66, 0.97)	-5.23 (-9.01, -1.45)
	ITT 365 days	0.88 (0.73, 1.06)	-3.17 (-7.56, 1.22)
	2-yr enrollment	0.82 (0.66, 1.03)	-4.81 (-9.45, -0.17)
	T1 exclusion	0.82 (0.66, 1.01)	-5.01 (-9.59, -0.43)
	Censor on alternative	0.79 (0.65, 0.97)	-5.05 (-9.07, -1.03)
	HbA1c restriction	0.77 (0.37, 1.57)	-3.87 (-14.09, 6.35)

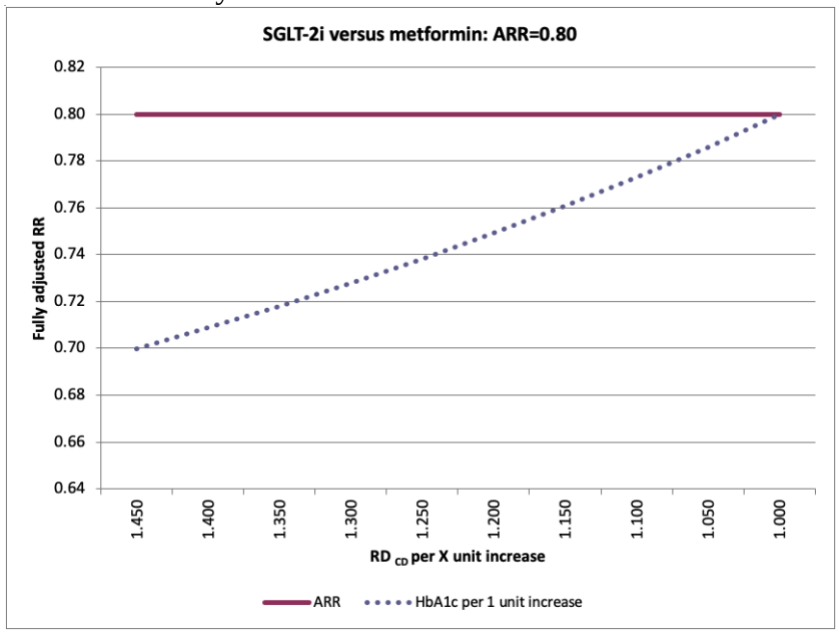
HR: hazard ratio; 95% CI: 95% confidence interval; IRD: incidence rate difference; PY: person-years; MI/stroke/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality; HHF/mortality: hospitalization for heart failure or all-cause mortality.
- Main: The main analysis.
- ITT 365 days: An intention-to-treat analysis by carrying forward the initial exposure for 365 days without considering treatment discontinuation or initiation of the comparator drug.
- 2-yr enrollment: A restricted analysis to individuals with continuous health insurance enrollment for at least two years before cohort entry.
- T1 exclusion: A restricted analysis, excluding the first time block, April 2013 through December 2014, immediately subsequent to the launch of SGLT-2i.
- Censor on alternative: An additional censoring on initiation of the comparator drug.
- HbA_{1c} restriction: A restricted analysis for a subset of the study population with baseline hemoglobin A_{1c} levels available to adjust for baseline glucose control.

Supplement Figure 4. [Sensitivity analysis] Bias analysis quantifying the impact on point estimates of increasing strength of associations between HbA_{1c} and the primary cardiovascular outcomes based on the observed residual difference in HbA_{1c} values between initiators of first-line SGLT-2i versus metformin.

A. MI/stroke/mortality



B. HHF/mortality



MI/stroke/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality; HHF/mortality: hospitalization for heart failure or all-cause mortality; SGLT-2i: sodium-glucose cotransporter-2 inhibitors; ARR: apparent (or observed) exposure relative risk; RR_{CD}: association between confounder and disease outcome; HbA_{1c}: hemoglobin A_{1c}.

Quantification of the potential bias associated with the observed imbalance in HbA_{1c} levels in the PS matched cohorts, using varying assumptions of exposure-outcome and confounder-outcome associations.
A. MI/stroke/mortality: If a 1%-point increase in HbA_{1c} would result in a 25% increase (RR_{CD}=1.25) in the risk of MI/stroke/mortality, the ARR of MI/stroke/mortality would have moved from 0.96 to 0.88 due to the residual confounding.
B. HHF/mortality: If a 1%-point increase in HbA_{1c} would result in a 25% (RR_{CD}=1.25) increase in the risk of HHF/mortality, the ARR of HHF/mortality would have moved from 0.80 to 0.74 due to the residual confounding.

Supplement Table 1. Simulated trial design framework.

Component	Target trial	Emulated trial using real-world data
Aim	To assess the risk of cardiovascular outcomes among adults with type 2 diabetes who initiated first-line SGLT-2i versus metformin.	Same.
Eligibility	Inclusion criteria • Type 2 diabetes • Aged ≥18 years (>65 years in Medicare) • Continuously enrolled in U.S. health insurance databases, Optum Clinformatics® Data Mart Database or IBM® MarketScan®, or Medicare fee-for-service for at least 365 days with complete medical coverage and pharmacy benefits Exclusion criteria • Prior use of any antidiabetic drugs before randomization • Without at least one prescription or a physician visit in each of two, six-month intervals before randomization • A history of gestational or secondary diabetes • A history of polycystic ovary syndrome • A history of organ transplant • A history of end-stage renal disease • A history of HIV/AIDS • A history of nursing home admission	Same. Unlike the target trial, we first identified individuals who filled a new prescription for SGLT-2i or metformin between April 1, 2013 and March 31, 2020, and then applied these eligibility criteria to ensure first-line use.
Treatment strategies	1. First-line SGLT-2i (canagliflozin, dapagliflozin, or empagliflozin) 2. First-line metformin	Same.
Treatment assignment	Patients were randomly assigned to either strategy	Individuals were non-randomly assigned to SGLT-2i if they filled a new prescription for SGLT-2i and to metformin if they filled a

		new prescription for metformin between April 1, 2013 and March 31, 2020 in Optum (December 31, 2018 in MarketScan and Medicare). Randomization was emulated by 1:2 propensity score matching, adjusting for pre-exposure prognostic patient characteristics, including demographics, diabetes-related and other comorbidities, concomitant medications, and measures of healthcare utilization (Supplement Table 2).
Follow-up	Follow-up started at treatment assignment and ends at diagnosis of the outcomes of interest, death, loss to follow-up, or on March 31, 2020 (administrative end of follow-up), whichever occurred first.	Same as for the target trial, but follow-up started on the day after the first prescription dispensing. Treatment discontinuation and disenrollment from health insurance were additionally considered as the end of follow-up.
Outcomes	Primary outcomes • A composite of hospitalization for acute myocardial infarction (MI), hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality (mortality) (MI/stroke/mortality) • A composite of hospitalization for heart failure (HHF) or mortality (HHF/mortality) Secondary outcomes • A composite of MI/stroke/HHF/mortality • Hospitalization for acute myocardial infarction • Hospitalization for ischemic or hemorrhagic stroke • All-cause mortality • Hospitalization for heart failure Safety events • Acute kidney injury • Bone fractures • Genital infections	Same. The outcomes were identified by using ICD-9/10-CM procedural and diagnosis codes (Supplement Table 8).

	• Severe hypoglycemia • Severe urinary tract infections • Diabetic ketoacidosis • Lower-limb amputations	
Causal contrast	Intention-to-treat effect (effect of being assigned to SGLT-2i vs. metformin at baseline, regardless of whether individuals administered the assigned medication after baseline estimated)	Average treatment effect in the population estimated with observational analogue of the per-protocol effect, i.e., effect of SGLT-2i vs. metformin among individuals who adhered to prescription medications.
Statistical analysis	Intention-to-treat effect estimated via comparison of the risk of the outcomes of interest among individuals assigned to each treatment strategy.	On-treatment effect (observational analogue of the per-protocol effect) was estimated, adjusting for baseline covariates via 1:2 propensity score matching. When estimating the on-treatment effect, continuous treatment status was assessed using days of supply in each prescription dispensing, allowing a 60 days of grace period between prescription refills, under the assumption that treatment discontinuation was not informative.
Estimand	The average treatment effect in the population (ATE)	An on-treatment estimate, with a grace period of 60 days between prescription refills, among the initiators of SGLT-2i and metformin who were well-balanced on all measured potential confounders

Supplement Table 2. Outcome definitions

Outcome	Codes	Care Setting	Position
Myocardial infarction	ICD-9 DX: 410.** (except 410.*2) ICD-10 DX: I21.0-I21.4, I22.*	Inpatient	Any
Ischemic or hemorrhagic stroke	ICD-9 DX: 430.**, 431.**, 433.*1, 434.** (excluding 434.x0), 436.** ICD-10 DX: I60.**, I61.*, I63.***	Inpatient	Primary
Hospitalization for heart failure	ICD-9 DX: 398.91, 402.*1, 404.*1, 404.*3, 428.** ICD-10 DX: I09.81, I11.0, I13.0, I13.2, I50.**	Inpatient	Any
Acute kidney injury	ICD-9 DX: 584.5*, 548.6*, 548.7*, 584.8*, 584.9* ICD-10 DX: N17.0*, N17.1*, N17.2*, N17.8*, N17.9*	Inpatient	Any
Bone fractures	**Hip fracture diagnosis** **Occurrence of Diagnosis Code 1 AND Procedure Code 1 on the same claim:** **Diagnosis Code 1** ICD-9 DX: 733.14, 733.96, 820.** ICD-10 DX: M80.05*A, M80.85*A, M84.359A, M84.451A, M84.452A, M84.459A, M84.551A, M84.552A, M84.553A, M84.559A, M84.651A, M84.652A, M84.653A, M84.659A, S72.0**A, S72.0**B, S72.0**C, S72.1**A, S72.1**B, S72.1**C, S72.2*XA, S72.2*XB, S72.2*XC, S79.0**A **Procedure Code 1** ICD-9 PX: 78.55, 79.05, 79.15, 79.25, 79.35, 79.65 ICD-10 PX: 0QB60ZZ, 0QB70ZZ, 0QB80ZZ, 0QB90ZZ, 0QBB0ZZ, 0QBC0ZZ, 0QH6*4Z, 0QH6*6Z, 0QH7*4Z, 0QH7*6Z, 0QH8*4Z, 0QH8*6Z, 0QH9*4Z, 0QH9*6Z, 0QHB*4Z, 0QHB*6Z, 0QHC*4Z, 0QHC*6Z, 0QS6***, 0QS7***, 0QS8***, 0QS9***, 0QSB***, 0QSC*** CPT-4: 27230, 27232, 27235-6, 27238, 27240, 27244-6, 27248, 27267, 27268, 27269, 27125, 27130	Inpatient	Any
	Pelvis fracture diagnosis ICD-9 DX: 808.**, 733.98 ICD-10 DX: M84.350A, S32.3**A, S32.3**B, S32.4**A, S32.4**B, S32.5**A, S32.5**B, S32.6**A, S32.6**B, S32.8**A, S32.8**B, S32.9XXA, S32.9XXB CPT-4: 27193, 27194, 27200, 27202, 27215, 27216, 27217, 27218. 27220, 27222, 27226, 27227, 27228	Inpatient, Outpatient	Any
	Radius/ulna fracture diagnosis **Occurrence of Diagnosis Code 2 AND Procedure Code 2 occurring within 30 days after Diagnosis Code 2:** **Diagnosis Code 2** ICD-9 DX: 733.12, 813.** ICD-10 DX: M80.03*A, M80.83*A, M84.43*A, M84.53*A, M84.63*A, S52.***A, S52.***B, S52.***C, S59.0**A, S59.1**A, S59.2**A **Procedure Code 2** ICD-9 PX: 78.53, 79.02, 79.12, 79.22, 79.32, 79.62	Inpatient, Outpatient	Any

	ICD-10 PX: 0PBH0ZZ, 0PBJ0ZZ, 0PBK0ZZ, 0PBL0ZZ, 0PHH*4Z, 0PHH*6Z, 0PHJ*4Z, 0PHJ*6Z, 0PHK*4Z, 0PHK*6Z, 0PHL*4Z, 0PHL*6Z, 0PSH***, 0PSJ***, 0PSK***, 0PSL*** CPT-4: 24620, 24625, 24635, 24650, 24655, 24660, 24665-6, 24670, 24680, 24685, 25500, 25505, 25510, 25515, 25530, 25535, 25540, 25545, 25560, 25565, 25570, 25575, 25600, 25605, 25610-1, 25615, 25620, 25650		
	Humerus fracture diagnosis **Occurrence of Diagnosis Code 3 AND Procedure Code 3 occurring within 30 days after Diagnosis Code 3:** **Diagnosis Code 3** ICD-9 DX: 733.11, 812.** ICD-10 DX: M80.02*A, M80.82*A, M84.42*A, M84.52*A, M84.62*A, S42.2**A, S42.2**B, S42.3**A, S42.3**B, S42.4**A, S42.4**B, S42.9**A, S42.9**B, S49.0**A, S49.1**A **Procedure Code 3** ICD-9 PX: 78.52, 79.01, 79.11, 79.21, 79.31, 79.61 ICD-10 PX: 0PBC0ZZ, 0PBD0ZZ, 0PBF0ZZ, 0PBG0ZZ, 0PHC*4Z, 0PHC*6Z, 0PHD*4Z, 0PHD*6Z, 0PHF*4Z, 0PHF*6Z, 0PHG*4Z, 0PHG*6Z, 0PSC***, 0PSD***, 0PSF***, 0PSG*** CPT-4: 23600, 23605, 23610, 23615, 23620, 23625, 23630, 23665, 23670, 23680, 24500, 24505, 24506, 24510, 24515, 24530, 24531, 24535, 24536, 24538, 24540, 24542, 24545, 24560, 24565, 24570, 24575, 24581, 24583, 24585-8, 24516	Inpatient, Outpatient	Any
Genital infections	ICD-9 DX: 112.1, 112.2, 616.1*, 605, 607.1 ICD-10 DX: B37.3, B37.42, B37.49, N47.1-N47.8, N48.1, N76.0-N76.3, N77.1	Inpatient, Outpatient	Any
Severe hypoglycemia	ICD-9 DX: 251.0, 251.1*, 251.2*, 250.8* ICD-10 DX: E10.641, E10.649, E10.69, E11.641, E11.649, E11.69, E13.641, E13.649, E13.69, E16.0, E16.1, E16.2 Outcomes identified by ICD-9 DX 250.8* were excluded if they co-occurred with one of the following diagnoses: ICD-9 DX: 259.8, 272.7, 681.**, 682.**, 686.9, 707.1*, 707.2*, 707.8, 707.9, 709.3, 730.0*, 730.1*, 730.2*, 731.8 ICD-10 DX: E34.1, E34.8, E35, E75.21, E75.22, E75.24*, E75.3, E77.*, I70.23*, I70.24*, I70.25, I70.33*, I70.34*, I70.35, I70.43*, I70.44*, I70.45, I70.53*, I70.54*, I70.55, I70.63*, I70.64*, I70.65, I70.73*, I70.74*, I70.75, K12.2, L02.01, L02.11, L02.21*, L02.31, L02.41*, L02.51*, L02.61*, L02.81*, L02.91, L03.***, L08.9, L89.000-L89.95 (except L89.46 and L89.96), L92.1, L94.2, L97.*** (except L97.**5, L97.**6, and L97.**8), L98.3, L98.4** (except L98.4*5, L98.4*6, and L98.4*8), L98.8, M46.2*, M86.***, M90.***	Inpatient Emergency	Primary Any
Severe urinary tract infections (UTIs)	**Primary UTI hospitalizations** ICD-9 DX: 590.** (pyelonephritis), 595.** (cystitis), 597.** (ureteritis), 599.0* ICD-10 DX: N10-N12, N13.6 (pyelonephritis), N15.1, N28.84, N28.85, N28.86, N30.** (cystitis), N34.** (ureteritis), N39.0	Inpatient	Primary
	Hospitalizations with sepsis and UTI ICD-9 DX: 038.** (septicemia), 790.7 (bacteremia), 995.9* (sepsis), 785.52 (septic shock)	Inpatient	Any

	ICD-10 DX: A32.7, A39.2, A39.4, A40.*, A41.*, A42.7, R65.2*, R78.81 **AND** ICD-9 DX: 590.** (pyelonephritis), 595.** (cystitis), 597.** (ureteritis), 599.0* ICD-10 DX: N10-N12, N13.6 (pyelonephritis), N15.1, N28.84, N28.85, N28.86, N30.** (cystitis), N34.** (ureteritis), N39.0		
	Hospitalizations with pyelonephritis ICD-9 DX: 590.** (pyelonephritis) ICD-10 DX: N10-N12, N13.6 (pyelonephritis), N15.1, N28.84, N28.85, N28.86	Inpatient	Any
Diabetic ketoacidosis	ICD-9 DX: 250.1* ICD-10 DX: E08.1*, E09.1*, E10.1*, E11.1*, E13.1*	Inpatient	Any
Lower-limb amputation	ICD-9 PX: 84.10-84.18 ICD-10 PX: 0Y6*** CPT-4: 27590-27592 (above knee), 27598 (knee), 27880-27889, 28800- 28825 (below knee)	Inpatient, Outpatient	Any

Supplement Table 3. Baseline patient characteristics

Category of patient characteristics	Variable(s)
Demographics	Age, sex, geographic region[*], Medicare Advantage[†], race[‡]
Lifestyle risk factors	Obesity or overweight, smoking
Claims-measured proxies of diabetes severity and duration	Diabetic nephropathy, diabetic neuropathy, diabetic retinopathy
Risk factors for prognosis of diabetes	CVD[§], CKD (stages 1-4)
Other comorbidities	Hyperlipidemia, hypertension, COPD, malignant neoplasm
Physician specialties[‖]	Cardiologist visits, endocrinologist visits, internist visits
Healthcare utilization as proxy for overall health status and care intensity, and claims-measured proxies of socioeconomic status (6)	Any recent hospitalizations[¶], average days of hospitalizations, number of ED visits, number of office visits, number of HbA_{1c} test orders, ratio of the number of brand name versus generic drug use[#], number of unique medications, copay for pharmacy cost, preventive healthcare service[**]
Concomitant medications	ACE inhibitors or ARBs Antithrombotic medications Beta blockers Calcium channel blockers Loop diuretics Statin Thiazides
Laboratory results[†]	HbA_{1c} (%)[††], eGFR (mL/min/1.73m^2) [‡‡], LDL (mmol/L [mg/dL]), HDL (mmol/L [mg/dL]), total cholesterol (mmol/L [mg/dL]), triglyceride (mmol/L [mg/dL])

CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department; HbA_{1c}: hemoglobin A_{1c}; ACE inhibitors: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers.

[*] Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)
South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)
Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)
West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

[†] Available for Clinformatics and MarketScan databases.

[‡] Available for Clinformatics and Medicare databases.

[§] Defined as history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

[‖] Defined as specialist visits occurred within 7 days prior to cohort entry.

[¶] Defined as any hospitalizations occurred within 30 days prior to cohort entry.

[#] Added 1 to both numerator and denominator, then log-transformed.

[**] Defined as administration of bone mineral density test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu or pneumococcal vaccine.

[††] Measured 180 days prior to or on cohort entry.

[‡‡] Estimated using the quadratic GFR equation: GFR = $\exp(1.911+\frac{5.249}{Serum\ creatinine}-\frac{2.114}{Serum\ creatinine^2}-0.00686*Age-0.205\ (if\ female))$. If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

Supplement Table 4. [Optum Clinformatics] Odds ratios and p-values for the association between covariates included in the propensity score models and the initiation of first-line SGLT-2i versus metformin.

	Time block 1		Time block 2		Time block 3		Time block 4	
Baseline characteristics*	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Demographics								
Age (year)	0.99 (0.98, 1.01)	0.30	0.99 (0.98, 1.00)	0.087	1.00 (0.99, 1.01)	0.66	0.99 (0.99, 1.00)	0.131
Gender (male vs. female [ref])	0.73 (0.58, 0.91)	0.006	1.17 (0.97, 1.41)	0.11	0.90 (0.77, 1.05)	0.189	1.13 (1.00, 1.27)	0.042
Region								
South (ref: Northeast)	1.10 (0.74, 1.63)	0.64	1.48 (1.08, 2.03)	0.015	1.06 (0.82, 1.38)	0.64	1.14 (0.94, 1.37)	0.192
Midwest (ref: Northeast)	0.88 (0.57, 1.36)	0.56	1.17 (0.82, 1.67)	0.39	0.91 (0.68, 1.21)	0.52	1.02 (0.82, 1.27)	0.84
West (ref: Northeast)	0.73 (0.45, 1.17)	0.195	0.85 (0.58, 1.24)	0.39	0.67 (0.49, 0.92)	0.013	0.80 (0.64, 1.01)	0.059
Medicare Advantage	0.18 (0.12, 0.28)	<0.001	0.56 (0.42, 0.73)	<0.001	0.51 (0.41, 0.63)	<0.001	0.90 (0.76, 1.05)	0.177
Race								
Non-White (ref: White)	0.59 (0.45, 0.76)	<0.001	0.90 (0.73, 1.11)	0.32	0.82 (0.69, 0.98)	0.025	0.90 (0.78, 1.04)	0.143
Missing (ref: White)	0.50 (0.24, 1.01)	0.054	0.96 (0.67, 1.38)	0.83	1.18 (0.89, 1.58)	0.25	1.19 (1.02, 1.38)	0.023
Life-style risk factors								
Obesity or overweight	1.23 (0.97, 1.56)	0.085	1.10 (0.91, 1.33)	0.34	1.25 (1.07, 1.45)	0.005	0.95 (0.84, 1.06)	0.35
Smoking	0.63 (0.41, 0.97)	0.035	0.73 (0.54, 0.98)	0.039	0.95 (0.77, 1.16)	0.60	0.98 (0.85, 1.13)	0.81
Comorbidities								
Diabetic nephropathy	1.75 (0.85, 3.60)	0.126	1.41 (0.86, 2.31)	0.178	1.90 (1.35, 2.67)	<0.001	1.63 (1.29, 2.05)	<0.001
Diabetic neuropathy	2.65 (1.76, 3.98)	<0.001	1.30 (0.92, 1.84)	0.137	1.43 (1.10, 1.87)	0.008	1.46 (1.21, 1.76)	<0.001
Diabetic retinopathy	1.04 (0.38, 2.86)	0.93	0.95 (0.44, 2.05)	0.90	1.06 (0.56, 2.02)	0.86	1.84 (1.33, 2.53)	<0.001
CVD	1.04 (0.45, 2.41)	0.92	0.99 (0.58, 1.67)	0.96	1.04 (0.69, 1.58)	0.85	1.04 (0.79, 1.36)	0.78
Acute MI§	N/A	N/A	1.25 (0.49, 3.23)	0.64	1.33 (0.66, 2.67)	0.42	1.03 (0.70, 1.52)	0.88
Old MI	1.71 (0.67, 4.37)	0.26	0.53 (0.23, 1.26)	0.152	0.60 (0.34, 1.05)	0.074	0.98 (0.75, 1.30)	0.91
Ischemic or hemorrhagic stroke	0.31 (0.11, 0.92)	0.034	1.06 (0.62, 1.80)	0.83	1.05 (0.70, 1.59)	0.82	1.22 (0.96, 1.56)	0.10
Transient ischemic attack	1.94 (0.62, 6.07)	0.25	0.67 (0.24, 1.87)	0.44	1.17 (0.57, 2.38)	0.67	0.71 (0.43, 1.17)	0.181
Other ischemic heart diseases	0.64 (0.26, 1.55)	0.32	1.03 (0.61, 1.74)	0.91	1.55 (1.02, 2.36)	0.041	1.77 (1.35, 2.30)	<0.001
Heart failure	1.13 (0.48, 2.66)	0.78	1.30 (0.75, 2.25)	0.36	1.05 (0.69, 1.59)	0.82	1.05 (0.83, 1.34)	0.67
Atherosclerotic peripheral vascular disease	1.18 (0.52, 2.67)	0.69	1.27 (0.76, 2.11)	0.36	1.03 (0.68, 1.55)	0.90	0.80 (0.62, 1.03)	0.082
Stable angina	3.03 (1.42, 6.49)	0.004	0.97 (0.51, 1.86)	0.93	1.23 (0.82, 1.84)	0.32	0.96 (0.75, 1.23)	0.75
Unstable angina	0.75 (0.21, 2.68)	0.66	0.64 (0.22, 1.80)	0.39	1.12 (0.63, 1.99)	0.70	1.22 (0.87, 1.72)	0.24
Hyperlipidemia	1.56 (1.18, 2.06)	0.002	1.59 (1.26, 2.00)	<0.001	1.42 (1.18, 1.71)	<0.001	1.11 (0.96, 1.28)	0.142
Hypertension	1.88 (1.42, 2.49)	<0.001	1.49 (1.17, 1.89)	0.001	1.53 (1.26, 1.87)	<0.001	1.56 (1.33, 1.83)	<0.001
CKD (stages 1-4)	0.95 (0.48, 1.89)	0.89	0.71 (0.44, 1.16)	0.176	1.04 (0.74, 1.46)	0.82	1.18 (0.95, 1.47)	0.137
COPD	1.19 (0.71, 1.98)	0.51	0.79 (0.52, 1.19)	0.26	1.16 (0.88, 1.54)	0.30	0.86 (0.71, 1.05)	0.147
Malignant Neoplasm	0.83 (0.49, 1.41)	0.48	1.20 (0.85, 1.70)	0.29	0.95 (0.70, 1.28)	0.72	1.01 (0.82, 1.24)	0.93
Physician specialties								
Cardiologists	0.68 (0.31, 1.47)	0.33	0.90 (0.53, 1.51)	0.68	0.49 (0.29, 0.80)	0.005	1.03 (0.80, 1.31)	0.84
Endocrinologists	0.98 (0.57, 1.68)	0.94	0.38 (0.19, 0.74)	0.005	0.61 (0.38, 0.98)	0.04	1.05 (0.78, 1.42)	0.74
Internists	0.39 (0.31, 0.49)	<0.001	0.34 (0.28, 0.41)	<0.001	0.31 (0.27, 0.36)	<0.001	0.36 (0.32, 0.40)	<0.001
Healthcare utilization								

Any recent hospitalizations	0.37 (0.09, 1.57)	0.176	0.62 (0.26, 1.48)	0.28	0.35 (0.14, 0.91)	0.03	1.07 (0.73, 1.58)	0.72
Average length of hospitalizations (day)	0.98 (0.90, 1.06)	0.60	1.00 (0.95, 1.05)	0.87	0.96 (0.90, 1.02)	0.149	0.93 (0.90, 0.97)	0.001
Number of ED visits	0.97 (0.92, 1.03)	0.29	1.00 (0.96, 1.03)	0.83	0.98 (0.95, 1.02)	0.33	0.98 (0.95, 1.01)	0.14
Number of office visits	0.99 (0.97, 1.00)	0.117	1.01 (0.99, 1.02)	0.36	1.01 (1.00, 1.01)	0.163	1.00 (0.99, 1.01)	0.87
Number of HbA_{1c} test orders	1.25 (1.13, 1.39)	<0.001	1.29 (1.19, 1.41)	<0.001	1.23 (1.15, 1.31)	<0.001	1.24 (1.18, 1.31)	<0.001
Brand/Generic ratio	1.12 (1.02, 1.23)	0.023	1.11 (1.03, 1.21)	0.009	1.09 (1.01, 1.16)	0.019	1.12 (1.06, 1.18)	<0.001
Number of unique medication use	1.02 (0.99, 1.04)	0.199	1.01 (1.00, 1.03)	0.143	1.01 (1.00, 1.02)	0.175	1.02 (1.01, 1.03)	<0.001
Copay for pharmacy cost ($)	1.00 (1.00, 1.00)	0.25	1.00 (1.00, 1.00)	0.124	1.00 (1.00, 1.00)	0.003	1.00 (1.00, 1.00)	0.098
Preventive healthcare service	0.85 (0.67, 1.08)	0.189	0.88 (0.71, 1.07)	0.20	0.93 (0.78, 1.11)	0.44	1.07 (0.93, 1.23)	0.32
Concomitant medications								
ACE inhibitors or ARBs	0.61 (0.48, 0.79)	<0.001	0.74 (0.60, 0.90)	0.003	0.74 (0.63, 0.88)	<0.001	0.75 (0.66, 0.85)	<0.001
Antithrombotic medications	1.29 (0.82, 2.03)	0.28	1.12 (0.81, 1.57)	0.49	0.77 (0.58, 1.02)	0.067	1.43 (1.21, 1.68)	<0.001
Beta blockers	0.72 (0.53, 0.99)	0.041	0.95 (0.76, 1.21)	0.69	0.83 (0.68, 1.01)	0.061	0.88 (0.76, 1.01)	0.063
Calcium channel blockers	0.80 (0.57, 1.10)	0.171	1.00 (0.79, 1.27)	0.99	0.83 (0.67, 1.01)	0.065	0.93 (0.81, 1.06)	0.28
Loop diuretics	1.13 (0.67, 1.91)	0.63	0.71 (0.45, 1.12)	0.144	1.17 (0.87, 1.59)	0.30	1.27 (1.04, 1.55)	0.02
Statin	0.61 (0.47, 0.78)	<0.001	0.64 (0.52, 0.79)	<0.001	0.71 (0.60, 0.84)	<0.001	0.72 (0.63, 0.82)	<0.001
Thiazides	0.82 (0.56, 1.21)	0.32	0.97 (0.72, 1.30)	0.82	0.74 (0.57, 0.96)	0.021	0.72 (0.60, 0.86)	<0.001
(Intercept)	0.03 (0.01, 0.06)	<0.001	0.02 (0.01, 0.04)	<0.001	0.02 (0.01, 0.04)	<0.001	0.02 (0.01, 0.03)	<0.001

* Refer to the legends for Supplement Table 7 for detailed descriptions of variables.

§ Acute MI was not included in the propensity score model for time block 1 because of the convergence problem.

Supplement Table 5. [IBM MarketScan] Odds ratios and p-values for the association between covariates included in the propensity score models and the initiation of first-line SGLT-2i versus metformin.

	Time block 1		Time block 2		Time block 3		Time block 4	
Baseline characteristics*	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Demographics								
Age (year)	1.00 (0.99, 1.01)	0.99	0.99 (0.99, 1.00)	0.051	1.00 (0.99, 1.01)	0.93	1.00 (0.99, 1.01)	0.56
Gender (male vs. female [ref])	1.04 (0.92, 1.17)	0.50	1.04 (0.93, 1.16)	0.45	1.01 (0.88, 1.15)	0.91	1.12 (0.93, 1.35)	0.23
Region								
South (ref: Northeast)	1.25 (1.07, 1.46)	0.005	1.04 (0.91, 1.20)	0.57	1.09 (0.92, 1.30)	0.31	0.80 (0.64, 1.00)	0.049
Midwest (ref: Northeast)	0.69 (0.57, 0.84)	<0.001	0.67 (0.56, 0.81)	<0.001	0.58 (0.46, 0.74)	<0.001	0.55 (0.41, 0.74)	<0.001
West (ref: Northeast)	0.55 (0.44, 0.69)	<0.001	0.57 (0.46, 0.71)	<0.001	0.64 (0.49, 0.82)	<0.001	0.41 (0.29, 0.59)	<0.001
Medicare Advantage								
Life-style risk factors								
Obesity or overweight	1.18 (1.03, 1.35)	0.016	1.04 (0.93, 1.17)	0.50	0.98 (0.86, 1.11)	0.72	0.97 (0.81, 1.16)	0.74
Smoking	0.70 (0.54, 0.91)	0.008	0.87 (0.71, 1.06)	0.165	0.72 (0.57, 0.91)	0.007	0.86 (0.64, 1.16)	0.33
Comorbidities								
Diabetic nephropathy	1.61 (0.99, 2.61)	0.054	1.19 (0.79, 1.79)	0.40	1.26 (0.83, 1.91)	0.28	1.33 (0.77, 2.28)	0.30
Diabetic neuropathy	1.65 (1.24, 2.19)	<0.001	2.03 (1.60, 2.57)	<0.001	1.63 (1.22, 2.18)	<0.001	1.59 (1.07, 2.37)	0.023
Diabetic retinopathy	2.18 (1.38, 3.44)	<0.001	2.30 (1.51, 3.52)	<0.001	0.66 (0.21, 2.09)	0.48	2.30 (1.19, 4.43)	0.013
CVD	0.81 (0.55, 1.20)	0.30	1.23 (0.87, 1.74)	0.24	1.25 (0.83, 1.88)	0.30	0.80 (0.45, 1.40)	0.43
Acute MI	1.08 (0.53, 2.20)	0.83	1.13 (0.59, 2.17)	0.71	1.50 (0.84, 2.68)	0.17	1.99 (1.01, 3.91)	0.047
Old MI	0.92 (0.49, 1.73)	0.79	1.66 (1.01, 2.72)	0.046	0.81 (0.44, 1.48)	0.49	1.17 (0.61, 2.25)	0.63
Ischemic or hemorrhagic stroke	1.01 (0.69, 1.50)	0.94	0.70 (0.47, 1.03)	0.068	1.11 (0.75, 1.66)	0.60	1.38 (0.82, 2.34)	0.23
Transient ischemic attack	1.45 (0.84, 2.53)	0.185	1.48 (0.90, 2.43)	0.125	0.84 (0.43, 1.64)	0.61	1.32 (0.58, 3.03)	0.51
Other ischemic heart diseases	1.31 (0.88, 1.96)	0.178	0.84 (0.59, 1.20)	0.34	0.97 (0.63, 1.47)	0.87	1.84 (1.03, 3.29)	0.039
Heart failure	0.89 (0.56, 1.41)	0.62	1.38 (0.96, 2.00)	0.084	1.13 (0.74, 1.73)	0.56	1.42 (0.82, 2.47)	0.21
Atherosclerotic peripheral vascular disease	1.50 (1.01, 2.22)	0.043	1.30 (0.90, 1.87)	0.157	0.93 (0.59, 1.46)	0.75	1.29 (0.70, 2.37)	0.42
Stable angina	0.92 (0.57, 1.49)	0.74	0.85 (0.52, 1.39)	0.52	1.32 (0.88, 1.98)	0.182	1.41 (0.86, 2.33)	0.176
Unstable angina	0.82 (0.42, 1.60)	0.57	0.81 (0.41, 1.58)	0.53	1.37 (0.82, 2.29)	0.22	0.56 (0.25, 1.26)	0.164
Hyperlipidemia	1.49 (1.30, 1.71)	<0.001	1.38 (1.21, 1.56)	<0.001	1.14 (0.99, 1.31)	0.074	1.29 (1.05, 1.59)	0.014
Hypertension	1.43 (1.24, 1.65)	<0.001	1.49 (1.30, 1.70)	<0.001	1.24 (1.05, 1.46)	0.012	1.48 (1.18, 1.87)	<0.001
CKD (stages 1-4)	1.01 (0.66, 1.56)	0.96	1.37 (0.99, 1.90)	0.061	0.89 (0.59, 1.36)	0.59	0.77 (0.41, 1.44)	0.41
COPD	0.91 (0.68, 1.23)	0.55	0.88 (0.67, 1.17)	0.38	1.01 (0.73, 1.39)	0.95	0.77 (0.46, 1.27)	0.30
Malignant Neoplasm	0.77 (0.59, 1.02)	0.071	0.74 (0.57, 0.97)	0.027	0.88 (0.66, 1.17)	0.37	1.04 (0.70, 1.54)	0.85
Physician specialties								
Cardiologists	0.59 (0.38, 0.91)	0.018	0.63 (0.43, 0.92)	0.018	0.91 (0.64, 1.30)	0.60	1.31 (0.86, 1.98)	0.21
Endocrinologists	1.23 (0.92, 1.65)	0.158	0.62 (0.45, 0.86)	0.004	0.67 (0.47, 0.97)	0.032	1.00 (0.62, 1.62)	0.99
Internists	0.57 (0.51, 0.64)	<0.001	0.44 (0.40, 0.49)	<0.001	0.40 (0.36, 0.46)	<0.001	0.49 (0.41, 0.58)	<0.001
Healthcare utilization								
Any recent hospitalizations	0.42 (0.24, 0.73)	0.002	0.20 (0.10, 0.41)	<0.001	0.28 (0.14, 0.54)	<0.001	0.56 (0.27, 1.17)	0.123
Average length of hospitalizations (day)	1.04 (0.93, 1.16)	0.50	0.98 (0.86, 1.11)	0.75	0.97 (0.84, 1.13)	0.73	0.73 (0.52, 1.01)	0.054
Number of ED visits	0.91 (0.86, 0.97)	0.004	0.94 (0.89, 0.99)	0.022	0.92 (0.86, 0.99)	0.019	0.96 (0.88, 1.04)	0.32

Number of office visits	1.00 (0.99, 1.00)	0.51	1.00 (1.00, 1.01)	0.178	1.01 (1.00, 1.01)	0.09	1.00 (0.99, 1.01)	0.97
Number of HbA_{1c} test orders	1.16 (1.10, 1.23)	<0.001	1.16 (1.11, 1.23)	<0.001	1.24 (1.17, 1.32)	<0.001	1.21 (1.11, 1.32)	<0.001
Brand/Generic ratio	1.15 (1.09, 1.21)	<0.001	1.13 (1.08, 1.18)	<0.001	1.13 (1.06, 1.20)	<0.001	1.19 (1.09, 1.30)	<0.001
Number of unique medication use	1.04 (1.03, 1.05)	<0.001	1.01 (1.00, 1.02)	0.003	1.01 (1.00, 1.02)	0.057	1.01 (0.99, 1.03)	0.30
Copay for pharmacy cost ($)	1.00 (1.00, 1.00)	0.024	1.00 (1.00, 1.00)	0.41	1.00 (1.00, 1.00)	0.72	1.00 (1.00, 1.00)	0.53
Preventive healthcare service	0.94 (0.82, 1.06)	0.31	0.91 (0.81, 1.03)	0.124	0.88 (0.77, 1.02)	0.082	0.79 (0.65, 0.96)	0.016
Concomitant medications								
ACE inhibitors or ARBs	0.69 (0.61, 0.79)	<0.001	0.77 (0.68, 0.87)	<0.001	0.83 (0.71, 0.96)	0.012	0.77 (0.63, 0.95)	0.013
Antithrombotic medications	1.19 (0.96, 1.48)	0.113	0.82 (0.66, 1.02)	0.077	1.15 (0.92, 1.44)	0.22	1.19 (0.88, 1.61)	0.26
Beta blockers	0.82 (0.70, 0.95)	0.01	0.89 (0.77, 1.03)	0.109	0.87 (0.74, 1.03)	0.105	0.89 (0.70, 1.12)	0.32
Calcium channel blockers	0.86 (0.73, 1.01)	0.061	0.83 (0.72, 0.96)	0.011	1.10 (0.94, 1.29)	0.24	0.93 (0.74, 1.17)	0.54
Loop diuretics	1.09 (0.85, 1.40)	0.49	1.25 (0.99, 1.57)	0.06	1.24 (0.95, 1.61)	0.119	1.03 (0.67, 1.58)	0.88
Statin	0.65 (0.57, 0.74)	<0.001	0.74 (0.66, 0.84)	<0.001	0.78 (0.68, 0.91)	<0.001	0.78 (0.64, 0.96)	0.021
Thiazides	0.69 (0.56, 0.84)	<0.001	0.79 (0.66, 0.94)	0.009	0.72 (0.58, 0.90)	0.003	0.71 (0.53, 0.97)	0.028
(Intercept)	0.01 (0.01, 0.02)	<0.001	0.04 (0.03, 0.06)	<0.001	0.02 (0.02, 0.04)	<0.001	0.03 (0.02, 0.06)	<0.001

* Refer to the legends for Supplement Table 8 for detailed descriptions of variables.

Supplement Table 6. [Medicare] Odds ratios and p-values for the association between covariates included in the propensity score models and the initiation of first-line SGLT-2i versus metformin.

	Time block 1		Time block 2		Time block 3		Time block 4	
Baseline characteristics*	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Demographics								
Age (year)	0.96 (0.94, 0.98)	<0.001	0.96 (0.94, 0.97)	<0.001	0.95 (0.93, 0.96)	<0.001	0.98 (0.97, 1.00)	0.021
Gender (male vs. female [ref])	1.34 (1.07, 1.66)	0.009	1.38 (1.19, 1.59)	<0.001	1.19 (1.01, 1.40)	0.034	1.21 (1.00, 1.46)	0.05
Region								
South (ref: Northeast)	0.76 (0.57, 0.99)	0.044	0.91 (0.77, 1.09)	0.30	0.90 (0.74, 1.10)	0.31	0.97 (0.76, 1.24)	0.81
Midwest (ref: Northeast)	0.67 (0.48, 0.94)	0.019	0.55 (0.43, 0.69)	<0.001	0.65 (0.50, 0.85)	0.001	0.77 (0.57, 1.04)	0.088
West (ref: Northeast)	0.80 (0.57, 1.11)	0.181	0.90 (0.72, 1.11)	0.31	0.97 (0.76, 1.23)	0.80	1.29 (0.99, 1.69)	0.064
Race								
Non-White (ref: White)	0.89 (0.66, 1.19)	0.42	0.84 (0.69, 1.02)	0.086	1.07 (0.87, 1.31)	0.51	1.02 (0.80, 1.30)	0.89
Life-style risk factors								
Obesity or overweight	1.21 (0.95, 1.54)	0.117	1.26 (1.09, 1.46)	0.002	1.00 (0.85, 1.17)	0.99	0.95 (0.79, 1.15)	0.61
Smoking	0.87 (0.64, 1.18)	0.37	0.92 (0.77, 1.11)	0.39	0.91 (0.74, 1.11)	0.34	0.79 (0.63, 1.00)	0.049
Comorbidities								
Diabetic nephropathy	1.76 (1.03, 3.04)	0.04	1.44 (1.03, 2.01)	0.034	1.09 (0.79, 1.51)	0.60	1.16 (0.84, 1.61)	0.36
Diabetic neuropathy	2.33 (1.72, 3.16)	<0.001	1.50 (1.21, 1.87)	<0.001	1.33 (1.05, 1.68)	0.018	1.68 (1.31, 2.14)	<0.001
Diabetic retinopathy	1.88 (1.09, 3.24)	0.024	1.58 (1.05, 2.38)	0.029	1.12 (0.66, 1.88)	0.68	2.19 (1.49, 3.22)	<0.001
CVD								
Acute MI§	1.36 (0.91, 2.03)	0.134	1.11 (0.86, 1.44)	0.41	0.80 (0.58, 1.10)	0.176	1.14 (0.82, 1.60)	0.44
Old MI	1.62 (0.82, 3.20)	0.167	0.97 (0.56, 1.67)	0.92	1.33 (0.84, 2.11)	0.23	0.74 (0.38, 1.45)	0.38
Ischemic or hemorrhagic stroke	0.60 (0.33, 1.09)	0.092	1.03 (0.73, 1.46)	0.87	1.17 (0.84, 1.62)	0.35	0.86 (0.57, 1.28)	0.45
Transient ischemic attack	1.05 (0.74, 1.49)	0.79	1.17 (0.93, 1.47)	0.18	0.92 (0.70, 1.20)	0.53	1.00 (0.76, 1.33)	0.98
Other ischemic heart diseases	0.39 (0.16, 0.96)	0.04	0.90 (0.59, 1.36)	0.6	1.10 (0.69, 1.76)	0.69	1.13 (0.68, 1.88)	0.63
Heart failure	1.16 (0.80, 1.69)	0.43	0.97 (0.76, 1.23)	0.79	1.70 (1.25, 2.32)	<0.001	1.55 (1.14, 2.12)	0.006
Atherosclerotic peripheral vascular disease	1.21 (0.83, 1.75)	0.32	1.17 (0.92, 1.50)	0.20	1.10 (0.84, 1.43)	0.50	1.25 (0.94, 1.66)	0.128
Stable angina	0.84 (0.59, 1.20)	0.34	1.16 (0.92, 1.46)	0.21	1.19 (0.92, 1.54)	0.185	1.07 (0.80, 1.43)	0.64
Unstable angina	0.86 (0.52, 1.42)	0.56	0.88 (0.62, 1.24)	0.46	1.21 (0.91, 1.61)	0.183	1.21 (0.88, 1.67)	0.24
Hyperlipidemia	0.97 (0.50, 1.91)	0.93	0.77 (0.46, 1.31)	0.34	1.43 (0.98, 2.09)	0.065	0.73 (0.43, 1.24)	0.24
Hypertension	1.39 (0.98, 1.97)	0.062	1.14 (0.93, 1.40)	0.22	1.20 (0.96, 1.51)	0.103	1.01 (0.77, 1.32)	0.94
CKD (stages 1-4)	1.55 (1.09, 2.21)	0.016	1.74 (1.37, 2.22)	<0.001	1.42 (1.09, 1.87)	0.011	1.31 (0.96, 1.78)	0.09
COPD	1.17 (0.80, 1.70)	0.41	1.47 (1.18, 1.83)	<0.001	1.57 (1.23, 2.00)	<0.001	1.72 (1.32, 2.24)	<0.001
Malignant Neoplasm	0.89 (0.66, 1.22)	0.48	0.84 (0.68, 1.03)	0.098	0.91 (0.72, 1.15)	0.42	0.77 (0.59, 1.02)	0.07
Physician specialties								
Cardiologists	0.86 (0.56, 1.32)	0.49	0.70 (0.51, 0.96)	0.027	0.95 (0.70, 1.30)	0.76	1.35 (0.99, 1.84)	0.055
Endocrinologists	0.60 (0.31, 1.14)	0.116	1.18 (0.87, 1.61)	0.30	0.95 (0.64, 1.40)	0.78	0.98 (0.64, 1.51)	0.93
Internists	0.50 (0.40, 0.61)	<0.001	0.48 (0.42, 0.55)	<0.001	0.53 (0.45, 0.62)	<0.001	0.47 (0.39, 0.56)	<0.001
Healthcare utilization								
Any recent hospitalizations	0.36 (0.15, 0.87)	0.023	0.58 (0.36, 0.95)	0.031	0.48 (0.27, 0.86)	0.013	0.53 (0.28, 0.98)	0.042
Average length of hospitalizations (day)	0.99 (0.93, 1.05)	0.69	1.00 (0.97, 1.03)	0.93	0.99 (0.95, 1.03)	0.73	0.97 (0.92, 1.02)	0.22

Number of ED visits	0.96 (0.86, 1.08)	0.54	0.91 (0.84, 0.99)	0.029	0.86 (0.78, 0.95)	0.003	0.89 (0.80, 0.99)	0.027
Number of office visits	1.00 (0.99, 1.02)	0.75	1.00 (0.99, 1.01)	0.56	1.01 (0.99, 1.02)	0.27	1.01 (1.00, 1.03)	0.085
Number of HbA_{1c} test orders	1.16 (1.06, 1.26)	0.001	1.15 (1.08, 1.22)	<0.001	1.05 (0.98, 1.13)	0.179	1.07 (0.99, 1.16)	0.10
Brand/Generic ratio	1.31 (1.19, 1.44)	<0.001	1.28 (1.20, 1.36)	<0.001	1.15 (1.07, 1.24)	<0.001	1.18 (1.09, 1.29)	<0.001
Number of unique medication use	1.03 (1.01, 1.05)	<0.001	1.02 (1.01, 1.03)	0.001	1.02 (1.01, 1.04)	<0.001	1.02 (1.00, 1.03)	0.014
Copay for pharmacy cost ($)	1.00 (1.00, 1.00)	0.41	1.00 (1.00, 1.00)	0.97	1.00 (1.00, 1.00)	0.50	1.00 (1.00, 1.00)	0.86
Preventive healthcare service	0.81 (0.61, 1.08)	0.152	0.96 (0.79, 1.18)	0.72	0.74 (0.60, 0.92)	0.006	0.95 (0.72, 1.24)	0.69
Concomitant medications								
ACE inhibitors or ARBs	0.78 (0.62, 0.98)	0.033	0.80 (0.69, 0.93)	0.003	0.83 (0.70, 0.99)	0.035	0.81 (0.67, 0.99)	0.04
Antithrombotic medications	1.14 (0.87, 1.49)	0.34	0.98 (0.82, 1.18)	0.85	1.05 (0.85, 1.28)	0.66	1.15 (0.92, 1.43)	0.24
Beta blockers	0.88 (0.70, 1.11)	0.28	0.92 (0.79, 1.07)	0.30	0.84 (0.70, 1.00)	0.048	0.94 (0.77, 1.15)	0.57
Calcium channel blockers	0.91 (0.72, 1.16)	0.46	0.99 (0.85, 1.16)	0.94	0.92 (0.77, 1.09)	0.33	0.80 (0.65, 0.98)	0.03
Loop diuretics	0.79 (0.56, 1.12)	0.184	1.21 (0.98, 1.49)	0.075	0.78 (0.61, 1.01)	0.061	0.91 (0.69, 1.21)	0.52
Statin	0.61 (0.49, 0.77)	<0.001	0.68 (0.58, 0.80)	<0.001	0.75 (0.63, 0.89)	0.001	0.70 (0.57, 0.86)	<0.001
Thiazides	0.98 (0.73, 1.30)	0.88	0.73 (0.59, 0.90)	0.003	0.94 (0.76, 1.16)	0.56	0.97 (0.75, 1.25)	0.81
(Intercept)	0.09 (0.02, 0.40)	0.002	0.24 (0.09, 0.67)	0.006	0.82 (0.26, 2.63)	0.74	0.07 (0.02, 0.23)	<0.001

* Refer to the legends for Supplement Table 9 for detailed descriptions of variables.

Supplement Table 7. [Optum Clinformatics] Patient characteristics before and after 1:2 propensity score matching. Values are number (percentage) unless otherwise specified.

	Before PS-matching			After PS-matching		
Baseline characteristics	**SGLT-2i (n=2,806)**	**Metformin (n=222,816)**	**SD**	**SGLT-2i (n=2,555)**	**Metformin (n=5,110)**	**SD**
Demographics						
Age (year; mean, std.dev)	59.32 (11.80)	60.58 (12.51)	0.10	59.21 (11.95)	59.52 (12.43)	0.03
Gender (male)	1499 (53.4)	117161 (52.6)	0.02	1351 (52.9)	2736 (53.5)	0.01
Region*						
Northeast	284 (10.1)	24765 (11.1)	0.03	253 (9.9)	554 (10.8)	0.03
CT	49 (1.7)	2524 (1.1)	0.05	42 (1.6)	89 (1.7)	0.01
NJ	66 (2.4)	5664 (2.5)	0.01	65 (2.5)	127 (2.5)	0.00
NY	101 (3.6)	9439 (4.2)	0.03	94 (3.6)	176 (3.4)	0.01
PA	47 (1.7)	2540 (1.1)	0.05	41 (1.6)	78 (1.5)	0.01
MA	12 (0.4)	1899 (0.9)	0.06	19 (0.7)	38 (0.7)	0.00
ME	2 (0.1)	511 (0.2)	0.03			
NH	1 (0.0)	511 (0.2)	0.06			
RI	5 (0.2)	1398 (0.6)	0.06			
VT	1 (0.0)	279 (0.1)	0.04			
South	1523 (54.3)	103461 (46.4)	0.16	1381 (54.1)	2700 (52.8)	0.02
AL	51 (1.8)	3123 (1.4)	0.03	46 (1.8)	88 (1.7)	0.01
AR	39 (1.4)	1894 (0.9)	0.05	35 (1.4)	75 (1.5)	0.01
FL	358 (12.8)	25182 (11.3)	0.05	329 (12.8)	668 (13.0)	0.01
GA	150 (5.3)	9904 (4.4)	0.04	137 (5.3)	309 (6.0)	0.03
LA	41 (1.5)	3054 (1.4)	0.01	37 (1.4)	79 (1.5)	0.01
MD	44 (1.6)	3926 (1.8)	0.02	41 (1.6)	91 (1.8)	0.02
NC	166 (5.9)	10018 (4.5)	0.06	154 (6.0)	286 (5.5)	0.02
OK	55 (2.0)	2658 (1.2)	0.06	43 (1.7)	93 (1.8)	0.01
SC	59 (2.1)	3401 (1.5)	0.05	51 (2.0)	94 (1.8)	0.01
TN	57 (2.0)	3647 (1.6)	0.03	51 (2.0)	105 (2.0)	0.00
TX	410 (14.6)	28837 (12.9)	0.05	380 (14.7)	779 (15.1)	0.01
VA	36 (1.3)	3907 (1.8)	0.04	36 (1.4)	73 (1.4)	0.00
DC	2 (0.1)	392 (0.2)	0.03	53 (2.1)	102 (2.0)	0.01
DE	6 (0.2)	176 (0.1)	0.03			
KY	16 (0.6)	1453 (0.7)	0.01			
MS	23 (0.8)	1524 (0.7)	0.01			
WV	10 (0.4)	365 (0.2)	0.04			
Midwest	596 (21.2)	46683 (21.0)	0.01	542 (21.2)	1127 (22.1)	0.02
IL	101 (3.6)	8143 (3.7)	0.01	89 (3.5)	167 (3.2)	0.02
IN	95 (3.4)	5205 (2.3)	0.07	83 (3.2)	173 (3.4)	0.01
MN	50 (1.8)	3896 (1.7)	0.01	42 (1.6)	82 (1.6)	0.00
MO	107 (3.8)	6232 (2.8)	0.06	96 (3.7)	214 (4.1)	0.02

NE	32 (1.1)	2001 (0.9)	0.02	28 (1.1)	54 (1.0)	0.01
OH	85 (3.0)	8604 (3.9)	0.05	81 (3.1)	146 (2.8)	0.02
WI	62 (2.2)	7050 (3.2)	0.06	57 (2.2)	113 (2.2)	0.00
IA	16 (0.6)	2281 (1.0)	0.04	59 (2.3)	112 (2.2)	0.01
KS	17 (0.6)	1261 (0.6)	0.00			
MI	24 (0.9)	1652 (0.7)	0.02			
ND	4 (0.1)	240 (0.1)	0.00			
SD	3 (0.1)	118 (0.1)	0.00			
West	403 (14.4)	47907 (21.5)	0.19	379 (14.8)	729 (14.3)	0.02
AZ	85 (3.0)	8671 (3.9)	0.05	83 (3.2)	151 (2.9)	0.02
CA	179 (6.4)	20094 (9.0)	0.10	171 (6.6)	336 (6.5)	0.00
CO	49 (1.7)	6003 (2.7)	0.07	47 (1.8)	94 (1.8)	0.00
WA	22 (0.8)	4152 (1.9)	0.10	22 (0.9)	48 (0.9)	0.00
AK	0 (0.0)	60 (0.0)	N/A	67 (2.6)	118 (2.3)	0.02
HI	6 (0.2)	497 (0.2)	0.00			
ID	5 (0.2)	656 (0.3)	0.02			
MT	1 (0.0)	127 (0.1)	0.04			
NM	6 (0.2)	1303 (0.6)	0.06			
NV	22 (0.8)	1390 (0.6)	0.02			
OR	12 (0.4)	2185 (1.0)	0.07			
UT	14 (0.5)	2597 (1.2)	0.08			
WY	2 (0.1)	172 (0.1)	0.00			
Medicare Advantage	1064 (37.9)	102563 (46.0)	0.16	998 (39.1)	1979 (38.7)	0.01
Race						
White	1667 (59.4)	129098 (57.9)	0.03	1512 (59.2)	2972 (58.2)	0.02
non-White	762 (27.2)	69350 (31.1)	0.09	703 (27.5)	1457 (28.5)	0.02
missing	377 (13.4)	24368 (10.9)	0.08	340 (13.3)	681 (13.3)	0.00
Life-style risk factors						
Obesity or overweight	1301 (46.4)	90659 (40.7)	0.11	1158 (45.3)	2244 (43.9)	0.03
Smoking	522 (18.6)	38837 (17.4)	0.03	466 (18.2)	954 (18.7)	0.01
Comorbidities						
Diabetic nephropathy	237 (8.4)	10751 (4.8)	0.15	184 (7.2)	388 (7.6)	0.01
Diabetic neuropathy	282 (10.0)	13288 (6.0)	0.15	219 (8.6)	427 (8.4)	0.01
Diabetic retinopathy	64 (2.3)	2671 (1.2)	0.08	46 (1.8)	83 (1.6)	0.01
CVD[§]	774 (27.6)	49490 (22.2)	0.12	630 (24.7)	1260 (24.7)	0.00
Myocardial infarction	128 (4.6)	7912 (3.6)	0.05	109 (4.3)	203 (4.0)	0.01
Ischemic or hemorrhagic stroke	156 (5.6)	10943 (4.9)	0.03	123 (4.8)	272 (5.3)	0.02
Transient ischemic attack	34 (1.2)	2999 (1.3)	0.01	26 (1.0)	55 (1.1)	0.01
Other ischemic heart diseases	584 (20.8)	33096 (14.9)	0.16	484 (18.9)	853 (16.7)	0.06
Heart failure	184 (6.6)	10909 (4.9)	0.07	149 (5.8)	278 (5.4)	0.02
Atherosclerotic peripheral vascular disease	153 (5.5)	10953 (4.9)	0.02	109 (4.3)	285 (5.6)	0.06
Angina	189 (6.7)	9197 (4.1)	0.12	153 (6.0)	257 (5.0)	0.04
Hyperlipidemia	2058 (73.3)	153510 (68.9)	0.10	1835 (71.8)	3679 (72.0)	0.00
Hypertension	2065 (73.6)	151844 (68.1)	0.12	1835 (71.8)	3704 (72.5)	0.01

CKD (stages 1-4)	258 (9.2)	15398 (6.9)	0.08	210 (8.2)	450 (8.8)	0.02
COPD	259 (9.2)	19968 (9.0)	0.01	230 (9.0)	466 (9.1)	0.00
Malignant Neoplasm	215 (7.7)	16502 (7.4)	0.01	187 (7.3)	394 (7.7)	0.01
Physician specialties‖						
Cardiologists	125 (4.5)	10771 (4.8)	0.02	107 (4.2)	221 (4.3)	0.01
Endocrinologists	93 (3.3)	4524 (2.0)	0.08	80 (3.1)	176 (3.4)	0.02
Internists	1210 (43.1)	154643 (69.4)	0.55	1185 (46.4)	2357 (46.1)	0.01
Healthcare utilization						
Any recent hospitalizations¶	53 (1.9)	7543 (3.4)	0.09	47 (1.8)	100 (2.0)	0.01
Average length of hospitalizations (day; mean, std.dev)	0.37 (1.72)	0.48 (2.50)	0.05	0.33 (1.47)	0.35 (1.54)	0.01
Number of ED visits (mean, std.dev)	0.95 (2.88)	0.90 (2.39)	0.02	0.93 (2.96)	0.87 (1.99)	0.02
Number of office visits (mean, std.dev)	11.22 (9.81)	10.06 (9.31)	0.12	10.85 (9.48)	10.74 (10.37)	0.01
Number of HbA_{1c} test orders (mean, std.dev)	1.89 (1.16)	1.56 (1.04)	0.30	1.83 (1.12)	1.80 (1.09)	0.02
Brand/Generic ratio# (mean, std.dev)	-1.67 (1.23)	-1.84 (1.20)	0.14	-1.72 (1.22)	-1.69 (1.23)	0.02
Number of unique medication use (mean, std.dev)	10.07 (8.52)	9.56 (7.57)	0.06	9.95 (8.11)	9.91 (8.34)	0.01
Copay for pharmacy cost ($; mean, std.dev)	370.69 (642.64)	327.77 (584.45)	0.07	358.06 (610.45)	348.02 (608.83)	0.02
Preventive healthcare service**	2054 (73.2)	161841 (72.6)	0.01	1856 (72.6)	3706 (72.5)	0.00
Concomitant medications						
ACE inhibitors or ARBs	1394 (49.7)	124616 (55.9)	0.13	1291 (50.5)	2586 (50.6)	0.00
Antithrombotic medications	428 (15.3)	26165 (11.7)	0.10	365 (14.3)	710 (13.9)	0.01
Beta blockers	787 (28.0)	64073 (28.8)	0.02	709 (27.7)	1474 (28.8)	0.02
Calcium channel blockers	591 (21.1)	51775 (23.2)	0.05	549 (21.5)	1078 (21.1)	0.01
Loop diuretics	264 (9.4)	16626 (7.5)	0.07	229 (9.0)	444 (8.7)	0.01
Statin	1355 (48.3)	122192 (54.8)	0.13	1260 (49.3)	2508 (49.1)	0.00
Thiazides	295 (10.5)	30016 (13.5)	0.09	275 (10.8)	532 (10.4)	0.01
Laboratory results						
HbA_{1c}†† (%; mean, std.dev)	7.71 (1.68)	7.35 (1.56)	0.22	7.72 (1.68)	7.23 (1.53)	0.30
Missing	1661 (59.2)	134186 (60.2)	0.02	1506 (58.9)	3004 (58.8)	0.00
eGFR4‡‡ (mL/min/1.73m^2; mean, std.dev)	117.39 (9.59)	116.43 (10.16)	0.10	117.49 (9.72)	117.27 (10.11)	0.02
Missing	1402 (50.0)	115977 (52.1)	0.04	1280 (50.1)	2594 (50.8)	0.01
LDL						
mmol/L (mean, std.dev)	2.42 (1.04)	2.57 (1.05)	0.14	2.45 (1.03)	2.54 (1.03)	0.09
mg/dL (mean, std.dev)	93.75 (40.22)	99.30 (40.51)	0.14	94.70 (39.88)	98.29 (39.76)	0.09
Missing	1548 (55.2)	126841 (56.9)	0.04	1407 (55.1)	2859 (55.9)	0.02
HDL						
mmol/L (mean, std.dev)	1.20 (0.36)	1.21 (0.36)	0.02	1.20 (0.36)	1.20 (0.34)	0.01
mg/dL (mean, std.dev)	46.38 (13.96)	46.66 (13.76)	0.02	46.35 (13.94)	46.51 (13.14)	0.01
Missing	1567 (55.8)	129887 (58.3)	0.05	1425 (55.8)	2932 (57.4)	0.03
Total cholesterol						
mmol/L (mean, std.dev)	4.64 (1.16)	4.78 (1.17)	0.12	4.65 (1.15)	4.72 (1.11)	0.06
mg/dL (mean, std.dev)	179.46 (44.75)	184.99 (45.13)	0.12	179.77 (44.44)	182.58 (43.05)	0.06
Missing	1549 (55.2)	127957 (57.4)	0.04	1410 (55.2)	2891 (56.6)	0.03
Triglyceride						
mmol/L (mean, std.dev)	2.12 (2.18)	2.06 (1.80)	0.03	2.10 (2.10)	2.00 (1.36)	0.06

mg/dL (mean, std.dev)	187.54 (192.96)	182.56 (159.54)	0.03	186.15 (186.03)	176.97 (120.60)	0.06
Missing	1553 (55.3)	128810 (57.8)	0.05	1414 (55.3)	2907 (56.9)	0.03

SD: standardized difference; std.dev: standard deviation; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; HbA_{1c}: hemoglobin A_{1c}; eGFR: estimated glomerular filtration rate; LDL: low-density lipoproteins; HDL: high-density lipoproteins.

* Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)
South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)
Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)
West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

Note for the descriptive statistics and standardized differences between individual states after PS-matching: For the sensitivity analysis viii for which we re-estimated the propensity scores after replacing the 4 census regions (Northeast, Midwest, South, and West) of the primary analysis with individual states, we combined states with very few individuals to improve the stability of the propensity score model prediction. In addition, these descriptive statistics and standardized differences were from the sensitivity analysis viii. That is, descriptive statistics and standardized differences for variables other than individual states are from the main analysis.

§ Defined as history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

‖ Defined as specialist visits occurred within 7 days prior to cohort entry.

¶ Defined as any hospitalizations occurred within 30 days prior to cohort entry.

Added 1 to both numerator and denominator, then log-transformed.

** Defined as administration of bone mineral density test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu or pneumococcal vaccine.

†† Measured 180 days prior to or on cohort entry.

‡‡ Estimated using the quadratic GFR equation: GFR = $\exp(1.911+\frac{5.249}{Serum\ creatinine}-\frac{2.114}{Serum\ creatinine^2}-0.00686*Age-0.205\ (if\ female))$. If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

Supplement Table 8. [IBM MarketScan] Patient characteristics before and after 1:2 propensity score matching. Values are number (percentage) unless otherwise specified.

	Before PS-matching			After PS-matching		
Baseline characteristics	**SGLT-2i (n=4,152)**	**Metformin (n=283,500)**	**SD**	**SGLT-2i (n=3,863)**	**Metformin (n=7,726)**	**SD**
Demographics						
Age (year; mean, std.dev)	53.92 (9.67)	55.20 (11.01)	0.12	53.80 (9.73)	53.79 (10.56)	0.00
Gender (male)	2110 (50.8)	147151 (51.9)	0.02	1938 (50.2)	3972 (51.4)	0.02
Region*						
Northeast	809 (19.5)	50065 (17.7)	0.05	739 (19.1)	1464 (18.9)	0.00
NJ	120 (2.9)	6019 (2.1)	0.05	115 (3.0)	241 (3.1)	0.01
NY	461 (11.1)	24290 (8.6)	0.08	419 (10.8)	812 (10.4)	0.01
PA	96 (2.3)	7356 (2.6)	0.02	92 (2.4)	172 (2.2)	0.01
CT	19 (0.5)	2765 (1.0)	0.06	39 (1.0)	65 (0.8)	0.02
MA	5 (0.1)	3176 (1.1)	0.13			
ME	8 (0.2)	1161 (0.4)	0.04			
NH	5 (0.1)	899 (0.3)	0.04			
RI	4 (0.1)	506 (0.2)	0.03			
VT	0 (0.0)	209 (0.1)	0.04			
South	2378 (57.3)	130360 (46.0)	0.23	2186 (56.6)	4400 (57.0)	0.01
AL	121 (2.9)	5748 (2.0)	0.06	107 (2.8)	254 (3.3)	0.03
FL	389 (9.4)	19992 (7.1)	0.08	361 (9.3)	729 (9.4)	0.00
GA	304 (7.3)	14888 (5.3)	0.08	289 (7.4)	595 (7.7)	0.01
KY	92 (2.2)	7653 (2.7)	0.03	90 (2.3)	177 (2.3)	0.00
LA	143 (3.4)	7991 (2.8)	0.03	131 (3.4)	262 (3.4)	0.00
MD	34 (0.8)	2748 (1.0)	0.02	32 (0.8)	62 (0.8)	0.00
MS	89 (2.1)	4048 (1.4)	0.05	84 (2.2)	185 (2.4)	0.01
NC	123 (3.0)	6612 (2.3)	0.04	116 (3.0)	236 (3.0)	0.00
OK	64 (1.5)	2886 (1.0)	0.05	61 (1.6)	104 (1.3)	0.03
SC	256 (6.2)	10091 (3.6)	0.12	227 (5.8)	486 (6.3)	0.02
TN	156 (3.8)	7107 (2.5)	0.07	141 (3.6)	244 (3.1)	0.03
TX	342 (8.2)	20639 (7.3)	0.03	330 (8.5)	645 (8.3)	0.01
VA	50 (1.2)	5858 (2.1)	0.07	50 (1.3)	95 (1.2)	0.01
AR	26 (0.6)	1500 (0.5)	0.01	44 (1.1)	87 (1.1)	0.00
DC	0 (0.0)	80 (0.0)	N/A			
DE	27 (0.7)	2316 (0.8)	0.01			
WV	15 (0.4)	992 (0.3)	0.02			
Midwest	585 (14.1)	61484 (21.7)	0.20	568 (14.7)	1116 (14.4)	0.01
IL	71 (1.7)	7139 (2.5)	0.06	69 (1.8)	140 (1.8)	0.00
IN	132 (3.2)	7146 (2.5)	0.04	119 (3.1)	262 (3.4)	0.02
MI	89 (2.1)	17584 (6.2)	0.21	83 (2.1)	179 (2.3)	0.01
MO	78 (1.9)	5707 (2.0)	0.01	76 (2.0)	145 (1.9)	0.01

OH	138 (3.3)	14517 (5.1)	0.09	136 (3.5)	278 (3.6)	0.01
WI	18 (0.4)	3026 (1.1)	0.08	18 (0.5)	29 (0.4)	0.01
IA	13 (0.3)	1567 (0.6)	0.04	54 (1.4)	97 (1.2)	0.02
KS	23 (0.6)	1467 (0.5)	0.01			
MN	9 (0.2)	1755 (0.6)	0.06			
ND	1 (0.0)	116 (0.0)	N/A			
NE	6 (0.1)	607 (0.2)	0.03			
SD	3 (0.1)	259 (0.1)	0.00			
West	380 (9.2)	41591 (14.7)	0.17	370 (9.6)	746 (9.7)	0.00
AZ	49 (1.2)	3924 (1.4)	0.02	46 (1.2)	88 (1.1)	0.01
CA	183 (4.4)	18814 (6.6)	0.10	180 (4.6)	343 (4.4)	0.01
WA	27 (0.7)	5460 (1.9)	0.11	26 (0.7)	57 (0.7)	0.00
AK	3 (0.1)	148 (0.1)	0.00	135 (3.5)	251 (3.2)	0.02
CO	17 (0.4)	2229 (0.8)	0.05			
HI	3 (0.1)	42 (0.0)	0.04			
ID	22 (0.5)	2330 (0.8)	0.04			
MT	1 (0.0)	301 (0.1)	0.04			
NM	6 (0.1)	1330 (0.5)	0.07			
NV	38 (0.9)	1936 (0.7)	0.02			
OR	14 (0.3)	2634 (0.9)	0.08			
UT	11 (0.3)	1469 (0.5)	0.03			
WY	0 (0.0)	148 (0.1)	0.04			
Medicare Advantage	384 (9.2)	43452 (15.3)	0.19	356 (9.2)	751 (9.7)	0.02
Life-style risk factors						
Obesity or overweight	1445 (34.8)	90601 (32.0)	0.06	1322 (34.2)	2672 (34.6)	0.01
Smoking	320 (7.7)	27125 (9.6)	0.07	297 (7.7)	580 (7.5)	0.01
Comorbidities						
Diabetic nephropathy	88 (2.1)	4303 (1.5)	0.05	75 (1.9)	157 (2.0)	0.01
Diabetic neuropathy	214 (5.2)	7535 (2.7)	0.13	151 (3.9)	326 (4.2)	0.02
Diabetic retinopathy	57 (1.4)	1642 (0.6)	0.08	34 (0.9)	61 (0.8)	0.01
CVD[†]	673 (16.2)	42535 (15.0)	0.03	519 (13.4)	1038 (13.4)	0.00
Myocardial infarction	87 (2.1)	5424 (1.9)	0.01	62 (1.6)	122 (1.6)	0.00
Ischemic or hemorrhagic stroke	135 (3.3)	9624 (3.4)	0.01	108 (2.8)	203 (2.6)	0.01
Transient ischemic attack	53 (1.3)	3029 (1.1)	0.02	42 (1.1)	55 (0.7)	0.04
Other ischemic heart diseases	449 (10.8)	28893 (10.2)	0.02	348 (9.0)	732 (9.5)	0.02
Heart failure	127 (3.1)	7427 (2.6)	0.03	94 (2.4)	173 (2.2)	0.01
Atherosclerotic peripheral vascular disease	130 (3.1)	7001 (2.5)	0.04	103 (2.7)	175 (2.3)	0.03
Angina	130 (3.1)	7420 (2.6)	0.03	98 (2.5)	185 (2.4)	0.01
Hyperlipidemia	2675 (64.4)	167628 (59.1)	0.11	2431 (62.9)	4913 (63.6)	0.01
Hypertension	2657 (64.0)	170389 (60.1)	0.08	2416 (62.5)	4872 (63.1)	0.01
CKD (stages 1-4)	105 (2.5)	6286 (2.2)	0.02	90 (2.3)	183 (2.4)	0.00
COPD	174 (4.2)	13389 (4.7)	0.03	161 (4.2)	342 (4.4)	0.01
Malignant Neoplasm	201 (4.8)	16906 (6.0)	0.05	191 (4.9)	403 (5.2)	0.01
Physician specialties[‖]						

Cardiologists	110 (2.6)	8816 (3.1)	0.03	92 (2.4)	201 (2.6)	0.01
Endocrinologists	145 (3.5)	6365 (2.2)	0.07	124 (3.2)	273 (3.5)	0.02
Internists	1934 (46.6)	181504 (64.0)	0.36	1875 (48.5)	3694 (47.8)	0.01
Healthcare utilization						
Any recent hospitalizations[¶]	42 (1.0)	7902 (2.8)	0.13	29 (0.8)	84 (1.1)	0.04
Average length of hospitalizations (day; mean, std.dev)	0.10 (0.48)	0.12 (0.49)	0.03	0.09 (0.48)	0.10 (0.50)	0.01
Number of ED visits (mean, std.dev)	0.51 (1.11)	0.55 (1.30)	0.04	0.50 (1.11)	0.49 (1.01)	0.00
Number of office visits (mean, std.dev)	11.88 (11.09)	10.93 (10.83)	0.09	11.64 (10.87)	11.63 (11.59)	0.00
Number of HbA_{1c} test orders (mean, std.dev)	1.57 (1.12)	1.30 (1.01)	0.25	1.52 (1.08)	1.50 (1.07)	0.02
Brand/Generic ratio[#] (mean, std.dev)	-1.47 (1.20)	-1.64 (1.16)	0.14	-1.49 (1.20)	-1.50 (1.17)	0.00
Number of unique medication use (mean, std.dev)	9.72 (7.83)	9.27 (7.19)	0.06	9.65 (7.64)	9.52 (7.49)	0.02
Copay for pharmacy cost ($; mean, std.dev)	229.54 (341.21)	209.62 (365.06)	0.06	229.37 (336.99)	220.28 (335.38)	0.03
Preventive healthcare service[**]	2751 (66.3)	188296 (66.4)	0.00	2562 (66.3)	5090 (65.9)	0.01
Concomitant medications						
ACE inhibitors or ARBs	2030 (48.9)	153709 (54.2)	0.11	1914 (49.5)	3833 (49.6)	0.00
Antithrombotic medications	420 (10.1)	27937 (9.9)	0.01	357 (9.2)	691 (8.9)	0.01
Beta blockers	965 (23.2)	72544 (25.6)	0.05	875 (22.7)	1726 (22.3)	0.01
Calcium channel blockers	801 (19.3)	59598 (21.0)	0.04	752 (19.5)	1537 (19.9)	0.01
Loop diuretics	283 (6.8)	16187 (5.7)	0.05	231 (6.0)	489 (6.3)	0.01
Statin	1804 (43.4)	140806 (49.7)	0.12	1690 (43.7)	3397 (44.0)	0.00
Thiazides	413 (9.9)	37075 (13.1)	0.10	394 (10.2)	810 (10.5)	0.01
Laboratory results						
HbA_{1c}[††] (%; mean, std.dev)	7.63 (1.77)	7.42 (1.58)	0.13	7.61 (1.78)	7.25 (1.50)	0.21
Missing	3886 (93.6)	266510 (94.0)	0.02	3622 (93.8)	7171 (92.8)	0.04
eGFR4[‡‡] (mL/min/1.73m^2; mean, std.dev)	121.68 (8.14)	120.70 (9.16)	0.11	121.79 (8.20)	121.84 (8.92)	0.01
Missing	3817 (91.9)	263358 (92.9)	0.04	3564 (92.3)	7051 (91.3)	0.04
LDL						
mmol/L (mean, std.dev)	2.58 (1.11)	2.64 (1.11)	0.05	2.64 (1.10)	2.69 (1.12)	0.04
mg/dL (mean, std.dev)	99.76 (42.76)	102.06 (42.90)	0.05	102.03 (42.44)	103.94 (43.38)	0.04
Missing	3846 (92.6)	263328 (92.9)	0.01	3588 (92.9)	7066 (91.5)	0.05
HDL						
mmol/L (mean, std.dev)	1.18 (0.36)	1.19 (1.69)	0.01	1.18 (0.35)	1.37 (4.64)	0.06
mg/dL (mean, std.dev)	45.60 (13.92)	46.07 (65.47)	0.01	45.68 (13.61)	52.78 (179.39)	0.06
Missing	3855 (92.8)	263898 (93.1)	0.01	3595 (93.1)	7077 (91.6)	0.05
Total cholesterol						
mmol/L (mean, std.dev)	4.75 (1.28)	4.80 (1.35)	0.03	4.82 (1.27)	4.84 (1.26)	0.02
mg/dL (mean, std.dev)	183.84 (49.39)	185.62 (52.34)	0.03	186.29 (48.98)	187.06 (48.90)	0.02
Missing	3850 (92.7)	264046 (93.1)	0.02	3591 (93.0)	7077 (91.6)	0.05
Triglyceride						
mmol/L (mean, std.dev)	1.98 (1.42)	2.04 (1.90)	0.04	1.98 (1.45)	1.94 (1.37)	0.03
mg/dL (mean, std.dev)	174.93 (125.67)	180.50 (168.18)	0.04	175.57 (128.34)	171.84 (121.45)	0.03
Missing	3850 (92.7)	264194 (93.2)	0.02	3591 (93.0)	7079 (91.6)	0.05

SD: standardized difference; std.dev: standard deviation; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; HbA_{1c}: hemoglobin A_{1c}; eGFR: estimated glomerular filtration rate; LDL: low-density lipoproteins; HDL: high-density lipoproteins.

[*] Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)
South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)
Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)
West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

Note for the descriptive statistics and standardized differences between individual states after PS-matching: For the sensitivity analysis viii for which we re-estimated the propensity scores after replacing the 4 census regions (Northeast, Midwest, South, and West) of the primary analysis with individual states, we combined states with very few individuals to improve the stability of the propensity score model prediction. In addition, these descriptive statistics and standardized differences were from the sensitivity analysis viii. That is, descriptive statistics and standardized differences for variables other than individual states are from the main analysis.

[§] Defined as history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

[‖] Defined as specialist visits occurred within 7 days prior to cohort entry.

[¶] Defined as any hospitalizations occurred within 30 days prior to cohort entry.

[#] Added 1 to both numerator and denominator, then log-transformed.

[**] Defined as administration of bone mineral density test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu or pneumococcal vaccine.

[††] Measured 180 days prior to or on cohort entry.

[‡‡] Estimated using the quadratic GFR equation: GFR = $\exp(1.911+\frac{5.249}{Serum\ creatinine} - \frac{2.114}{Serum\ creatinine^2} - 0.00686 * Age - 0.205\ (if\ female))$. If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

Supplement Table 9. [Medicare] Patient characteristics before and after 1:2 propensity score matching. Values are number (percentage) unless otherwise specified.

	Before PS-matching			After PS-matching		
Baseline characteristics	**SGLT-2i (n=2,376)**	**Metformin (n=313,657)**	**SD**	**SGLT-2i (n=2,195)**	**Metformin (n=4,390)**	**SD**
Demographics						
Age (year; mean, std.dev)	71.98 (5.66)	73.05 (5.95)	0.18	72.04 (5.66)	72.05 (5.38)	0.00
Gender (male)	1271 (53.5)	147100 (46.9)	0.13	1149 (52.3)	2310 (52.6)	0.01
Region*						
Northeast	552 (23.2)	60030 (19.1)	0.10	502 (22.9)	997 (22.7)	0.00
CT	35 (1.5)	3359 (1.1)	0.04	32 (1.4)	75 (1.7)	0.02
MA	24 (1.0)	6845 (2.2)	0.10	24 (1.1)	44 (1.0)	0.01
NJ	167 (7.0)	13204 (4.2)	0.12	150 (6.7)	290 (6.4)	0.01
NY	206 (8.7)	18672 (6.0)	0.10	191 (8.5)	405 (9.0)	0.02
PA	103 (4.3)	12568 (4.0)	0.02	97 (4.3)	215 (4.8)	0.02
ME	3 (0.1)	1717 (0.5)	0.07	17 (0.8)	33 (0.7)	0.01
NH	5 (0.2)	1772 (0.6)	0.06			
RI	6 (0.3)	956 (0.3)	0.00			
VT	3 (0.1)	937 (0.3)	0.04			
South	992 (41.8)	127973 (40.8)	0.02	912 (41.5)	1809 (41.2)	0.01
AL	55 (2.3)	6167 (2.0)	0.02	49 (2.2)	99 (2.2)	0.00
AR	22 (0.9)	3870 (1.2)	0.03	22 (1.0)	42 (0.9)	0.01
FL	178 (7.5)	24353 (7.8)	0.01	175 (7.8)	340 (7.5)	0.01
GA	64 (2.7)	8584 (2.7)	0.00	63 (2.8)	138 (3.1)	0.02
KY	44 (1.9)	5539 (1.8)	0.01	40 (1.8)	100 (2.2)	0.03
LA	37 (1.6)	4491 (1.4)	0.02	33 (1.5)	46 (1.0)	0.05
MD	51 (2.1)	6805 (2.2)	0.01	50 (2.2)	109 (2.4)	0.01
MS	29 (1.2)	4030 (1.3)	0.01	28 (1.2)	68 (1.5)	0.03
NC	89 (3.7)	11088 (3.5)	0.01	86 (3.8)	168 (3.7)	0.01
OK	46 (1.9)	4946 (1.6)	0.02	42 (1.9)	90 (2.0)	0.01
SC	52 (2.2)	6913 (2.2)	0.00	51 (2.3)	112 (2.5)	0.01
TN	50 (2.1)	7191 (2.3)	0.01	47 (2.1)	94 (2.1)	0.00
TX	192 (8.1)	19854 (6.3)	0.07	179 (7.9)	312 (6.9)	0.04
VA	46 (1.9)	9398 (3.0)	0.07	45 (2.0)	87 (1.9)	0.01
DC	1 (0.0)	339 (0.1)	0.04	36 (1.6)	81 (1.8)	0.02
DE	20 (0.8)	1860 (0.6)	0.02			
WV	16 (0.7)	2545 (0.8)	0.01			
Midwest	354 (14.9)	70070 (22.3)	0.19	349 (15.9)	722 (16.4)	0.01
IL	54 (2.3)	13592 (4.3)	0.11	54 (2.4)	104 (2.3)	0.01
IN	65 (2.7)	7737 (2.5)	0.01	62 (2.8)	125 (2.8)	0.00
MI	47 (2.0)	12378 (3.9)	0.11	47 (2.1)	104 (2.3)	0.01
MO	46 (1.9)	6375 (2.0)	0.01	45 (2.0)	72 (1.6)	0.03

OH	68 (2.9)	10754 (3.4)	0.03	68 (3.0)	131 (2.9)	0.01
IA	12 (0.5)	4643 (1.5)	0.10	74 (3.3)	154 (3.4)	0.01
KS	16 (0.7)	3627 (1.2)	0.05			
MN	1 (0.0)	2079 (0.7)	0.12			
ND	4 (0.2)	878 (0.3)	0.02			
NE	14 (0.6)	2374 (0.8)	0.02			
SD	5 (0.2)	1068 (0.3)	0.02			
WI	22 (0.9)	4565 (1.5)	0.06			
West	478 (20.1)	55584 (17.7)	0.06	432 (19.7)	862 (19.6)	0.00
AZ	50 (2.1)	5604 (1.8)	0.02	47 (2.1)	105 (2.3)	0.01
CA	306 (12.9)	28563 (9.1)	0.12	285 (12.7)	560 (12.4)	0.01
NV	30 (1.3)	2458 (0.8)	0.05	23 (1.0)	48 (1.1)	0.01
AK	3 (0.1)	459 (0.1)	0.00	90 (4.0)	153 (3.4)	0.03
CO	15 (0.6)	2894 (0.9)	0.03			
HI	25 (1.1)	986 (0.3)	0.10			
ID	1 (0.0)	1239 (0.4)	0.09			
MT	6 (0.3)	996 (0.3)	0.00			
NM	5 (0.2)	1940 (0.6)	0.06			
OR	6 (0.3)	2915 (0.9)	0.08			
UT	8 (0.3)	1553 (0.5)	0.03			
WA	20 (0.8)	5339 (1.7)	0.08			
WY	3 (0.1)	638 (0.2)	0.03			
Race						
White	1979 (83.3)	260964 (83.2)	0.00	1832 (83.5)	3608 (82.2)	0.03
non-White	397 (16.7)	52693 (16.8)	0.00	363 (16.5)	782 (17.8)	0.03
missing	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Life-style risk factors						
Obesity or overweight	917 (38.6)	94950 (30.3)	0.18	832 (37.9)	1598 (36.4)	0.03
Smoking	511 (21.5)	63116 (20.1)	0.03	478 (21.8)	905 (20.6)	0.03
Comorbidities						
Diabetic nephropathy	170 (7.2)	10892 (3.5)	0.16	134 (6.1)	278 (6.3)	0.01
Diabetic neuropathy	324 (13.6)	21839 (7.0)	0.22	257 (11.7)	495 (11.3)	0.01
Diabetic retinopathy	84 (3.5)	5070 (1.6)	0.12	61 (2.8)	105 (2.4)	0.02
CVD[†]	1205 (50.7)	132854 (42.4)	0.17	1107 (50.4)	2214 (50.4)	0.00
Myocardial infarction	171 (7.2)	18431 (5.9)	0.05	153 (7.0)	279 (6.4)	0.02
Ischemic or hemorrhagic stroke	312 (13.1)	36080 (11.5)	0.05	288 (13.1)	582 (13.3)	0.00
Transient ischemic attack	68 (2.9)	9280 (3.0)	0.01	63 (2.9)	143 (3.3)	0.02
Other ischemic heart diseases	897 (37.8)	93010 (29.7)	0.17	823 (37.5)	1574 (35.9)	0.03
Heart failure	362 (15.2)	35338 (11.3)	0.12	329 (15.0)	580 (13.2)	0.05
Atherosclerotic peripheral vascular disease	319 (13.4)	32856 (10.5)	0.09	289 (13.2)	536 (12.2)	0.03
Angina	222 (9.3)	20418 (6.5)	0.11	204 (9.3)	378 (8.6)	0.02
Hyperlipidemia	2027 (85.3)	261927 (83.5)	0.05	1864 (84.9)	3762 (85.7)	0.02
Hypertension	2114 (89.0)	267229 (85.2)	0.11	1940 (88.4)	3899 (88.8)	0.01
CKD (stages 1-4)	358 (15.1)	27959 (8.9)	0.19	300 (13.7)	559 (12.7)	0.03

COPD	381 (16.0)	48668 (15.5)	0.01	364 (16.6)	721 (16.4)	0.00
Malignant Neoplasm	391 (16.5)	46855 (14.9)	0.04	355 (16.2)	716 (16.3)	0.00
Physician specialties[‖]						
Cardiologists	171 (7.2)	23109 (7.4)	0.01	154 (7.0)	296 (6.7)	0.01
Endocrinologists	111 (4.7)	8162 (2.6)	0.11	88 (4.0)	195 (4.4)	0.02
Internists	1090 (45.9)	201946 (64.4)	0.38	1072 (48.8)	2114 (48.2)	0.01
Healthcare utilization						
Any recent hospitalizations[¶]	53 (2.2)	16345 (5.2)	0.16	49 (2.2)	95 (2.2)	0.00
Average length of hospitalizations (day; mean, std.dev)	0.70 (2.25)	0.78 (2.51)	0.03	0.68 (2.23)	0.65 (2.06)	0.02
Number of ED visits (mean, std.dev)	0.43 (1.00)	0.48 (1.12)	0.05	0.43 (1.02)	0.40 (0.92)	0.03
Number of office visits (mean, std.dev)	11.52 (8.11)	9.90 (7.23)	0.21	11.18 (7.50)	11.01 (7.90)	0.02
Number of HbA_{1c} test orders (mean, std.dev)	2.14 (1.26)	1.87 (1.13)	0.22	2.10 (1.22)	2.11 (1.15)	0.01
Brand/Generic ratio[#] (mean, std.dev)	-1.69 (1.19)	-1.90 (1.17)	0.18	-1.74 (1.18)	-1.72 (1.18)	0.02
Number of unique medication use (mean, std.dev)	12.91 (8.82)	11.81 (7.82)	0.13	12.89 (8.53)	12.65 (8.72)	0.03
Copay for pharmacy cost ($; mean, std.dev)	513.74 (701.32)	433.45 (645.49)	0.12	506.75 (687.03)	507.67 (742.14)	0.00
Preventive healthcare service[**]	2025 (85.2)	268453 (85.6)	0.01	1884 (85.8)	3765 (85.8)	0.00
Concomitant medications						
ACE inhibitors or ARBs	1440 (60.6)	200577 (63.9)	0.07	1356 (61.8)	2720 (62.0)	0.00
Antithrombotic medications	636 (26.8)	69738 (22.2)	0.11	583 (26.6)	1153 (26.3)	0.01
Beta blockers	1080 (45.5)	142961 (45.6)	0.00	1000 (45.6)	2021 (46.0)	0.01
Calcium channel blockers	713 (30.0)	99727 (31.8)	0.04	676 (30.8)	1329 (30.3)	0.01
Loop diuretics	399 (16.8)	46720 (14.9)	0.05	362 (16.5)	669 (15.2)	0.03
Statin	1483 (62.4)	213162 (68.0)	0.12	1405 (64.0)	2844 (64.8)	0.02
Thiazides	353 (14.9)	54236 (17.3)	0.07	332 (15.1)	648 (14.8)	0.01

SD: standardized difference; std.dev: standard deviation; CVD: cardiovascular disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ED: emergency department; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers.

[*] Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, VT)
South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, WV)
Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI)
West (AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, WY)

Note for the descriptive statistics and standardized differences between individual states after PS-matching: For the sensitivity analysis viii for which we re-estimated the propensity scores after replacing the 4 census regions (Northeast, Midwest, South, and West) of the primary analysis with individual states, we combined states with very few individuals to improve the stability of the propensity score model prediction. In addition, these descriptive statistics and standardized differences were from the sensitivity analysis viii. That is, descriptive statistics and standardized differences for variables other than individual states are from the main analysis.

[§] Defined as history of myocardial infarction, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure.

[‖] Defined as specialist visits occurred within 7 days prior to cohort entry.

[¶] Defined as any hospitalizations occurred within 30 days prior to cohort entry.

[#] Added 1 to both numerator and denominator, then log-transformed.

[**] Defined as administration of bone mineral density test, colonoscopy, fecal occult blood test, mammography, pap smear, prostate-specific antigen (PSA) test, flu or pneumococcal vaccine.

Supplement Table 10. Duration of follow-up and censoring reasons after 1:2 propensity score matching.

	Overall (n=25,839)	SGLT-2i (n=8,613)	Metformin (n=17,226)
MI/stroke/mortality composite outcome			
Follow-up (days; mean, std.dev)	356 (365)	326 (333)	371 (379)
Follow-up (days; median, 25th and 75th IQR)	215 (106-465)	202 (88-419)	223 (113-498)
Censoring reasons (%)			
Treatment discontinuation	13824 (53.5)	4906 (57.0)	8918 (51.8)
End of the study period (Mar/31/2021)	6051 (23.4)	1857 (21.6)	4194 (24.3)
Disenrollment	5207 (20.2)	1647 (19.1)	3560 (20.7)
Nursing home admission	359 (1.4)	88 (1.0)	271 (1.6)
Occurrence of a study outcome	398 (1.5)	115 (1.3)	283 (1.6)
HHF/mortality composite outcome			
Follow-up (days; mean, std.dev)	358 (367)	328 (335)	373 (381)
Follow-up (days; median, 25th and 75th IQR)	216 (108-468)	203 (89-422)	224 (114-501)
Censoring reasons; n (%)			
Treatment discontinuation	13893 (53.8)	4930 (57.2)	8963 (52.0)
End of the study period (Mar/31/2021)	6094 (23.6)	1865 (21.7)	4229 (24.6)
Disenrollment	5225 (20.2)	1652 (19.2)	3573 (20.7)
Nursing home admission	378 (1.5)	96 (1.1)	282 (1.6)
Occurrence of a study outcome	249 (1.0)	70 (0.8)	179 (1.0)

SGLT-2i: sodium-glucose cotransporter-2 inhibitors; MI/stroke/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality; HHF/mortality: hospitalization for heart failure or all-cause mortality; Std.dev: standard deviation; IQR: interquartile range.

Supplement Table 11. Unadjusted and propensity score (PS) adjusted database-specific number of events, incidence rates, hazard ratios, and incidence rate differences for cardiovascular and safety outcomes, comparing SGLT-2i versus metformin.

		Clinformatics				MarketScan				Medicare				Pooled			
		Crude		PS adjusted		Crude		PS adjusted		Crude		PS adjusted		Crude		PS adjusted	
Outcomes	Effect measures	SGLT-2i (n=2,794)	Metformin (n=222,695)	SGLT-2i (n=2,555)	Metformin (n=5,110)	SGLT-2i (n=4,137)	Metformin (n=283,365)	SGLT-2i (n=3,863)	Metformin (n=7,726)	SGLT-2i (n=2,372)	Metformin (n=313,631)	SGLT-2i (n=2,195)	Metformin (n=4,390)	SGLT-2i (n=9,303)	Metformin (n=819,691)	SGLT-2i (n=8,613)	Metformin (n=17,226)
MI/stroke/mortality	N events (IR/1000 PY)	41 (17.5)	4201 (18.1)	34 (16.1)	91 (19.2)	24 (6.3)	1954 (6.9)	19 (5.3)	52 (6.8)	64 (30.1)	12963 (30)	62 (31.4)	140 (27.2)	129 (15.6)	19118 (20.2)	115 (15)	283 (16.2)
	HR (95% CI)	0.96 (0.71-1.3)	-	0.82 (0.55-1.2)	-	0.9 (0.6-1.3)	-	0.77 (0.45-1.3)	-	0.97 (0.76-1.2)	-	1.1 (0.84-1.5)	-	0.96 (0.8-1.14)	-	0.96 (0.77-1.19)	-
	IRD (95% CI)	-0.54 (-5.94, 4.85)	-	-3.15 (-9.85, 3.55)	-	-0.66 (-3.19, 1.87)	-	-1.54 (-4.54, 1.47)	-	0.16 (-7.24, 7.55)	-	4.21 (-4.82, 13.23)	-	-4.63 (-7.33, -1.93)	-	-1.21 (-4.52, 2.11)	-
HHF/mortality	N events (IR/1000 PY)	40 (16.9)	5151 (22.2)	38 (17.8)	109 (23)	21 (5.5)	2460 (8.7)	19 (5.3)	61 (8)	88 (41.6)	19100 (44.6)	84 (42.7)	240 (47.4)	149 (17.9)	26711 (28.4)	141 (18.3)	410 (23.5)
	HR (95% CI)	0.76 (0.55-1)	-	0.76 (0.52-1.1)	-	0.62 (0.4-0.96)	-	0.65 (0.39-1.1)	-	0.88 (0.71-1.1)	-	0.87 (0.67-1.1)	-	0.8 (0.68-0.94)	-	0.8 (0.66-0.97)	-
	IRD (95% CI)	-5.27 (-10.56, 0.02)	-	-5.18 (-12.31, 1.95)	-	-3.25 (-5.62, -0.88)	-	-2.72 (-5.83, 0.38)	-	-3.04 (-11.75, 5.67)	-	-4.77 (-15.69, 6.15)	-	-10.44 (-13.33, -7.54)	-	-5.23 (-9.01, -1.45)	-
MI/stroke/HHF/mortality	N events (IR/1000 PY)	70 (30.1)	6904 (30)	62 (29.5)	147 (31.3)	39 (10.2)	3846 (13.7)	34 (9.5)	95 (12.5)	108 (51.3)	22572 (53.2)	103 (52.6)	276 (54.8)	217 (26.3)	33322 (35.6)	199 (26)	518 (29.9)
	HR (95% CI)	0.99 (0.78-1.2)	-	0.92 (0.68-1.2)	-	0.74 (0.54-1)	-	0.75 (0.51-1.1)	-	0.91 (0.75-1.1)	-	0.92 (0.74-1.2)	-	0.9 (0.79-1.03)	-	0.89 (0.75-1.05)	-
	IRD (95% CI)	0.13 (-6.95, 7.21)	-	-1.84 (-10.76, 7.07)	-	-3.47 (-6.71, -0.24)	-	-3.02 (-7.07, 1.04)	-	-1.87 (-11.57, 7.83)	-	-2.23 (-14.28, 9.81)	-	-9.29 (-12.82, -5.77)	-	-3.87 (-8.31, 0.56)	-
MI	N events (IR/1000 PY)	17 (7.2)	1528 (6.6)	13 (6.1)	37 (7.8)	13 (3.4)	1286 (4.6)	10 (2.8)	40 (5.2)	15 (7)	3287 (7.6)	15 (7.6)	49 (9.5)	45 (5.4)	6101 (6.4)	38 (4.9)	126 (7.2)
	HR (95% CI)	1.1 (0.67-1.7)	-	0.77 (0.41-1.5)	-	0.74 (0.43-1.3)	-	0.53 (0.26-1.1)	-	0.89 (0.53-1.5)	-	0.77 (0.43-1.4)	-	0.91 (0.68-1.22)	-	0.7 (0.48-1)	-
	IRD (95% CI)	0.68 (-2.78, 4.14)	-	-1.66 (-5.83, 2.51)	-	-1.16 (-3.02, 0.69)	-	-2.46 (-4.82, -0.1)	-	-0.53 (-4.1, 3.04)	-	-1.93 (-6.59, 2.73)	-	-1.01 (-2.6, 0.58)	-	-2.25 (-4.26, -0.25)	-
Stroke	N events (IR/1000 PY)	17 (7.2)	1354 (5.8)	15 (7)	32 (6.7)	10 (2.6)	590 (2.1)	8 (2.2)	11 (1.4)	17 (8)	2417 (5.6)	16 (8.1)	20 (3.9)	44 (5.3)	4361 (4.6)	39 (5)	63 (3.6)
	HR (95% CI)	1.2 (0.75-1.9)	-	1 (0.54-1.9)	-	1.2 (0.66-2.3)	-	1.5 (0.61-3.8)	-	1.3 (0.84-2.2)	-	1.9 (0.98-3.7)	-	1.27 (0.94-1.7)	-	1.38 (0.92-2.07)	-
	IRD (95% CI)	1.4 (-2.04, 4.83)	-	0.31 (-3.95, 4.56)	-	0.52 (-1.1, 2.14)	-	0.78 (-0.97, 2.53)	-	2.43 (-1.37, 6.23)	-	4.23 (-0.08, 8.53)	-	0.7 (-0.87, 2.26)	-	1.47 (-0.34, 3.29)	-
All-cause mortality	N events (IR/1000 PY)	8 (3.4)	1714 (7.3)	7 (3.3)	32 (6.7)	1 (0.3)	126 (0.4)	1 (0.3)	2 (0.3)	36 (16.8)	7933 (18.1)	35 (17.6)	80 (15.4)	45 (5.4)	9773 (10.2)	43 (5.5)	114 (6.5)
	HR (95% CI)	0.47 (0.24-0.94)	-	0.48 (0.21-1.1)	-	0.56 (0.078-4)	-	1 (0.091-11)	-	0.9 (0.65-1.2)	-	1.1 (0.77-1.7)	-	0.79 (0.59-1.06)	-	0.97 (0.68-1.38)	-
	IRD (95% CI)	-3.95 (-6.31, -1.59)	-	-3.43 (-6.78, -0.07)	-	-0.18 (-0.7, 0.33)	-	0.02 (-0.64, 0.67)	-	-1.31 (-6.82, 4.21)	-	2.23 (-4.5, 8.97)	-	-4.85 (-6.44, -3.27)	-	-0.91 (-2.95, 1.13)	-
HHF	N events (IR/1000 PY)	34 (14.4)	3777 (16.3)	33 (15.5)	86 (18.2)	20 (5.2)	2368 (8.4)	18 (5)	59 (7.7)	63 (29.8)	12907 (30.2)	60 (30.5)	181 (35.8)	117 (14.1)	19052 (20.2)	111 (14.4)	326 (18.7)
	HR (95% CI)	0.86 (0.62-1.2)	-	0.83 (0.56-1.2)	-	0.62 (0.4-0.96)	-	0.64 (0.37-1.1)	-	0.9 (0.7-1.1)	-	0.8 (0.6-1.1)	-	0.83 (0.69-1)	-	0.78 (0.63-0.97)	-
	IRD (95% CI)	-1.88 (-6.75, 2.99)	-	-2.67 (-9.2, 3.87)	-	-3.19 (-5.5, -0.88)	-	-2.74 (-5.77, 0.29)	-	-0.38 (-7.75, 6.99)	-	-5.3 (-14.61, 4.01)	-	-6.15 (-8.72, -3.59)	-	-4.3 (-7.66, -0.94)	-

		Clinformatics				MarketScan				Medicare				Pooled			
		Crude		PS adjusted		Crude		PS adjusted		Crude		PS adjusted		Crude		PS adjusted	
Outcomes	Effect measures	SGLT-2i (n=2,794)	Metformin (n=222,695)	SGLT-2i (n=2,555)	Metformin (n=5,110)	SGLT-2i (n=4,137)	Metformin (n=283,365)	SGLT-2i (n=3,863)	Metformin (n=7,726)	SGLT-2i (n=2,372)	Metformin (n=313,631)	SGLT-2i (n=2,195)	Metformin (n=4,390)	SGLT-2i (n=9,303)	Metformin (n=819,691)	SGLT-2i (n=8,613)	Metformin (n=17,226)
AKI	N events (IR/1000 PY)	25 (10.6)	3267 (14.1)	22 (10.3)	79 (16.6)	26 (6.8)	2547 (9)	23 (6.4)	60 (7.8)	56 (26.5)	11159 (25.9)	52 (26.4)	143 (27.9)	107 (12.9)	16973 (18)	97 (12.6)	282 (16.1)
	HR (95% CI)	0.74 (0.5-1.1)	-	0.61 (0.38-0.98)	-	0.74 (0.51-1.1)	-	0.8 (0.5-1.3)	-	0.95 (0.73-1.2)	-	0.89 (0.65-1.2)	-	0.85 (0.7-1.02)	-	0.79 (0.63-1)	-
	IRD (95% CI)	-3.49 (-7.66, 0.68)	-	-6.32 (-11.97, -0.66)	-	-2.26 (-4.89, 0.37)	-	-1.48 (-4.76, 1.79)	-	0.54 (-6.41, 7.48)	-	-1.48 (-9.98, 7.03)	-	-5.1 (-7.56, -2.65)	-	-3.52 (-6.65, -0.39)	-
Bone fractures	N events (IR/1000 PY)	6 (2.5)	730 (3.1)	6 (2.8)	13 (2.7)	9 (2.3)	705 (2.5)	8 (2.2)	21 (2.7)	<11* (4.2)	2590 (6)	<11* (4)	32 (6.2)	24 (2.9)	4025 (4.2)	22 (2.8)	66 (3.7)
	HR (95% CI)	0.81 (0.36-1.8)	-	1 (0.38-2.6)	-	0.94 (0.49-1.8)	-	0.78 (0.35-1.8)	-	0.7 (0.36-1.3)	-	0.62 (0.28-1.3)	-	0.81 (0.54-1.21)	-	0.76 (0.47-1.24)	-
	IRD (95% CI)	-0.59 (-2.63, 1.45)	-	0.09 (-2.6, 2.78)	-	-0.15 (-1.69, 1.39)	-	-0.53 (-2.46, 1.4)	-	-1.73 (-4.5, 1.03)	-	-2.14 (-5.66, 1.38)	-	-1.35 (-2.51, -0.19)	-	-0.9 (-2.4, 0.59)	-
Genital infections	N events (IR/1000 PY)	129 (56.4)	4342 (18.9)	117 (56.7)	114 (24.4)	203 (54.9)	6002 (21.6)	190 (54.7)	192 (25.6)	103 (49.8)	7741 (18.1)	97 (50.5)	103 (20.2)	435 (54)	18085 (19.3)	404 (54.1)	409 (23.7)
	HR (95% CI)	2.7 (2.3-3.3)	-	2.3 (1.7-2.9)	-	2.5 (2.2-2.8)	-	2.1 (1.7-2.5)	-	2.5 (2-3)	-	2.3 (1.8-3.1)	-	2.56 (2.32-2.81)	-	2.19 (1.91-2.51)	-
	IRD (95% CI)	37.52 (27.77, 47.27)	-	32.29 (21.09, 43.5)	-	33.33 (25.76, 40.91)	-	29.08 (20.5, 37.65)	-	31.69 (22.06, 41.31)	-	30.3 (19.52, 41.08)	-	34.69 (29.61, 39.78)	-	30.48 (24.72, 36.23)	-
Severe hypoglycemia	N events (IR/1000 PY)	7 (3)	580 (2.5)	6 (2.8)	15 (3.1)	5 (1.3)	381 (1.3)	5 (1.4)	9 (1.2)	11 (5.2)	977 (2.2)	<11* (4.5)	14 (2.7)	23 (2.8)	1938 (2)	20 (2.6)	38 (2.2)
	HR (95% CI)	1.2 (0.55-2.4)	-	0.88 (0.34-2.3)	-	0.94 (0.39-2.3)	-	1.1 (0.38-3.4)	-	2.2 (1.2-4)	-	1.7 (0.75-4.1)	-	1.51 (1-2.28)	-	1.25 (0.72-2.16)	-
	IRD (95% CI)	0.47 (-1.73, 2.67)	-	-0.34 (-3.09, 2.41)	-	-0.05 (-1.19, 1.1)	-	0.21 (-1.23, 1.64)	-	2.92 (-0.13, 5.97)	-	1.84 (-1.44, 5.13)	-	0.72 (-0.41, 1.85)	-	0.43 (-0.89, 1.75)	-
Severe UTIs	N events (IR/1000 PY)	9 (3.8)	933 (4)	8 (3.7)	15 (3.1)	8 (2.1)	911 (3.2)	7 (1.9)	17 (2.2)	18 (8.4)	4311 (9.9)	16 (8.1)	44 (8.5)	35 (4.2)	6155 (6.5)	31 (4)	76 (4.3)
	HR (95% CI)	0.96 (0.5-1.8)	-	1.2 (0.51-2.9)	-	0.64 (0.32-1.3)	-	0.85 (0.35-2.1)	-	0.8 (0.5-1.3)	-	0.94 (0.53-1.7)	-	0.8 (0.57-1.11)	-	0.98 (0.64-1.49)	-
	IRD (95% CI)	-0.2 (-2.7, 2.3)	-	0.6 (-2.44, 3.64)	-	-1.14 (-2.6, 0.31)	-	-0.29 (-2.06, 1.49)	-	-1.49 (-5.4, 2.43)	-	-0.43 (-5.12, 4.25)	-	-2.29 (-3.68, -0.89)	-	-0.31 (-2.02, 1.4)	-
DKA	N events (IR/1000 PY)	2 (0.8)	243 (1)	1 (0.5)	5 (1)	3 (0.8)	333 (1.2)	3 (0.8)	8 (1)	<11* (1.9)	208 (0.5)	<11* (2)	<11* (0.2)	<11* (1.1)	784 (0.8)	<11* (1)	14 (0.8)
	HR (95% CI)	0.73 (0.18-2.9)	-	0.4 (0.047-3.5)	-	0.63 (0.2-2)	-	0.75 (0.2-2.8)	-	3.3 (1.2-8.9)	-	10 (1.1-93)	-	1.35 (0.7-2.61)	-	1.12 (0.41-3.06)	-
	IRD (95% CI)	-0.2 (-1.37, 0.98)	-	-0.58 (-1.87, 0.72)	-	-0.4 (-1.29, 0.5)	-	-0.21 (-1.4, 0.97)	-	1.4 (-0.44, 3.23)	-	1.82 (-0.19, 3.83)	-	0.26 (-0.45, 0.96)	-	0.24 (-0.59, 1.07)	-
LLA	N events (IR/1000 PY)	0 (0)	205 (0.9)	0 (0)	4 (0.8)	4 (1)	175 (0.6)	4 (1.1)	7 (0.9)	<11* (0.9)	437 (1)	<11* (1)	<11* (0.8)	<11* (0.7)	817 (0.9)	<11* (0.8)	15 (0.9)
	HR (95% CI)	3e-07 (0-Inf)	-	8.5e-09 (0-Inf)	-	1.7 (0.62-4.5)	-	1.2 (0.35-4.1)	-	0.86 (0.21-3.4)	-	1.2 (0.21-6.4)	-	1.34 (0.6-3)	-	1.19 (0.44-3.22)	-
	IRD (95% CI)	-0.88 (-1, -0.76)	-	-0.84 (-1.66, -0.02)	-	0.42 (-0.6, 1.45)	-	0.19 (-1.08, 1.47)	-	-0.06 (-1.36, 1.23)	-	0.24 (-1.35, 1.82)	-	-0.14 (-0.72, 0.44)	-	-0.08 (-0.83, 0.68)	-

N: number; IR: incidence rate; PY: person-years; HR: hazard ratio; 95% CI: 95% confidence interval; IRD: incidence rate difference; MI/stroke/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality; HHF/mortality: hospitalization for heart failure or all-cause mortality; MI/stroke/HHF/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, hospitalization for heart failure, or all-cause mortality; AKI: acute kidney injury; UTI: urinary track infection; DKA: diabetic ketoacidosis; LLA: lower-limb amputation.

* In accordance with the data use agreement, we do not report information for frequency cells with less than 11 cases. These are noted as <11.

Supplement Table 12. [Sensitivity analysis] Number of events, incidence rates, hazard ratios, and incidence rate differences for cardiovascular outcomes, comparing first-line SGLT-2i and metformin against DPP-4i after 1:1 propensity score matching.

	First-line SGLT-2i versus DPP-4i*				First-line metformin versus DPP-4i†			
	SGLT-2i (n=7,823)	DPP-4i (n=7,823)			Metformin (n=30,214)	DPP-4i (n=30,214)		
Mean f/u (days; mean, std.dev)	334 (342)	327 (343)			428 (446)	338 (380)		
Median f/u (days; median, 25th and 75th IQR)	207 (93-429)	194 (91-422)			242 (118-590)	179 (88-433)		
Outcomes	N events (IR/1000 PY)	N events (IR/1000 PY)	HR (95% CI)	IRD (95% CI)	N events (IR/1000 PY)	N events (IR/1000 PY)	HR (95% CI)	IRD (95% CI)
Primary								
MI/stroke/mortality	118 (16.5)	166 (23.7)	0.73 (0.57, 0.92)	-7.19 (-11.86, -2.51)	1247 (35.2)	1264 (45.2)	0.80 (0.74, 0.86)	-9.98 (-13.14, -6.81)
HHF/mortality	142 (19.8)	239 (34.4)	0.60 (0.49, 0.74)	-14.57 (-20.01, -9.13)	2041 (58.6)	2170 (79.6)	0.77 (0.73, 0.82)	-21.02 (-25.22, -16.81)
Secondary								
MI/stroke/HHF/mortality	196 (27.5)	302 (43.7)	0.65 (0.54, 0.78)	-16.18 (-22.44, -9.92)	2363 (68.4)	2439 (90.1)	0.80 (0.75, 0.84)	-21.74 (-26.26, -17.23)
MI	41 (5.7)	63 (9.0)	0.65 (0.44, 0.96)	-3.24 (-6.06, -0.43)	326 (9.2)	302 (10.8)	0.88 (0.75, 1.03)	-1.58 (-3.15, -0.01)
Stroke	38 (5.3)	39 (5.5)	0.98 (0.63, 1.54)	-0.25 (-2.67, 2.17)	253 (7.1)	209 (7.4)	0.98 (0.82, 1.18)	-0.33 (-1.66, 1.01)
All-cause mortality	45 (6.2)	72 (10.2)	0.67 (0.46, 0.97)	-3.95 (-6.92, -0.97)	758 (21.2)	844 (29.9)	0.72 (0.65, 0.80)	-8.67 (-11.19, -6.16)
HHF	109 (15.2)	193 (27.8)	0.57 (0.45, 0.72)	-12.56 (-17.41, -7.71)	1520 (43.6)	1636 (60.0)	0.78 (0.73, 0.84)	-16.41 (-20.05, -12.76)

SGLT-2i: sodium-glucose cotransporter-2 inhibitors; DPP-4i: dipeptidyl peptidase-4 inhibitors; std.dev: standard deviation; IQR: interquartile range; N: number; IR: incidence rate; PY: person-years; HR: hazard ratio; 95% CI: 95% confidence interval; IRD: incidence rate difference; MI/stroke/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality; HHF/mortality: hospitalization for heart failure or all-cause mortality; MI/stroke/HHF/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, hospitalization for heart failure, or all-cause mortality.

* SGLT-2i versus DPP-4i in a 1:1 (a caliper width of 0.01 of the standard deviation of the logit of the PS) PS matched cohort.

† Metformin versus DPP-4i in a 1:1 (a caliper width of 0.001 of the standard deviation of the logit of the PS) PS matched cohort.

Supplement Table 13. [Sensitivity analysis] Hazard ratios (95% confidence interval) for the primary outcomes with or without adjustment for state-level geographic areas.

	Primary results	State-adjusted* results
Outcomes	HR (95% CI)	HR (95% CI)
Primary		
MI/stroke/mortality	0.96 (0.77, 1.19)	0.98 (0.78-1.21)
HHF/mortality	0.80 (0.66, 0.97)	0.81 (0.67-0.99)

HR: hazard ratio; 95% CI: 95% confidence interval; MI/stroke/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality; HHF/mortality: hospitalization for heart failure or all-cause mortality.

* Detailed descriptions for this analysis could be found from the 'Rationale for sensitivity analyses' on page 4 of this file.

Supplement Table 14. [Sensitivity analysis] The primary outcomes for individual SGLT-2i compared with metformin, after 1:2 propensity score matching.

		Results for individual SGLT-2i						Primary results	
		Canagliflozin versus metformin		Dapagliflozin versus metformin		Empagliflozin versus metformin		SGLT-2i versus metformin	
Exposures / **Outcomes**		Canagliflozin (n=4,025)	Metformin (n=8,050)	Dapagliflozin (n=2,004)	Metformin (n=4,008)	Empagliflozin (n=2,762)	Metformin (n=5,524)	SGLT-2i (n=8,613)	Metformin (n=17,226)
Primary									
MI/stroke/mortality	HR (95% CI)	1.04 (0.77-1.41)	-	1.2 (0.66-2.18)	-	1.12 (0.76-1.64)	-	0.96 (0.77, 1.19)	-
	IRD (95% CI)	-0.01 (-4.49, 4.46)	-	0.41 (-5.3, 6.11)	-	1.61 (-5.61, 8.83)	-	-1.21 (-4.52, 2.11)	-
	N events (IR/1000 PY)	62 (14.9)	138 (15.0)	16 (9.8)	35 (9.4)	40 (19.6)	81 (18.0)	115 (15.0)	283 (16.2)
HHF/mortality	HR (95% CI)	0.9 (0.68-1.18)	-	1.07 (0.62-1.85)	-	0.78 (0.55-1.09)	-	0.80 (0.66, 0.97)	-
	IRD (95% CI)	-2.91 (-7.87, 2.05)	-	-0.68 (-7.01, 5.64)	-	-7.14 (-15.36, 1.09)	-	-5.23 (-9.01, -1.45)	-
	N events (IR/1000 PY)	73 (17.5)	188 (20.4)	19 (11.6)	46 (12.3)	46 (22.5)	133 (29.6)	141 (18.3)	410 (23.5)

SGLT-2i: sodium-glucose cotransporter-2 inhibitors; MI/stroke/mortality: a composite of hospitalization for acute myocardial infarction, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality; HHF/mortality: hospitalization for heart failure or all-cause mortality; HR: hazard ratio; 95% CI: 95% confidence interval; IRD: incidence rate difference; N: number; IR: incidence rate; PY: person-years.

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