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Cardiovascular Outcomes in Patients Initiating First-Line Treatment of Type 2 Diabetes With Sodium–Glucose Cotransporter-2 Inhibitors Versus Metformin

A Cohort Study

HoJin Shin, BPharm, PhD; Sebastian Schneeweiss, MD, ScD; Robert J. Glynn, ScD, PhD; and Elisabetta Patorno, MD, DrPH

Background: Evidence on the risk for cardiovascular events associated with use of first-line sodium–glucose cotransporter-2 inhibitors (SGLT-2i) compared with metformin is limited.

Objective: To assess cardiovascular outcomes among adults with type 2 diabetes (T2D) who initiated first-line treatment with SGLT-2i versus metformin.

Design: Population-based cohort study.

Setting: Claims data from 2 large U.S. commercial and Medicare databases (April 2013 to March 2020).

Participants: Patients with T2D aged 18 years and older (>65 years in Medicare) initiating treatment with SGLT-2i or metformin during April 2013 to March 2020, without any use of antidiabetic medications before cohort entry, were identified. After 1:2 propensity score matching in each database, pooled hazard ratios (HRs) and 95% CIs were reported.

Intervention: First-line SGLT-2i (canagliflozin, empagliflozin, or dapagliflozin) or metformin.

Measurements: Primary outcomes were a composite of hospitalization for myocardial infarction (MI), hospitalization for ischemic or hemorrhagic stroke or all-cause mortality (MI/stroke/mortality), and a composite of hospitalization for heart failure (HHF) or all-cause mortality (HHF/mortality). Safety outcomes including genital infections were assessed.

Results: Among 8613 first-line SGLT-2i initiators matched to 17 226 metformin initiators, SGLT-2i initiators had a similar risk for MI/stroke/mortality (HR, 0.96; 95% CI, 0.77 to 1.19) and a lower risk for HHF/mortality (HR, 0.80; CI, 0.66 to 0.97) during a mean follow-up of 12 months. Initiators receiving SGLT-2i showed a lower risk for HHF (HR, 0.78; CI, 0.63 to 0.97), a numerically lower risk for MI (HR, 0.70; CI, 0.48 to 1.00), and similar risk for stroke, mortality, and MI/stroke/HHF/mortality compared with metformin. Initiators receiving SGLT-2i had a higher risk for genital infections (HR, 2.19; CI, 1.91 to 2.51) and otherwise similar safety as those receiving metformin.

Limitation: Treatment selection was not randomized.

Conclusion: As first-line T2D treatment, initiators receiving SGLT-2i showed a similar risk for MI/stroke/mortality, lower risk for HHF/mortality and HHF, and a similar safety profile except for an increased risk for genital infections compared with those receiving metformin.

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Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have demonstrated benefits relative to placebo from cardiovascular outcome trials (CVOTs) (1), including a risk reduction in hospitalization for heart failure (HHF) in study populations with cardiovascular disease (CVD) or at high cardiovascular risk (2–5). These benefits informed subsequent drug-label expansions of SGLT-2i (6–8). In addition, beginning in 2018, SGLT-2i have been endorsed as a preferred second-line treatment (9, 10) and have recently been recommended as first-line agent for patients with type 2 diabetes (T2D) and CVD (11).

In contrast to the evidence for benefits of SGLT-2i generated by large CVOTs involving thousands of patients with T2D, the evidence for metformin comes primarily from subgroup findings of the U.K. Prospective Diabetes Study (12), in which 342 participants randomly assigned to metformin had reduced risk for myocardial infarction (MI) and all-cause mortality compared with diet alone. A trial comparing dapagliflozin with metformin is expected to complete in 2025 (13). However, the trial results may not be informative for persons with a history of CVD, representing 16% to 19% of patients in need of first-line antidiabetic treatment (14, 15), because those with established CVD are excluded. Also, power to demonstrate effects on cardiovascular outcomes may be limited because of low expected cardiovascular event rates in this relatively healthier population. Therefore, well-designed large nonrandomized studies could provide information on the cardiovascular effectiveness and safety of first-line SGLT-2i (16–18) in a timely manner when there is increased interest in advancing SGLT-2i to first-line treatment, especially for patients with existing CVD (19). The findings from claims-based nonrandomized studies, which emulated randomized trials of SGLT-2i, further strengthen the viability of such studies (20). However, existing studies have focused on the effects of SGLT-2i as second-line treatment (21–23); they might

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have included non–first-line users (24) or captured data incompletely from electronic health records (25).

We evaluated the risk for cardiovascular events among adults with T2D who initiated treatment with first-line SGLT-2i versus metformin in clinical practice.

METHODS

Study Data

We used data from 2 large commercial U.S. health insurance databases—Optum Clinformatics Data Mart and IBM MarketScan—and Medicare fee for service. The commercial databases included persons with employer-sponsored health insurance or a Medicare Advantage insurance plan across the United States. The Medicare database included beneficiaries aged 65 years and older. These databases contained deidentified individual-level, longitudinal information on demographics, diagnoses, and procedures, and outpatient prescription dispensations recorded during billing of all health care encounters. The study was approved by the Mass General Brigham Institutional Review Board before data collection; licensing agreements were in place. Access to the data and analytics infrastructure can be shared for relevant requests.

Study Design and Eligibility Criteria

We designed an observational study to emulate a target trial comparing the risk for cardiovascular events associated with first-line SGLT-2i versus metformin in real-world patients with T2D, using U.S. claims data (see **Supplement Table 1** [available at Annals.org] for the simulated trial design framework). Eligible persons were aged 18 years and older (>65 years in Medicare), had at least 1 diagnosis of T2D (inpatient or outpatient International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 250.x0 or 250.x2 through 30 September 2015, or Tenth Revision, Clinical Modification [ICD-10-CM] code E11.xxx thereafter) at any point before cohort entry (26, 27), and had continuous health care insurance enrollment with complete medical coverage and pharmacy benefits for at least 365 days before cohort entry. We excluded persons with missing information on age, sex, and region. To ensure the identification of first-line use, we excluded persons who used any antidiabetic drugs at any point before or on cohort entry. To reduce surveillance variability, we also excluded those who did not have at least 1 prescription or physician visit in both of 2 periods (−365 days to −183 days and −182 days to −1 day) before cohort entry (28). Other ineligible persons had a history of gestational or secondary diabetes, polycystic ovary syndrome, organ transplant, end-stage renal disease, HIV/AIDS, or nursing home admission at any point before cohort entry (**Figure 1**; **Supplement Figure 1**, available at Annals.org).

Exposure and Follow-up

Before applying the eligibility criteria, we identified persons who filled a new prescription for first-line SGLT-2i (canagliflozin, empagliflozin, or dapagliflozin) or metformin between 1 April 2013 (consistent with the launch of SGLT-2i in the United States) and 31 March 2020 in Optum (31 December 2018 in MarketScan and Medicare). The first dispensing date of the study drugs was defined as cohort entry. We excluded persons who initiated treatment with SGLT-2i and metformin simultaneously on cohort entry.

Follow-up began on the day after cohort entry and continued until the occurrence of a study outcome, death, treatment discontinuation (with an interval between prescription refills >60 days) (29), disenrollment, or end of the study period, whichever occurred first (**Figure 1**; **Supplement Figure 1**).

Outcomes

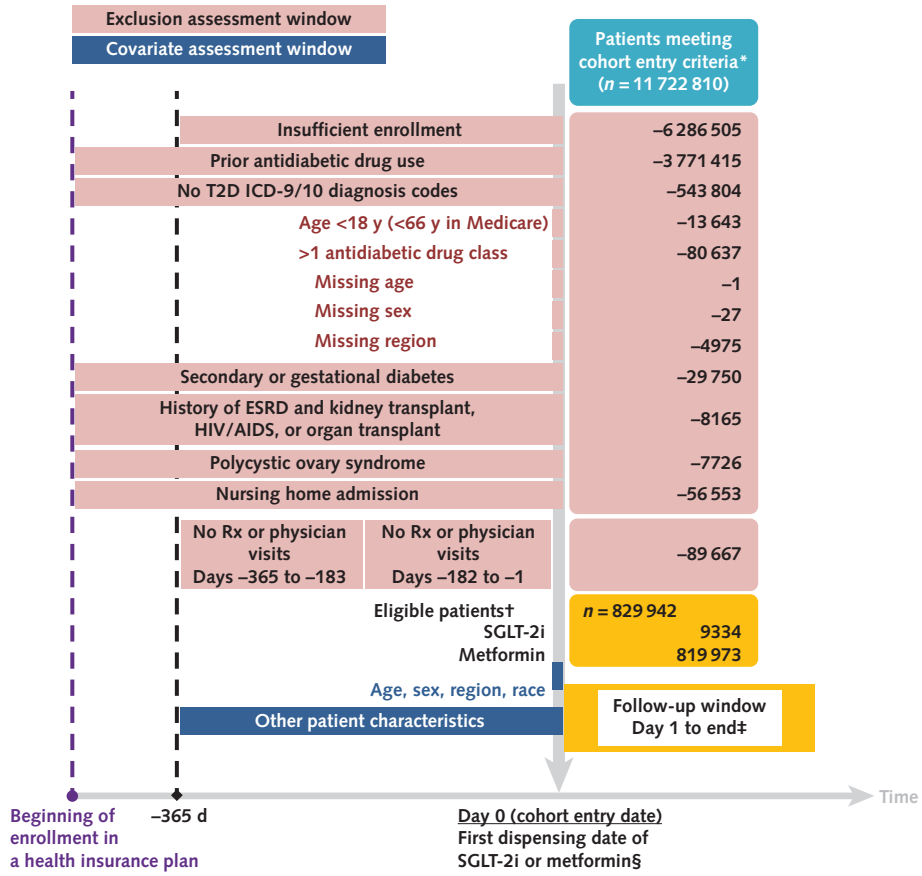
Primary outcomes were a composite of hospitalization for acute MI, hospitalization for ischemic or hemorrhagic stroke, or all-cause mortality (hereafter called "mortality") (MI/stroke/mortality), and a composite of HHF or all-cause mortality (HHF/mortality). Secondary outcomes were the individual components of the primary outcomes and a composite of MI/stroke/HHF/mortality. Safety events included acute kidney injury, bone fractures, genital infections, severe hypoglycemia, severe urinary tract infections, diabetic ketoacidosis, and lower-limb amputations. Genital infections also functioned as a positive tracer outcome to assess the validity of the study results (30–32).

The outcomes were identified by using validated ICD-9/10-CM procedural and diagnosis codes (**Supplement Table 2**, available at Annals.org). Validation studies for the claims-based algorithms for the cardiovascular end points showed positive predictive values above 80% (33–36). All-cause mortality was ascertained from 4 sources for Clinformatics: Centers for Medicare & Medicaid Services data, the Social Security Administration Death Master File (37), hospital discharge status indicating death, and death as a reason for insurance coverage discontinuation. All-cause mortality was ascertained through hospital discharge status indicating death for MarketScan (38) and through the Master Beneficiary summary file for Medicare (39). Validation studies for the claims-based algorithms for the safety outcomes—acute kidney injury, bone fractures, severe hypoglycemia, and diabetic ketoacidosis—also showed positive predictive values above 80% (40–45). For the safety outcomes—genital infections, severe urinary tract infections, and lower-limb amputations—without a validation study, we adapted definition codes from other's studies (32, 46–48).

Patient Characteristics

Patient characteristics were selected based on subject knowledge about confounders and predictors of the outcomes; they were measured during the 365 days before or on cohort entry. These included demographics, diabetes-related and other comorbidities, concomitant medications, and measures of health care use (**Supplement Table 3**, available at Annals.org). Laboratory test results were available for approximately 15% of the population through linkage with national laboratory test provider chains.

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



ESRD = end-stage renal disease; ICD-9/10 = International Classification of Diseases, Ninth and Tenth Revisions; Rx = prescription; SGLT-2i = sodium–glucose cotransporter-2 inhibitors; T2D = type 2 diabetes.

* Cohort entry criteria: initiation of either SGLT-2i or metformin between 1 April 2013 and 31 March 2020 (31 December 2018 for MarketScan and Medicare).

† Persons who were censored on cohort entry were additionally excluded.

‡ Follow-up ends at the earliest of: outcome, death, discontinuation of study drugs, disenrollment, or end of the study period.

§ April 2013 to March 2020.

Statistical Analysis

To emulate randomization, we used propensity score (PS) matching. We chose the ratio of 1:2 for matching to improve statistical efficiency because the number of metformin initiators was much larger compared with SGLT-2i initiators. The ratio also allowed us to retain as many SGLT-2i initiators as possible (92%) because increasing the matching ratio would result in excluding more SGLT-2i initiators with a caliper. Therefore, the estimand of this study was an on-treatment estimate, with a grace period of 60 days between prescription refills, among the initiators receiving SGLT-2i or metformin who were well balanced on all measured potential confounders.

To mitigate the potential channeling bias due to the selective prescription of SGLT-2i that changed over time since market launch, the study period was stratified into 4 consecutive calendar time blocks (T1, April 2013 through December 2014; T2, January 2015 through June 2016; T3, July 2016 through December 2017; and T4, January 2018 through March 2020) (49, 50). Within each database, time block–specific predicted probabilities of receiving first-line SGLT-2i versus metformin as treatment of T2D were estimated from logistic regression models (51) that included all prespecified baseline covariates except for laboratory values, which were not available for all patients (see **Supplement Tables 4 to 6** [available at Annals.org] for the results of the PS models). The missing-indicator method was used to treat missing values for the race variable in Optum, assuming missingness was conditionally independent of the outcomes (52). Within strata of time block, to reduce residual confounding and retain the same persons for the main and subgroup analyses of CVD, we then 1:2 matched patients on the PS using a caliper width of 0.001 of the SD of the logit of the PS and baseline CVD (53–55). During the baseline period, CVD was defined as a history of MI, stable or unstable angina, other ischemic

Table. Baseline Characteristics of Patients Initiating Treatment With SGLT-2i Versus Metformin Before and After 1:2 PS Matching

Baseline Characteristics	Before PS Matching			After PS Matching		
	SGLT-2i (*n* = 9334)	Metformin (*n* = 819 973)	Standardized Difference	SGLT-2i (*n* = 8613)	Metformin (*n* = 17 226)	Standardized Difference
Demographics						
Mean age (SD), *y*	60.14 (12.03)	63.49 (12.61)	0.27	60.05 (12.14)	60.14 (12.55)	0.01
Sex, male, *n (%)*	4880 (52.3)	411 412 (50.2)	0.04	4438 (51.5)	9018 (52.4)	0.02
Region, *n (%)**						
Northeast	1645 (17.6)	134 860 (16.4)	0.03	1494 (17.3)	3015 (17.5)	0.00
South	4893 (52.4)	361 794 (44.1)	0.17	4479 (52.0)	8909 (51.7)	0.01
Midwest	1535 (16.4)	178 237 (21.7)	0.13	1459 (16.9)	2965 (17.2)	0.01
West	1261 (13.5)	145 082 (17.7)	0.12	1181 (13.7)	2337 (13.6)	0.00
Medicare Advantage, *n (%)*†	1448 (20.8)	146 015 (28.8)	0.19	1354 (21.1)	2730 (21.3)	0.00
Race, *n (%)*‡						
White	3646 (70.4)	390 062 (72.7)	0.05	3344 (70.4)	6580 (69.3)	0.02
Non-White	1159 (22.4)	122 043 (22.7)	0.01	1066 (22.4)	2239 (23.6)	0.03
Missing	377 (7.3)	24 368 (4.5)	0.12	340 (7.2)	681 (7.2)	0.00
Lifestyle risk factors, *n (%)*						
Obesity or overweight	3663 (39.2)	276 210 (33.7)	0.12	3312 (38.5)	6514 (37.8)	0.01
Smoking	1353 (14.5)	129 078 (15.7)	0.03	1241 (14.4)	2439 (14.2)	0.01
Comorbidities, *n (%)*						
Diabetic nephropathy	495 (5.3)	25 946 (3.2)	0.11	393 (4.6)	823 (4.8)	0.01
Diabetic neuropathy	820 (8.8)	42 662 (5.2)	0.14	627 (7.3)	1248 (7.2)	0.00
Diabetic retinopathy	205 (2.2)	9383 (1.1)	0.08	141 (1.6)	249 (1.4)	0.02
CVD§	2652 (28.4)	224 879 (27.4)	0.02	2256 (26.2)	4512 (26.2)	0.00
Myocardial infarction	386 (4.1)	31 767 (3.9)	0.01	324 (3.8)	604 (3.5)	0.01
Ischemic or hemorrhagic stroke	603 (6.5)	56 647 (6.9)	0.02	519 (6.0)	1057 (6.1)	0.00
Transient ischemic attack	155 (1.7)	15 308 (1.9)	0.02	131 (1.5)	253 (1.5)	0.00
Other ischemic heart diseases	1930 (20.7)	154 999 (18.9)	0.04	1655 (19.2)	3159 (18.3)	0.02
Heart failure	673 (7.2)	53 674 (6.5)	0.03	572 (6.6)	1031 (6.0)	0.03
Atherosclerotic peripheral vascular disease	602 (6.4)	50 810 (6.2)	0.01	501 (5.8)	996 (5.8)	0.00
Angina	541 (5.8)	37 035 (4.5)	0.06	455 (5.3)	820 (4.8)	0.02
Hyperlipidemia	6760 (72.4)	583 065 (71.1)	0.03	6130 (71.2)	12 354 (71.7)	0.01
Hypertension	6836 (73.2)	589 462 (71.9)	0.03	6191 (71.9)	12 475 (72.4)	0.01
CKD (stages 1–4)	721 (7.7)	49 643 (6.1)	0.07	600 (7.0)	1192 (6.9)	0.00
COPD	814 (8.7)	82 025 (10.0)	0.04	755 (8.8)	1529 (8.9)	0.00
Malignant neoplasm	807 (8.6)	80 263 (9.8)	0.04	733 (8.5)	1513 (8.8)	0.01
Physician specialties, *n (%)*‖						
Cardiologists	406 (4.3)	42 696 (5.2)	0.04	353 (4.1)	718 (4.2)	0.00
Endocrinologists	349 (3.7)	19 051 (2.3)	0.08	292 (3.4)	644 (3.7)	0.02
Internists	4234 (45.4)	538 093 (65.6)	0.42	4132 (48.0)	8165 (47.4)	0.01
Health care use						
Any recent hospitalizations, *n (%)*¶	148 (1.6)	31 790 (3.9)	0.14	125 (1.5)	279 (1.6)	0.01
Mean average length of hospitalizations (SD), *d*	0.33 (1.53)	0.47 (2.07)	0.07	0.31 (1.44)	0.31 (1.39)	0.00
Mean number of ED visits (SD)	0.62 (1.83)	0.62 (1.63)	0.00	0.61 (1.86)	0.58 (1.37)	0.02
Mean number of office visits (SD)	11.59 (10.02)	10.30 (9.18)	0.13	11.29 (9.70)	11.21 (10.40)	0.01
Mean number of HbA_{1c} test orders (SD)	1.81 (1.19)	1.59 (1.09)	0.19	1.76 (1.15)	1.75 (1.12)	0.01
Mean brand–generic ratio (SD)**	−1.59 (1.21)	−1.79 (1.18)	0.17	−1.62 (1.21)	−1.61 (1.20)	0.01
Mean number of unique medication uses (SD)	10.64 (8.41)	10.32 (7.63)	0.04	10.56 (8.13)	10.43 (8.18)	0.02
Mean copay for pharmacy cost (SD), *U.S. dollars*	344.32 (560.75)	327.35 (554.41)	0.03	338.24 (542.55)	331.41 (560.59)	0.01
Preventive health care service, *n (%)*††	6830 (73.2)	618 590 (75.4)	0.05	6302 (73.2)	12 561 (72.9)	0.01
Concomitant medications, *n (%)*						
ACE inhibitors or ARBs	4864 (52.1)	478 902 (58.4)	0.13	4561 (53.0)	9139 (53.1)	0.00
Antithrombotic medications	1484 (15.9)	123 840 (15.1)	0.02	1305 (15.2)	2554 (14.8)	0.01
β-blockers	2832 (30.3)	279 578 (34.1)	0.08	2584 (30.0)	5221 (30.3)	0.01
Calcium-channel blockers	2105 (22.6)	211 100 (25.7)	0.07	1977 (23.0)	3944 (22.9)	0.00
Loop diuretics	946 (10.1)	79 533 (9.7)	0.01	822 (9.5)	1602 (9.3)	0.01
Statin	4642 (49.7)	476 160 (58.1)	0.17	4355 (50.6)	8749 (50.8)	0.00
Thiazides	1061 (11.4)	121 327 (14.8)	0.10	1001 (11.6)	1990 (11.6)	0.00

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Baseline Characteristics	Before PS Matching			After PS Matching		
	SGLT-2i (*n* = 9334)	Metformin (*n* = 819 973)	Standardized Difference	SGLT-2i (*n* = 8613)	Metformin (*n* = 17 226)	Standardized Difference
Laboratory results†						
Mean HbA_{1c} (SD), %‡‡	7.70 (1.69)	7.36 (1.56)	0.21	7.70 (1.70)	7.24 (1.53)	0.29
Missing	5547 (79.7)	400 696 (79.1)	0.01	5128 (79.9)	10 175 (79.3)	0.02
Mean eGFR4 (SD), *mL/min/1.73 m²*§§	119.95 (9.00)	118.82 (9.84)	0.12	120.08 (9.08)	120.02 (9.68)	0.01
Missing	5219 (75.0)	379 335 (74.9)	0.00	4844 (75.5)	9645 (75.1)	0.01
Mean LDL (SD)						
mmol/L	2.46 (1.05)	2.58 (1.06)	0.12	2.49 (1.05)	2.58 (1.05)	0.09
mg/dL	94.93 (40.79)	99.78 (40.94)	0.12	96.12 (40.47)	99.57 (40.67)	0.09
Missing	5394 (77.5)	390 169 (77.1)	0.01	4995 (77.8)	9925 (77.3)	0.01
Mean HDL (SD)						
mmol/L	1.20 (0.36)	1.20 (0.78)	0.01	1.20 (0.36)	1.24 (2.24)	0.03
mg/dL	46.23 (13.95)	46.56 (30.05)	0.01	46.22 (13.87)	47.95 (86.71)	0.03
Missing	5422 (77.9)	393 785 (77.8)	0.00	5020 (78.2)	10 009 (78.0)	0.01
Mean total cholesterol (SD)						
mmol/L	4.66 (1.18)	4.79 (1.20)	0.1	4.68 (1.17)	4.75 (1.15)	0.06
mg/dL	180.31 (45.70)	185.10 (46.44)	0.1	181.02 (45.40)	183.59 (44.47)	0.06
Missing	5399 (77.6)	392 003 (77.4)	0.00	5001 (77.9)	9968 (77.7)	0.01
Mean triglyceride (SD)						
mmol/L	2.09 (2.05)	2.06 (1.82)	0.02	2.08 (1.99)	1.98 (1.36)	0.05
mg/dL	185.09 (181.89)	182.21 (161.05)	0.02	184.11 (176.41)	175.80 (120.79)	0.05
Missing	5403 (77.7)	393 004 (77.6)	0.00	5005 (78.0)	9986 (77.8)	0.00

ACE inhibitor = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; ED = emergency department; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PS = propensity score; SGLT-2i = sodium–glucose cotransporter-2 inhibitor.

* Northeast (Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont); South (Alabama; Arkansas; Delaware; Florida; Georgia; Kentucky; Louisiana; Maryland; Mississippi; North Carolina; Oklahoma; South Carolina; Tennessee; Texas; Virginia; Washington, DC; West Virginia); Midwest (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin); West (Alaska, Arizona, California, Colorado, Hawai'i, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, Wyoming).

† Pooled across Clinformatics and MarketScan databases.

‡ Pooled across 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 that occurred within 7 days before cohort entry.

¶ Defined as any hospitalizations that occurred within 30 days before 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 before or on cohort entry.

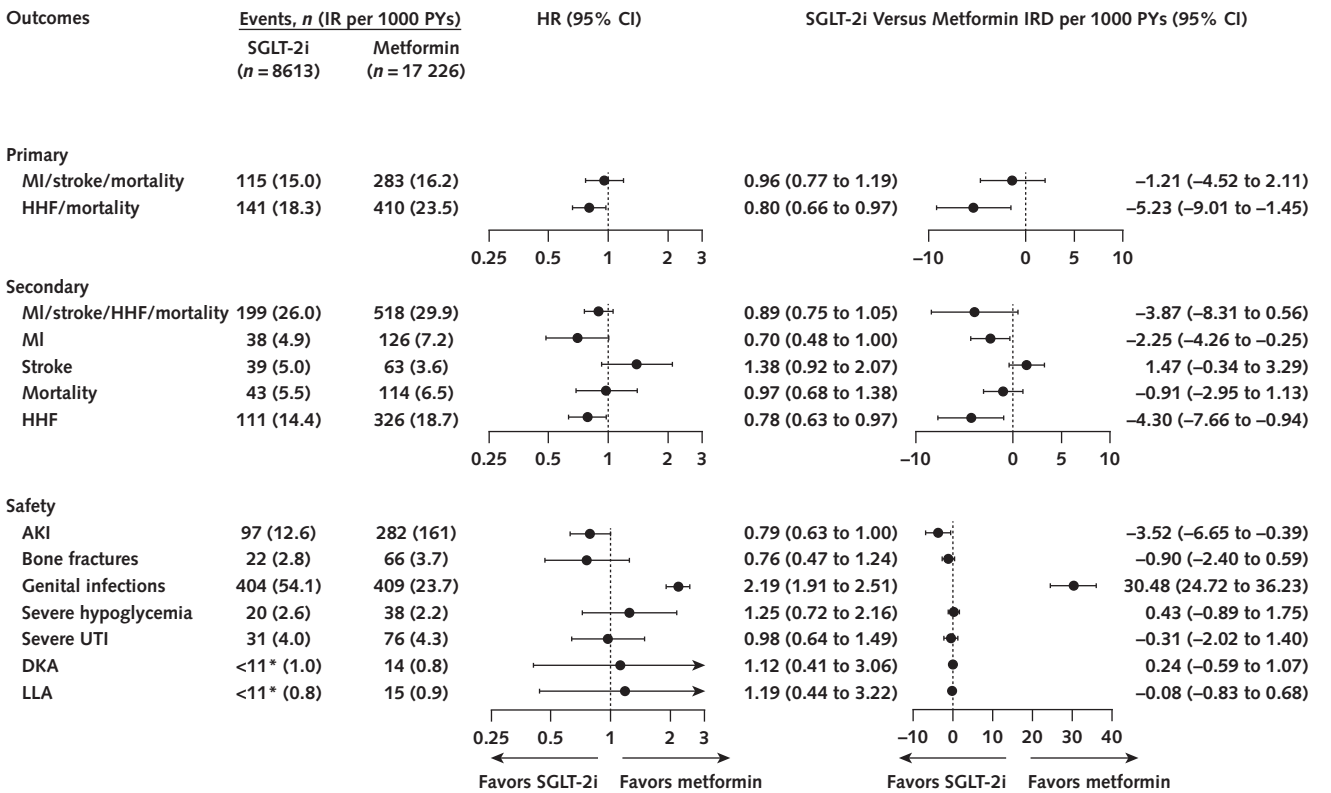
§§ Estimated using the quadratic GFR equation: GFR = exp(1.911 + [5.249/serum creatinine] − [2.114/serum creatinine^2] − 0.00686 × age − 0.205 (if female)). If serum creatinine <0.8 mg/dL, use 0.8 for serum creatinine.

heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure, based on the treatment guidelines for T2D (9).

Within each database, covariate balance between the exposure groups before and after PS matching was assessed using standardized differences greater than 0.1, defined as meaningful imbalances for confounding a treatment effect association (56, 57). We pooled patient characteristics across 3 databases and calculated standardized differences. The balance in laboratory test results was also examined after PS matching to evaluate the potential for residual confounding because laboratory test results were not included in the PS models. We calculated database-specific unadjusted and PS-matched numbers of events, incidence rates (IRs), and IR differences (IRDs) per 1000 person-years (1000 PYs) with 95% CIs for all outcomes. Within each database, time block–specific PS-matched cohorts were aggregated for outcome regression (58), and hazard ratios (HRs) with 95% CIs were estimated using proportional hazards models without further adjustment (59). Database-specific HRs were combined using a fixed-effect meta-analysis (60). Subgroup analyses by baseline CVD were conducted, applying a χ^2 test for homogeneity (61).

We performed several sensitivity analyses to demonstrate the robustness of our findings (see the **Supplement** [available at Annals.org] for more details): i) the first study time block (April 2013 to December 2014) was excluded from the analysis because of the lack of adequate equipoise between the treatment groups in the early phase of postmarketing (62); ii) the study cohorts were restricted to persons with continuous health insurance enrollment for at least 2 years before cohort entry to assess the effect of the probable inclusion of prior antidiabetic drug users; iii) an intention-to-treat analysis was conducted to address potential informative censoring by carrying forward the initial

Figure 2. Number of events, incidence rates, hazard ratios, and incidence rate differences for cardiovascular and safety outcomes, comparing SGLT-2i versus metformin after 1:2 propensity score matching.



AKI = acute kidney injury; DKA = diabetic ketoacidosis; HHF = hospitalization for heart failure; HR = hazard ratio; IR = incidence rate; IRD = incidence rate difference; LLA = lower-limb amputation; MI = myocardial infarction; PYs = person-years; SGLT-2i = sodium–glucose cotransporter-2 inhibitors; UTI = urinary tract infection.

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

exposure for 365 days without considering treatment discontinuation or the initiation of the comparator drug (63); iv) in addition, we censored persons on initiation of treatment with the comparator drug during the follow-up period to evaluate potential exposure misclassification because 16% of SGLT-2i initiators started treatment with metformin, whereas 2% of metformin initiators started treatment with SGLT-2i after cohort entry (data not shown); v) for a subset of the study population with baseline hemoglobin A_{1c} (HbA_{1c}) levels available, we reestimated the PS, further conditioning on HbA_{1c} levels, to adjust for baseline glucose control; vi) we quantified the bias associated with the imbalance in baseline HbA_{1c} levels across treatment groups after PS matching (64); vii) to assess the effect of unmeasured socioeconomic status (20), we evaluated cardiovascular end points of first-line SGLT-2i and metformin against first-line dipeptidyl peptidase-4 inhibitors (DPP-4i), which cost more than metformin without a known effect on the cardiovascular outcomes of interest among adults with T2D (9); viii) we reestimated the PSs after replacing the 4 census regions (northeast, midwest, south, and west) of the primary analysis with 50 states and 1 federal district in the PS models to explore the presence of potential residual confounding because of geographic variation in clinical care; and ix) we evaluated the effect of individual SGLT-2i versus metformin on the primary cardiovascular outcomes.

All analyses were performed using R version 3.6.2 (65), with analytic files generated using the Aetion Evidence Platform v4.10 (66–68).

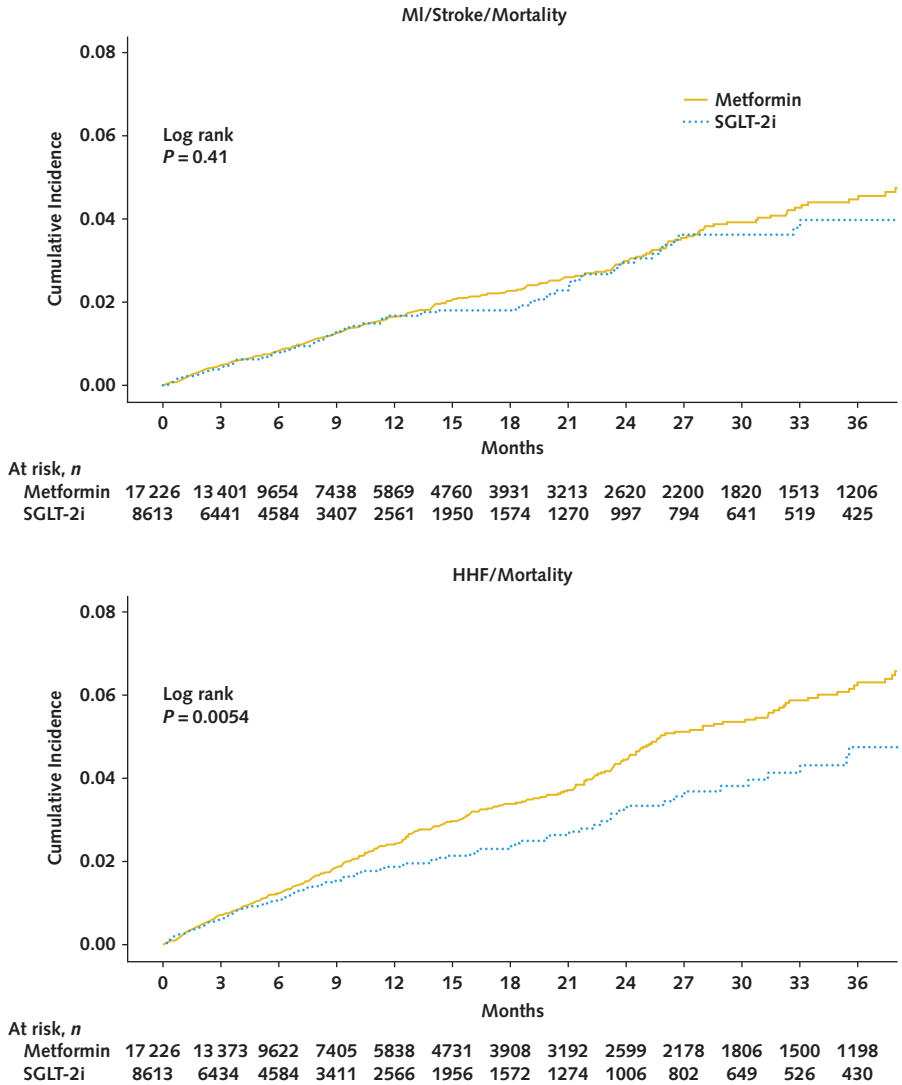
Role of the Funding Source

The funder had no role in the design, conduct, or analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

We identified 9334 initiators of SGLT-2i and 819 973 initiators of metformin as first-line T2D treatment (**Figure 1**; **Supplement Figure 1**). Before PS matching, SGLT-2i initiators were younger, had a similar burden of CVD, more likely had diabetic nephropathy and neuropathy, had greater office visits or HbA_{1c} test orders, and fewer recent hospitalizations compared with metformin initiators (**Table**). The same pattern of differences in patient characteristics was observed across all 3 databases except SGLT-2i initiators had a higher burden of CVD in Clinformatics and Medicare, and had a similar burden of diabetic nephropathy

Figure 3. Kaplan–Meier curves of cumulative incidence for primary outcomes, comparing SGLT-2i versus metformin after 1:2 propensity score matching.

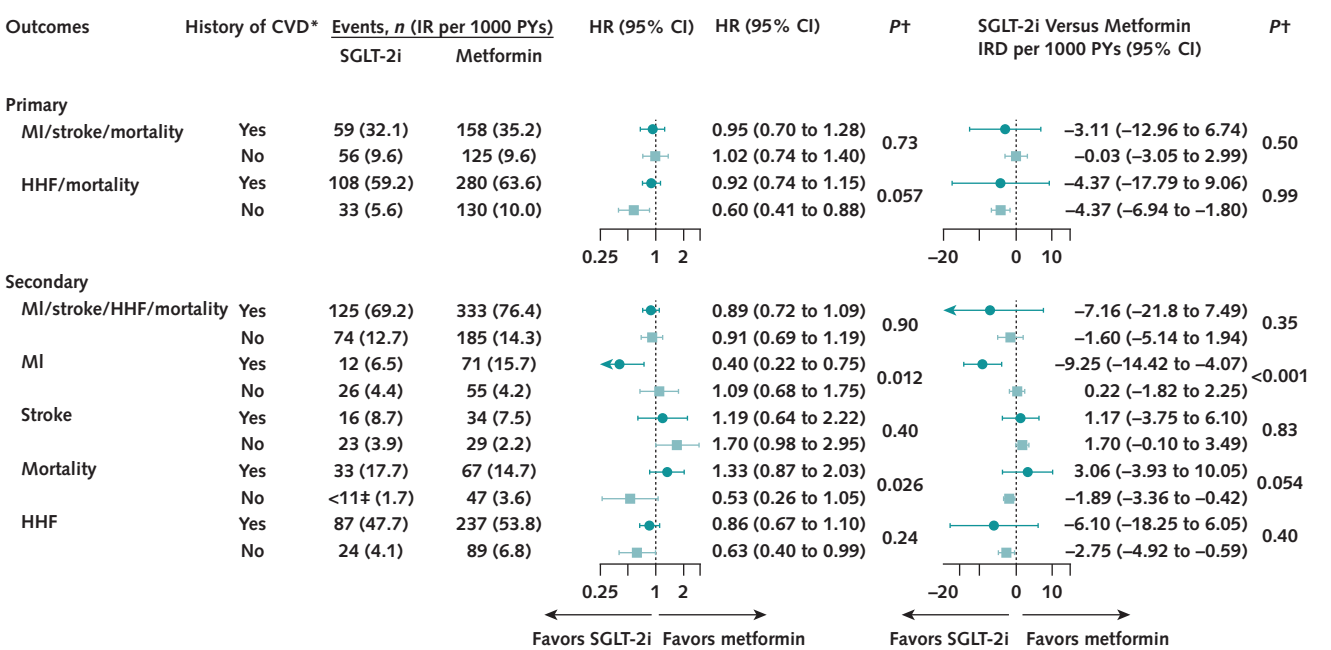


HHF = hospitalization for heart failure; MI = myocardial infarction; SGLT-2i = sodium-glucose cotransporter-2 inhibitors. **Top.** MI/stroke/mortality. **Bottom.** HHF/mortality.

in MarketScan compared with metformin initiators (**Supplement Tables 7 to 9**, available at Annals.org). After PS matching of 8613 SGLT-2i initiators to 17 226 metformin initiators, patient characteristics were well balanced between treatment groups (standardized difference < 0.1) (56, 57), including laboratory test results, except for higher HbA_{1c} levels (0.46 percentage points) among SGLT-2i initiators. The mean follow-up times on treatment were 10.7 months (median, 6.6 months) for SGLT-2i and 12.2 months (median, 7.3 months) for metformin, and most patients were censored due to treatment discontinuation (54%), end of the study period (24%), or disenrollment (20%) (**Supplement Table 10**, available at Annals.org).

After PS matching, the IRs per 1000 PYs comparing SGLT-2i versus metformin were 15.0 versus 16.2 for MI/stroke/mortality (HR, 0.96 [95% CI, 0.77 to 1.19]; IRD, −1.21 [CI, −4.52 to 2.11] per 1000 PYs), and 18.3 versus 23.5 for HHF/mortality (HR, 0.80 [CI, 0.66 to 0.97]; IRD, −5.23 [CI, −9.01 to −1.45] per 1000 PYs) (**Figure 2**; **Supplement Table 11**, available at Annals.org). The PS-matched Kaplan–Meier curves for HHF/mortality diverged after 6 months (**Figure 3**). Compared with metformin, SGLT-2i showed a lower risk for HHF (HR, 0.78 [CI, 0.62 to 0.97]), a numerically lower risk for MI (HR, 0.70 [CI, 0.48 to 1.00]), and similar risk for stroke, mortality, and MI/stroke/HHF/mortality (**Figure 2**; **Supplement Figure 2**, available at Annals.org). The risk for safety events was similar, except SGLT-2i showed an increased risk for genital infections (HR, 2.19 [CI, 1.91 to 2.51]; IRD, 30.48 [CI, 24.72 to 36.23] per 1000 PYs) (**Figure 2**), most of which were captured in an outpatient setting (>99%; data not shown).

Figure 4. Cardiovascular outcomes by subgroups of CVD, comparing SGLT-2i versus metformin after 1:2 propensity score matching.



CVD = cardiovascular disease; HHF = hospitalization for heart failure; HR = hazard ratio; IR = incidence rate; IRD = incidence rate difference; MI = myocardial infarction; PYs = person-years; SGLT-2i = sodium–glucose cotransporter-2 inhibitors.

* CVD history was defined as history of MI, stable or unstable angina, other ischemic heart diseases, transient ischemic attack, stroke, atherosclerotic peripheral vascular disease, or heart failure; number of patients with a history of CVD were SGLT-2i (*n* = 2256) and metformin (*n* = 4512); and number of patients without a history of CVD were SGLT-2i (*n* = 6357) and metformin (*n* = 12 714).

† *P* value of homogeneity.

‡ In accordance with the data use agreement, we do not report information for frequency cells with fewer than 11 case patients. These are noted as <11.

Our findings remained consistent in sensitivity analyses (**Supplement Figure 3**, available at Annals.org), including an intention-to-treat analysis that shifted the point estimate of HHF/mortality expectedly toward the null. Bias quantification suggested that our results were conservative given observed imbalances in HbA_{1c} levels between SGLT-2i and metformin (7.70% vs. 7.24% after PS matching) (**Supplement Figure 4**, available at Annals.org). A sensitivity analysis evaluating first-line SGLT-2i and metformin against DPP-4i (**Supplement Table 12**, available at Annals.org) demonstrated no cardiovascular benefit of DPP-4i as expected, suggesting that confounding due to unmeasured socioeconomic status was unlikely. The results from the state-adjusted analysis were consistent with the primary findings (**Supplement Table 13**, available at Annals.org). A sensitivity analysis of individual SGLT-2i compared with metformin did not show substantial deviations from the primary findings (**Supplement Table 14**, available at Annals.org).

Status-specific results for CVD were largely consistent with our primary findings. Compared with metformin, SGLT-2i showed a lower risk for MI in patients with existing CVD (*P* value for homogeneity = 0.012) (**Figure 4**).

DISCUSSION

In this population-based cohort study, patients initiating treatment with first-line SGLT-2i had a similar risk for MI/stroke/mortality and lower risk for HHF/mortality and HHF compared with those initiating treatment with metformin. The risk for adverse events was similar except for an increased risk for genital infections among SGLT-2i initiators.

Across all CVOTs, SGLT-2i showed a 27% to 35% reduction in the risk for HHF relative to placebo, implying a class effect through hemodynamic pathways (69). These trial findings and the postulated biological mechanisms support our finding of a lower risk for HHF for first-line SGLT-2i when compared with metformin. In addition, a meta-analysis of CVOTs for SGLT-2i showed a risk reduction for MI but not for stroke, suggesting a cardiac preload effect with relatively early manifestation (70) and explaining our finding of a lower MI risk when comparing SGLT-2i and metformin, particularly among patients with existing CVD (71). Compared with metformin, SGLT-2i showed a similar risk for mortality. In large CVOTs, individual SGLT-2i demonstrated inconsistent mortality efficacy relative to placebo (69, 72). Because of the limited number of initiators for each of the individual SGLT-2i during the study period, we were unable to assess the effectiveness of individual SGLT-2i versus metformin regarding mortality.

This study strengthened our previous exploratory report (24) by: i) considering all-available history before cohort entry to ensure first-line antidiabetic medication use; ii) accounting for potential biases due to confounding

evolving over time by fitting time-stratified PS models; iii) assessing residual confounding by inspecting balance in laboratory values after PS adjustment and conducting a sensitivity analysis investigating the effect of the potential imbalances in socioeconomic status; iv) comprehensively evaluating cardiovascular and mortality outcomes; and v) improving the representativeness of the study population by including 2 U.S. nationwide commercial and Medicare databases.

This study has limitations. Patients treated with antidiabetic medications prior to the year before cohort entry might have entered our study population if they discontinued health insurance enrollment during this time. However, a sensitivity analysis, requiring at least 2 years of continuous enrollment before cohort entry with no use of any antidiabetic medications, showed results similar to the primary findings. Second, we cannot completely rule out confounding by some unmeasured characteristics, such as duration and severity of diabetes and socioeconomic status. However, adjusting for many claims-measured proxies of disease duration and severity would reduce bias markedly (73). In addition, any residual confounding because of imbalances in duration and severity of diabetes might have favored metformin because SGLT-2i initiators had a higher burden of diabetes-related comorbidities, indicating longer and more severe diabetes (74). A sensitivity analysis comparing first-line SGLT-2i versus DPP-4i and metformin versus DPP-4i suggested that bias due to unmeasured socioeconomic status was unlikely. Moreover, a sensitivity analysis that excluded the first study time block (April 2013 to December 2014), in which confounding was most likely because of the largest observed differences in patient characteristics across exposure groups, did not change our primary findings. Third, cardiovascular-specific death could not be measured in claims data and all-cause mortality might have diluted a potential mortality benefit (75). Last, the information on all-cause mortality was underreported in commercial databases, particularly in MarketScan because only inpatient death was ascertained, although the relative risk estimates for mortality should be conservative assuming nondifferential underreporting.

In conclusion, first-line T2D treatment with SGLT-2i showed a similar risk for MI/stroke/mortality and a lower risk for HHF/mortality, which was driven by a lower risk for HHF, compared with metformin. Metformin and SGLT-2i showed similar safety profiles except for an increased risk for genital infections, which may be less serious than other safety outcomes and can be appropriately managed (76). Although our findings may support the use of SGLT-2i as first-line T2D treatment of cardiovascular outcomes, further research, that is, a randomized clinical trial, is warranted to establish more robust evidence.

From Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (H.S., R.J.G., E.P.); and Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (S.S.).

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Reproducible Research Statement: *Study protocol and Statistical code:* Available from Dr. Shin (e-mail, hos739@mail.harvard.edu). *Data set:* Available from data vendors through a data use agreement.

Corresponding Author: HoJin Shin, BPharm, PhD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street (Suite 3030), Boston, MA 02120; e-mail, hos739@mail.harvard.edu.

Author contributions are available at Annals.org.

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Author Contributions: Conception and design: H. Shin, S. Schneeweiss, E. Patorno.
Analysis and interpretation of the data: H. Shin, S. Schneeweiss, R.J. Glynn, E. Patorno.
Drafting of the article: H. Shin.
Critical revision of the article for important intellectual content: H. Shin, S. Schneeweiss, R.J. Glynn, E. Patorno.
Final approval of the article: H. Shin, S. Schneeweiss, R.J. Glynn, E. Patorno.
Provision of study materials or patients: H. Shin, S. Schneeweiss.
Statistical expertise: H. Shin, S. Schneeweiss, R.J. Glynn.
Administrative, technical, or logistic support: H. Shin, E. Patorno.
Collection and assembly of data: H. Shin, S. Schneeweiss, E. Patorno.