Comparative Effectiveness and Safety of Sodium–Glucose Cotransporter 2 Inhibitors Versus Glucagon-Like Peptide 1 Receptor Agonists in Older Adults

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CARDIOVASCULAR AND METABOLIC RISK

OBJECTIVE

Both sodium–glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RA) demonstrated cardiovascular benefits in randomized controlled trials of patients with type 2 diabetes (T2D) generally <65 years old and mostly with cardiovascular disease. We aimed to evaluate the comparative effectiveness and safety of SGLT2i and GLP-1RA among real-world older adults.

RESEARCH DESIGN AND METHODS

Using Medicare data (April 2013–December 2016), we identified 90,094 propensity score–matched (1:1) T2D patients ≥66 years old initiating SGLT2i or GLP-1RA. Primary outcomes were major adverse cardiovascular events (MACE) (i.e., myocardial infarction, stroke, or cardiovascular death) and hospitalization for heart failure (HHF). Other outcomes included diabetic ketoacidosis (DKA), genital infections, fractures, lower-limb amputations (LLA), acute kidney injury (AKI), severe urinary tract infections, and overall mortality. We estimated hazard ratios (HRs) and rate differences (RDs) per 1,000 person-years, controlling for 140 baseline covariates.

RESULTS

Compared with GLP-1RA, SGLT2i initiators had similar MACE risk (HR 0.98 [95% CI 0.87, 1.10]; RD −0.38 [95% CI −2.48, 1.72]) and reduced HHF risk (HR 0.68 [95% CI 0.57, 0.80]; RD −3.23 [95% CI −4.68, −1.77]), over a median follow-up of ∼6 months. They also had 0.7 more DKA events (RD 0.72 [95% CI 0.02, 1.41]), 0.9 more LLA (RD 0.90 [95% CI 0.10, 1.70]), 57.1 more genital infections (RD 57.08 [95% CI 53.45, 60.70]), and 7.1 fewer AKI events (RD −7.05 [95% CI −10.27, −3.83]) per 1,000 person-years.

CONCLUSIONS

Among older adults, those taking SGLT2i had similar MACE risk, decreased HHF risk, and increased risk of DKA, LLA, and genital infections versus those taking GLP-1RA.

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The aging of the U.S. population is a significant driver of the type 2 diabetes (T2D) epidemic (1). Approximately 25% of people over the age of 65 years have diabetes, and this proportion is expected to rise to >30% by 2050 (2). Patients with diabetes are at high risk for developing cardiovascular disease (CVD) and associated morbidity and mortality, and this risk increases dramatically with age, with cardiovascular events being the primary cause of morbidity and mortality in older adults with T2D (3).

In recent large cardiovascular outcome trials (CVOTs), mandated by regulators to assess the cardiovascular safety of antidiabetes medications, glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium–glucose cotransporter 2 inhibitors (SGLT2i) showed superiority to placebo in reducing the risk of major adverse cardiovascular events (MACE) (4–9), cardiovascular mortality (4,8), all-cause mortality (4,8,10), and nephropathy progression (4,5,7,11–13), with SGLT2i also reducing the risk of hospitalization for heart failure (HHF) (8,9,11). This new evidence prompted guidelines to recommend the initiation of an SGLT2i or a GLP-1RA among patients with high cardiovascular risk or patients with established atherosclerotic CVD, heart failure, or chronic kidney disease (3). However, the comparative effectiveness of these classes of medications in older adults, who represent the majority of patients with T2D, remains largely unknown, as CVOTs have not compared these agents head-to-head, and as these trials were conducted among selected populations with a mean age generally <65 years and mostly with preexisting CVD. Furthermore, as information on potential unintended harms of SGLT2i is rapidly accumulating, e.g., diabetic ketoacidosis (DKA), bone fractures, lower-limb amputations (LLA), and severe urinary tract infections (UTI) (9,14–16), it is critical to understand their safety in older individuals with diabetes. These patients have increased occurrence of multiple comorbidities, polypharmacy, reduced functional status, accelerated muscle loss, and common geriatric syndromes, such as frailty, and thus may be at greater risk of drug-related adverse events compared with younger individuals.

Our primary objective was to evaluate the cardiovascular effectiveness associated with the initiation of SGLT2i compared with GLP-1RA in a population-based cohort of older adults as treated in routine clinical care. Our secondary objective was to assess the safety of SGLT2i versus GLP-1RA with regard to outcomes relevant to older patients.

RESEARCH DESIGN AND METHODS

Data Source, Study Cohort, and Drug Exposure

Data were collected from Medicare Fee-for-Service Parts A (inpatient coverage), B (outpatient coverage), and D (prescription benefits). Medicare is a U.S. federal health insurance program that provides health care to legal residents in the U.S. at least 65 years of age and patients with disabilities. This database covers ~50 million people and contains demographic information, health plan enrollment status, longitudinal patient-level information on all reimbursed medical services, and both inpatient and outpatient diagnoses and procedures along with pharmacy-dispensing records, including information on medication start and refill, strength, quantity, and days' supply. Information on the exact date and cause of death was available for the entire study period through linking with the National Death Index (NDI) file.

The Institutional Review Board of Partners Healthcare approved the study. A licensing agreement was in place.

The study population included patients aged 66 years or older who initiated an SGLT2i, i.e., canagliflozin, dapagliflozin, or empagliflozin, or a GLP-1RA, i.e., albiglutide, dulaglutide, exenatide, or liraglutide, between 1 April 2013 (consistent with the release of the first SGLT2i in the U.S.) and 31 December 2016. Cohort entry was the day of the first filled prescription of any of the drugs above, defined as no use of either SGLT2i or GLP-1RA in the previous year among patients who had 12 or more months of continuous enrollment prior to cohort entry. A recorded diagnosis of T2D was required during the year prior to drug initiation. Patients were excluded if they had a diagnosis of type 1 or secondary diabetes, malignancy, end-stage renal disease, HIV, organ transplant, or a nursing home admission at baseline. To address the potential for unmeasured confounding associated with the high risk for recurrence, we excluded patients with a hospitalization for acute myocardial infarction, coronary revascularization, unstable angina, ischemic or hemorrhagic stroke, a transient ischemic attack, and heart failure in the 60 days prior to cohort entry (Supplementary Table 1 and Supplementary Fig. 1).

Follow-up for study outcomes began on the day after cohort entry and continued in an "as-treated" approach until treatment discontinuation or switch to a drug in the comparator class, the occurrence of a specific study outcome, death, end of continuous health plan enrollment, or end of the study period (31 December 2016)—whichever came first. We extended the exposure effect window until 60 days after the expiration of the last prescription's supply.

Study Outcomes

The primary outcomes included 1) MACE, i.e., a hospitalization for acute myocardial infarction, ischemic or hemorrhagic stroke, or cardiovascular mortality, and 2) HHF. In prior studies, the positive predictive values of claims-based algorithms for myocardial infarction, stroke, and HHF were at least 84% (17–20). Causes of death were determined through NDI linkage. Cardiovascular deaths were identified through recorded ICD-10 codes (I00–I99); only primary causes of death were considered (21). Secondary effectiveness outcomes were the individual components of the composite cardiovascular outcome, all-cause mortality, a composite outcome of MACE or HHF, and a composite of myocardial infarction, stroke, HHF, or all-cause mortality. Safety outcomes included DKA requiring hospitalization, LLA requiring surgery, nonvertebral bone fractures (fracture of humerus, wrist, or hip requiring intervention, or pelvis fracture), genital infections (inpatient or outpatient episodes), acute kidney injury (AKI) requiring hospitalization, and severe UTI, defined as those requiring hospitalization. Definitions were either validated against medical records (22–26) or previously used in pharmacoepidemiologic studies with assessment of glucose-lowering medications (27,28). (See Supplementary Table 2 for definitions.)

Patient Characteristics

Patient baseline characteristics were measured during the 12 months before and including the date of cohort entry. Covariates of interest included demographics (age, sex, and race), calendar time (in quarters and days), comorbidities, diabetes-specific complications, use of diabetes drugs, use of other medications, indicators of health care use as proxy for overall disease state, surveillance, and intensity of care. To address potential confounding by frailty, we also used a claims-based frailty index (29). Patient characteristics were defined with use of ICD-9 or ICD-10 diagnosis or procedure codes, Current Procedural Terminology, 4th Edition, procedure codes, and National Drug Code (pharmacy). A complete

list of baseline patient characteristics can be found in Supplementary Table 3.

Statistical Analysis

Baseline characteristics were cross tabulated by treatment group. To control for imbalances in patient characteristics, we calculated an exposure propensity score (PS) as the predicted probability of receiving SGLT2i versus GLP-1RA treatment, conditional on 140 baseline characteristics, using a multivariable logistic regression model. All variables in Supplementary Table 3 were included, and no further selection was conducted. Patients were 1:1 PS matched by use of the nearest neighbor methodology with a maximum caliper of 0.01 of the PS (Supplementary Fig. 2). Postmatching covariate balance between treatments was assessed by the calculation of standardized differences for each covariate, with meaningful imbalances set at values >0.1 (30). For all outcomes, we calculated PS-matched numbers of events and incidence rates, as well as hazard ratios (HRs), and rate differences (RDs), each with 95% CIs. For primary end points, both overall and within strata defined by presence of CVD at baseline, we also obtained Kaplan-Meier plots of cumulative incidence and compared incidence rates between treatment groups with log-rank tests.

To address potential informative censoring, in sensitivity analyses we carried forward the exposure to the first-used medication for 365 days without considering drug discontinuation or switching, mimicking an "intention-to-treat" approach. To assess potential effect modification by CVD, we also conducted subgroup analyses for primary outcomes and selected secondary outcomes stratified by history of CVD at baseline, defined as history of myocardial infarction, unstable angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral arterial disease or surgery, and lower-extremity amputation. The association with primary outcomes was also assessed in subgroup analyses by age (66–74 years and 75+ years), history of chronic kidney disease, and presence of metformin at cohort entry. Within each subgroup, the PS was reestimated and PS matching was reperformed, and the presence of effect

measure modification across categories was evaluated on the relative and absolute scale with the Wald test for homogeneity.

All analyses were performed with the Aetion Evidence Platform, version 3.2, with R, version 3.2 (31), and with SAS 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Study Cohort and Patient Characteristics

After inclusion and exclusion criteria were applied, we identified 72,900 patients initiating SGLT2i and 64,417 patients initiating GLP-1RA, resulting in 90,094 PS-matched (1:1) patients, with 45,047 in each group (Table 1 and Supplementary Fig. 1).

Before PS matching, compared with patients initiating a GLP-1RA, patients initiating a SGLT2i were slightly older, more frequently were male, with a lower burden of comorbidities, as measured by the Combined Comorbidity Score (32), and were slightly less frail, as measured with a claims-based frailty index (29). SGLT2i initiators were less likely to use insulin at baseline, or to have seen an endocrinologist, and more likely to be on baseline treatment with metformin and dipeptidyl peptidase 4 inhibitors. All differences in patient characteristics were well balanced (as assessed by standardized differences, <0.1) after PS matching, with 70% of GLP-1RA initiators successfully matched to an SGLT2i initiator. The average age was 72 years, 46% of study participants were male, and 83% were White; 33% had history of ischemic heart disease, 11% had history of stroke, 11% had history of heart failure, and 58% were treated with metformin and 24% with insulin during the previous year (Table 1 and Supplementary Table 3). Canagliflozin and liraglutide were the most frequently initiated agents within the SGLT2i and GLP-1RA classes (77% and 59%, respectively) (Supplementary Table 4).

After PS matching, the mean and median follow-up time on treatment were 8.5 and 5.5 months, respectively. More than 20,000 patients had follow-up time >1 year, and >5,000 patients had follow-up time >2 years. Most patients were censored due to treatment discontinuation (54%) or end of the study period, i.e., 31 December 2016 (34%) (Supplementary Table 5).

Absolute and Relative Hazards of Primary and Secondary Outcomes

After PS matching, the incidence rates per 1,000 person-years in SGLT2i versus GLP-1RA initiators, respectively, were 18.0 vs. 18.4 for MACE and 7.0 vs. 10.3 for HHF (Table 2). Compared with GLP-1RA, the initiation of SGLT2i was associated with a similar risk of MACE (HR 0.98 [95% CI 0.87, 1.10]) and with a 32% decreased risk of HHF (HR 0.68 [95% CI 0.57, 0.80]), corresponding to 3.2 fewer cases per 1,000 person-years (RD −3.23 [95% CI −4.68, −1.77]). Kaplan-Meier curves comparing the cumulative incidence of MACE and HHF among initiators of SGLT2i versus GLP-1RA were consistent with these findings, with the curves for HHF separating early and within the first 6 months of treatment initiation (Fig. 1A and B). The proportional hazards assumption, which was assessed by testing of the significance of the interaction term between exposure and time, was not violated. No differences in the risk of the individual components of the MACE outcome were observed between the two exposure groups (HR 0.98 [95% CI 0.84, 1.16] for myocardial infarction, HR 1.04 [95% CI 0.86, 1.27] for stroke, and HR 0.83 [95% CI 0.64, 1.07] for cardiovascular mortality), as also was the case for the risk of all-cause mortality (HR 0.95 [95% CI 0.81, 1.11]) and the composite outcome of myocardial infarction, stroke, HHF, or all-cause mortality (HR 0.92 [95% CI 0.84, 1.002]).

For the safety outcomes, SGLT2i initiators had a 46% increase in the risk of DKA (HR 1.46 [95% CI 1.02, 2.07]), a 44% increased risk of LLA (HR 1.44 [95% CI 1.06, 1.96]), and a 3.4-fold increase in the risk of genital infections (HR 3.34 [95% CI 3.08, 3.62]), corresponding to 0.7, 0.9, and 57.1 more events in 1,000 person-years, respectively, compared with GLP-1RA initiators (Table 3). A post hoc analysis, which evaluated the risk of genital infections among males and females separately, found that SGLT2i was associated with 27.1 more events in males and 90.3 more events in females compared with GLP-1RA (Supplementary Table 6). The risk of bone fractures and severe UTI did not differ among patients initiating SGLT2i versus GLP-1RA. There was a 15% decreased risk of AKI associated with SGLT2i (HR 0.85 [95% CI 0.79, 0.92]) compared with GLP-1RA,

Table 1—Selected baseline characteristics of patients initiating SGLT2i versus GLP-1RA before and after 1:1 PS matching

Baseline characteristics	Before PS matching			After PS matching		
	SGLT2i (N = 72,900)	GLP-1RA (N = 64,417)	St. Diff.	SGLT2i (N = 45,047)*	GLP-1RA (N = 45,047)*	St. Diff.
Demographics						
Age, mean (SD)	71.98 (5.28)	71.43 (4.94)	0.11	71.56 (5.01)	71.56 (5.03)	0.00
Male, n (%)	35,982 (49.4)	28,044 (43.5)	0.12	20,541 (45.6)	20,720 (46.0)	−0.01
Race/ethnicity, n (%)						
White	58,251 (79.9)	54,125 (84.0)	−0.11	37,588 (83.4)	37,520 (83.3)	0.00
Black	5,281 (7.2)	4,997 (7.8)	−0.02	3,396 (7.5)	3,388 (7.5)	0.00
Asian	3,434 (4.7)	1,433 (2.2)	0.14	1,138 (2.5)	1,177 (2.6)	−0.01
Hispanic	2,601 (3.6)	1,719 (2.7)	0.05	1,284 (2.9)	1,300 (2.9)	0.00
Other	3,333 (4.6)	2,143 (3.3)	0.06	1,641 (3.6)	1,662 (3.7)	−0.01
Burden of comorbidities, mean (SD)						
Combined Comorbidity Score†	2.94 (2.03)	3.45 (2.32)	−0.23	3.16 (2.15)	3.17 (2.15)	0.00
Frailty score (29)	0.18 (0.06)	0.19 (0.06)	−0.17	0.19 (0.06)	0.19 (0.06)	0.00
Diabetes-related conditions, n (%)						
Diabetic nephropathy	6,614 (9.1)	9,850 (15.3)	−0.19	5,132 (11.4)	5,122 (11.4)	0.00
Diabetic retinopathy	7,664 (10.5)	7,888 (12.2)	−0.05	4,966 (11.0)	4,958 (11.0)	0.00
Diabetic neuropathy	17,187 (23.6)	18,251 (28.3)	−0.11	11,721 (26.0)	11,709 (26.0)	0.00
Diabetes with peripheral circulatory disorders	5,841 (8.0)	5,689 (8.8)	−0.03	3,708 (8.2)	3,783 (8.4)	−0.01
Diabetic foot	1,897 (2.6)	2,329 (3.6)	−0.06	1,378 (3.1)	1,393 (3.1)	0.00
Lower-extremity amputation	264 (0.4)	355 (0.6)	−0.03	210 (0.5)	204 (0.5)	0.00
Hypoglycemia	3,529 (4.8)	3,725 (5.8)	−0.04	2,303 (5.1)	2,330 (5.2)	0.00
DKA	244 (0.3)	298 (0.5)	−0.03	157 (0.3)	182 (0.4)	−0.02
Diabetes treatment						
No. of antidiabetes drugs at cohort entry, mean (SD)	2.65 (1.00)	2.49 (0.98)	0.16	2.54 (0.98)	2.53 (0.99)	0.01
No previous use of diabetes treatment, n (%)¶	2,609 (3.6)	2,954 (4.6)	−0.05	1,957 (4.3)	1,939 (4.3)	0.00
Monotherapy, n (%)	2,332 (3.2)	2,663 (4.1)	−0.05	1,768 (3.9)	1,752 (3.9)	0.00
Long-term use of insulin, n (%)§	5,969 (8.2)	9,620 (14.9)	−0.21	5,201 (11.5)	5,257 (11.7)	−0.01
Diabetes drug on the day of entry to the cohort, n (%)						
Metformin	46,049 (63.2)	34,419 (53.4)	0.20	26,190 (58.1)	26,086 (57.9)	0.00
Sulfonylureas	29,266 (40.1)	23,039 (35.8)	0.09	16,839 (37.4)	16,725 (37.1)	0.01
DPP-4 inhibitors	24,783 (34.0)	13,425 (20.8)	0.30	10,923 (24.2)	11,004 (24.4)	0.00
Glitazones	5,846 (8.0)	4,853 (7.5)	0.02	3,491 (7.7)	3,518 (7.8)	0.00
Insulin	12,742 (17.5)	18,853 (29.3)	−0.28	10,847 (24.1)	10,741 (23.8)	0.01
Lifestyle factors, n (%)						
Obesity	17,621 (24.2)	21,980 (34.1)	−0.22	13,436 (29.8)	13,414 (29.8)	0.00
Overweight	3,812 (5.2)	2,822 (4.4)	0.04	2,111 (4.7)	2,124 (4.7)	0.00
Smoking	11,579 (15.9)	11,207 (17.4)	−0.04	7,721 (17.1)	7,692 (17.1)	0.00
Other comorbidities at baseline, n (%)			0.00			
CVD‖	31,888 (43.7)	30,563 (47.4)	−0.07	20,366 (45.2)	20,385 (45.3)	0.00
Ischemic heart disease	23,018 (31.6)	22,084 (34.3)	−0.06	14,763 (32.8)	14,729 (32.7)	0.00
Acute myocardial infarction	1,126 (1.5)	1,098 (1.7)	−0.02	712 (1.6)	740 (1.6)	0.00
Coronary revascularization	587 (0.8)	650 (1.0)	−0.02	395 (0.9)	403 (0.9)	0.00
Heart failure	7,082 (9.7)	8,801 (13.7)	−0.12	5,144 (11.4)	5,170 (11.5)	0.00
Atrial fibrillation	7,353 (10.1)	7,398 (11.5)	−0.05	4,861 (10.8)	4,911 (10.9)	0.00
Ischemic or hemorrhagic stroke	8,145 (11.2)	7,549 (11.7)	−0.02	5,138 (11.4)	5,114 (11.4)	0.00
Transient ischemic attack	1,787 (2.5)	1,666 (2.6)	−0.01	1,138 (2.5)	1,163 (2.6)	−0.01
Peripheral arterial disease or surgery	9,041 (12.4)	8,811 (13.7)	−0.04	5,736 (12.7)	5,808 (12.9)	−0.01
Hypertension	66,311 (91.0)	59,585 (92.5)	−0.05	41,326 (91.7)	41,323 (91.7)	0.00
Hyperlipidemia	65,426 (89.7)	58,092 (90.2)	−0.02	40,488 (89.9)	40,413 (89.7)	0.01
Chronic obstructive pulmonary disease	8,524 (11.7)	9,187 (14.3)	−0.08	5,848 (13.0)	5,883 (13.1)	0.00
Pneumonia	2,614 (3.6)	2,902 (4.5)	−0.05	1,823 (4.0)	1,824 (4.0)	0.00
Obstructive sleep apnea	8,084 (11.1)	10,876 (16.9)	−0.17	6,416 (14.2)	6,453 (14.3)	0.00
Osteoarthritis	21,613 (29.6)	21,292 (33.1)	−0.08	14,256 (31.6)	14,227 (31.6)	0.00
Chronic kidney disease	9,037 (12.4)	14,729 (22.9)	−0.28	7,294 (16.2)	7,437 (16.5)	−0.01
Chronic kidney disease, stage 3+	5,303 (7.3)	10,773 (16.7)	−0.29	4,753 (10.6)	4,784 (10.6)	0.00
AKI	1,994 (2.7)	3,281 (5.1)	−0.12	1,603 (3.6)	1,636 (3.6)	0.00
Edema‡	8,391 (11.5)	10,311 (16.0)	−0.13	6,160 (13.7)	6,140 (13.6)	0.00

Table 1—Continued

	Before PS matching			After PS matching		
Baseline characteristics	SGLT2i (N = 72,900)	GLP-1RA (N = 64,417)	St. Diff.	SGLT2i (N = 45,047)*	GLP-1RA (N = 45,047)*	St. Diff.
Fractures	3,275 (4.5)	3,369 (5.2)	−0.03	2,254 (5.0)	2,233 (5.0)	0.00
Falls	3,067 (4.2)	3,246 (5.0)	−0.04	2,135 (4.7)	2,110 (4.7)	0.00
Osteoporosis	7,303 (10.0)	6,151 (9.5)	0.02	4,240 (9.4)	4,248 (9.4)	0.00
Genital infections	2,223 (3.0)	2,128 (3.3)	−0.02	1,452 (3.2)	1,477 (3.3)	−0.01
UTIs	11,375 (15.6)	12,191 (18.9)	−0.09	7,780 (17.3)	7,723 (17.1)	0.01
Dementia	3,341 (4.6)	2,987 (4.6)	0.00	2,088 (4.6)	2,025 (4.5)	0.00
Other medication use, n (%)						
ACE inhibitors	33,901 (46.5)	30,726 (47.7)	−0.02	21,199 (47.1)	21,233 (47.1)	0.00
Angiotensin II receptor blockers	27,012 (37.1)	24,298 (37.7)	−0.01	16,850 (37.4)	16,789 (37.3)	0.00
β-Blockers	34,537 (47.4)	32,856 (51.0)	−0.07	22,216 (49.3)	22,153 (49.2)	0.00
Calcium channel blockers	24,372 (33.4)	22,530 (35.0)	−0.03	15,368 (34.1)	15,335 (34.0)	0.00
Thiazides	10,890 (14.9)	11,390 (17.7)	−0.08	7,439 (16.5)	7,463 (16.6)	0.00
Loop diuretics	12,008 (16.5)	16,050 (24.9)	−0.21	9,146 (20.3)	9,241 (20.5)	0.00
Other diuretics	2,532 (3.5)	3,496 (5.4)	−0.09	1,970 (4.4)	2,024 (4.5)	0.00
Nitrates	6,163 (8.5)	6,430 (10.0)	−0.05	4,053 (9.0)	4,145 (9.2)	−0.01
Digoxin	2,027 (2.8)	1,768 (2.7)	0.01	1,214 (2.7)	1,206 (2.7)	0.00
Statins	56,268 (77.2)	50,333 (78.1)	−0.02	34,874 (77.4)	34,877 (77.4)	0.00
Antiplatelets	12,197 (16.7)	11,104 (17.2)	−0.01	7,476 (16.6)	7,542 (16.7)	0.00
Anticoagulants	6,063 (8.3)	6,399 (9.9)	−0.06	4,137 (9.2)	4,159 (9.2)	0.00
Oral corticosteroids	19,502 (26.8)	18,269 (28.4)	−0.04	12,463 (27.7)	12,434 (27.6)	0.00
Bisphosphonates	2,971 (4.1)	2,267 (3.5)	0.03	1,589 (3.5)	1,586 (3.5)	0.00
Antibiotics targeting UTIs	20,633 (28.3)	20,628 (32.0)	−0.08	13,699 (30.4)	13,711 (30.4)	0.00
Opioids	23,530 (32.3)	25,056 (38.9)	−0.14	16,301 (36.2)	16,305 (36.2)	0.00
Benzodiazepines	10,203 (14.0)	9,803 (15.2)	−0.03	6,746 (15.0)	6,747 (15.0)	0.00
Measures of health care use						
Hospitalization within prior 30 days, n (%)	717 (1.0)	812 (1.3)	−0.03	501 (1.1)	491 (1.1)	0.00
Hospitalization during prior 31–365 days, n (%)	6,842 (9.4)	7,762 (12.0)	−0.08	4,771 (10.6)	4,768 (10.6)	0.00
No. of hospital days, mean (SD)	0.67 (3.05)	0.91 (3.60)	−0.07	0.77 (3.37)	0.78 (3.43)	0.00
No. of emergency department visits, mean (SD)	0.71 (1.78)	0.86 (1.94)	−0.08	0.79 (1.85)	0.79 (1.86)	0.00
No. of office visits, mean (SD)	10.72 (7.60)	12.16 (8.36)	−0.18	11.36 (7.90)	11.36 (7.75)	0.00
Endocrinologist visit within prior 30 days, n (%)	8,789 (12.1)	11,963 (18.6)	−0.18	6,840 (15.2)	6,829 (15.2)	0.00
Endocrinologist visit during prior 31–365 days, n (%)	10,873 (14.9)	12,883 (20.0)	−0.13	7,891 (17.5)	7,875 (17.5)	0.00
Cardiologist visit within prior 30 days, n (%)	7,051 (9.7)	6,869 (10.7)	−0.03	4,486 (10.0)	4,563 (10.1)	0.00
Cardiologist visit during prior 31–365 days, n (%)	27,931 (38.3)	27,491 (42.7)	−0.09	18,155 (40.3)	18,210 (40.4)	0.00
No. of electrocardiograms, mean (SD)	1.13 (1.91)	1.27 (2.11)	−0.07	1.19 (1.98)	1.19 (2.03)	0.00
Echocardiogram, n (%)	15,297 (21.0)	15,410 (23.9)	−0.07	9,995 (22.2)	10,044 (22.3)	0.00
Number of distinct prescriptions, mean (SD)	13.35 (6.03)	14.73 (6.25)	−0.22	14.04 (6.24)	14.04 (5.94)	0.00
No. of HbA$_{1c}$ tests ordered, mean (SD)	2.81 (1.36)	2.89 (1.42)	−0.06	2.85 (1.37)	2.84 (1.37)	0.01

DPP-4, dipeptidyl peptidase 4; HbA$_{1c}$, hemoglobin A$_{1c}$; St. Diff, standardized differences, i.e., the difference in means or proportions divided by the pooled SD (30). *Canagliflozin, 76.9%; dapagliflozin, 13.1%; empagliflozin, 11.1%; liraglutide, 58.7%; exenatide, 23.5%; dulaglutide, 14.8%; albiglutide, 3.0%. †Gagne et al. (32). ¶Defined as patients without any use of glucose-lowering medications during the 12 months prior to cohort entry. §Based on ICD coding. ‖Defined as history of myocardial infarction, unstable angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral arterial disease or surgery, or lower-extremity amputation. ‡Localized, generalized, or unspecified edema.

corresponding to 7.1 fewer events in 1,000 person-years.

Sensitivity and Subgroup Analyses
Primary and secondary findings remained consistent when we carried forward the exposure to the first-used medication for 365 days without considering drug discontinuation or switching (Supplementary Table 7).

Subgroup analyses by history of CVD showed results consistent with the primary MACE findings, though there was evidence of effect heterogeneity on both the relative and the absolute scale (Fig. 2). The initiation of SGLT2i versus GLP-1RA was associated with a similar relative risk reduction in HHF across the two subgroups, whereas a larger absolute risk reduction (corresponding to 5.9 fewer events in 1,000 person-years) was observed among patients with CVD (Fig. 1C–F and Fig. 2). In assessment of selected secondary outcomes, SGLT2i versus GLP-1RA

Table 2—Number of events, person-time, and incidence rates for cardiovascular effectiveness outcomes in 1:1 PS-matched initiators of SGLT2i versus GLP-1RA

	SGLT2i (N = 45,047)	GLP-1RA (N = 45,047)	SGLT2i vs. GLP-1RA	
			HR (95% CI)	RD/1,000 PY (95% CI)
Primary outcomes				
MACE*	597 (17.99)	553 (18.37)	0.98 (0.87, 1.10)	−0.38 (−2.48, 1.72)
HHF	234 (7.02)	309 (10.25)	0.68 (0.57, 0.80)	−3.23 (−4.68, −1.77)
Secondary effectiveness outcomes				
MI	301 (9.05)	277 (9.18)	0.98 (0.84, 1.16)	−0.14 (−1.63, 1.35)
Ischemic or hemorrhagic stroke	214 (6.43)	187 (6.19)	1.04 (0.86, 1.27)	0.24 (−1.00, 1.47)
Cardiovascular mortality	115 (3.44)	124 (4.10)	0.83 (0.64, 1.07)	−0.65 (−1.61, 0.30)
All-cause mortality	310 (9.28)	293 (9.68)	0.95 (0.81, 1.11)	−0.40 (−1.91, 1.12)
MACE or HHF†	803 (24.24)	820 (27.33)	0.89 (0.80, 0.98)	−3.09 (−5.60, −0.58)
MI, stroke, HHF, or all-cause mortality	985 (29.74)	970 (32.33)	0.92 (0.84, 1.002)	−2.59 (−5.35, 0.16)

Data are N events (incidence rate/1,000 person-years) unless otherwise indicated. MI, myocardial infarction; PY, person-years. *Hospitalization for myocardial infarction, ischemic or hemorrhagic stroke, or cardiovascular mortality. †Hospitalization for myocardial infarction, ischemic or hemorrhagic stroke, cardiovascular mortality, or HHF.

initiation appeared to have greater benefits with respect to the risk of cardiovascular death (HR 0.67 [95% CI 0.50, 0.90]; RD −2.59 [95% CI −4.50, −0.68]) and all-cause mortality (HR 0.82 [95% CI 0.68, 0.99]; RD −2.79 [95% CI −5.61, 0.03]) among patients with CVD, whereas no difference in risk of these outcomes was noted between the two agents among patients without CVD. Results from subgroup analyses by age, history of chronic kidney disease, and presence of metformin at cohort entry were consistent with primary findings and did not show effect heterogeneity on either the relative or the absolute scale (Supplementary Fig. 3).

CONCLUSIONS

In a large population-based cohort study of ~90,000 older adults with T2D in the U.S. with mean age of 72 years, we found similar risk of MACE, and a 32% decreased risk of HHF, among SGLT2i initiators compared with GLP-1RA initiators. SGLT2i initiation was associated with a 46% increased risk of DKA, a 44% increased risk of amputations, and a 3.3-fold increased risk of genital infections, corresponding to 0.7, 0.9, and 57.1 more cases per 1,000 person-years. Conversely, SGLT2i initiators had a 15% decreased risk of AKI (7.1 fewer events per 1,000 person-years) and no difference in the risks of fractures or severe UTI.

We observed some evidence of heterogeneity in the comparative effectiveness of SGLT2i versus GLP-1RA depending on the presence of baseline C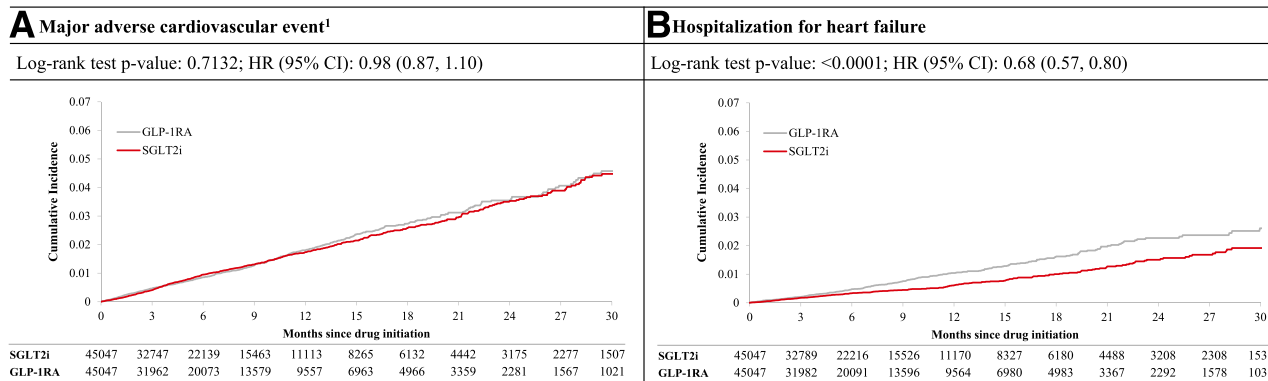VD. Among patients with history of CVD, the initiation of SGLT2i was associated with reductions in the risk of HHF (5.9 fewer events per 1,000 person-years), cardiovascular death (2.6 fewer events per 1,000 person-years), and all-cause mortality (2.8 fewer events per 1,000 person-years) compared with GLP-1RA. Among those without history of CVD, SGLT2i versus GLP-1RA initiation produced reductions in HHF, though with a benefit of substantially lower magnitude (1.1 fewer events per 1,000 person-years) and no benefit in the risk of the other effectiveness outcomes.

This study complements available information from published CVOTs (4–11), including two recent meta-analyses of trials evaluating SGLT2i and GLP-1RA, showing a more marked benefit of SGLT2i in prevention of HHF (33,34). Our study focuses on routinely treated patients on average 10 years older than the patients included in these trials, providing information on a subset of the population with diabetes underrepresented in CVOTs. It includes patients across a broader spectrum of CVDs at baseline, allowing for the exploration of drug effectiveness among patients with and without established CVD. Our study identifies a population of patients 5 to 10 times larger than the populations included in trials, allowing for the investigation of adverse events associated with the use of these classes of medications with greater precision and in an older population particularly vulnerable to them. Finally, it provides comprehensive information on the comparative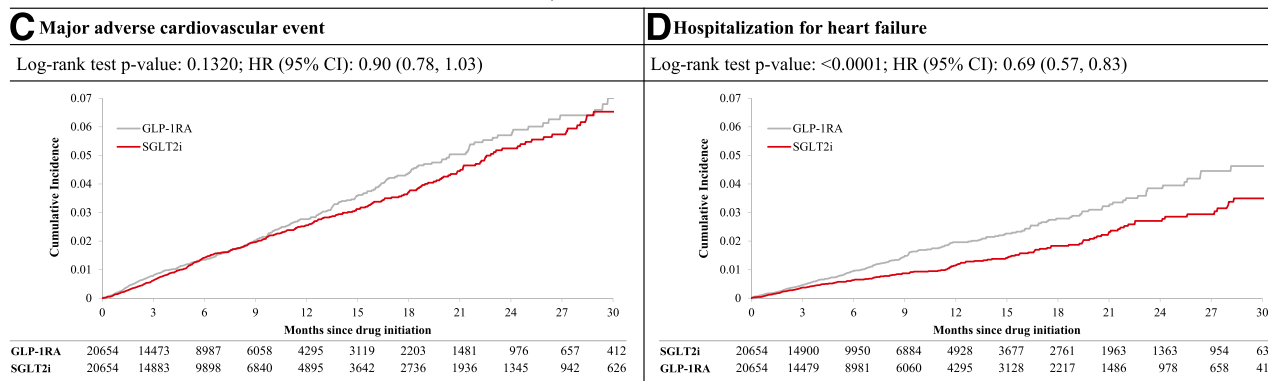 effectiveness and safety of the two drug classes currently recommended among T2D patients with atherosclerotic CVD, heart failure, or chronic kidney disease through a direct contrast of these agents as used in routine care and with use of data collected prior to the large dissemination of the evidence demonstrating their cardiovascular or renal benefits, thus limiting chances of channeling bias.

While a direct comparison of the SGLT2i and GLP-1RA class with regard to cardiovascular effectiveness outcomes and mortality has not been addressed in a population-based investigation, information on their comparative safety has been reported for selected outcomes in previous 1:1 PS-matched analyses involving adult patients (28,35,36). In spite of the difference in mean age between our population and these cohorts (72 vs. 54–61 years), our results for DKA, fractures, LLA, and severe UTI are consistent with the findings from these studies. Two studies recently reported on the association between SGLT2i and LLA (37,38); while the former study confirmed an increased risk of LLA among older canagliflozin initiators with baseline CVD, the latter did not observe an association between SGLT2i and LLA. The lack of an association in the latter investigation may be due to the different representation of canagliflozin in the population of SGLT2i users, the younger age, or the difference in study design, i.e., prevalent new-user design. Nevertheless, our study, which included >45,000 older patients exposed to SGLT2i, allowed us
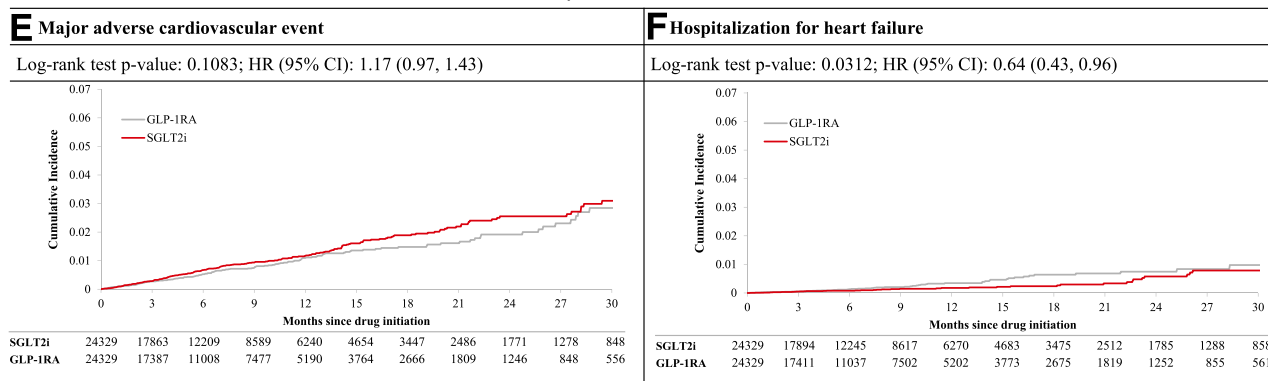
Overall population

A Major adverse cardiovascular event[1]

Log-rank test p-value: 0.7132; HR (95% CI): 0.98 (0.87, 1.10)

B Hospitalization for heart failure

Log-rank test p-value: <0.0001; HR (95% CI): 0.68 (0.57, 0.80)

	0	3	6	9	12	15	18	21	24	27	30
SGLT2i	45047	32747	22139	15463	11113	8265	6132	4442	3175	2277	1507
GLP-1RA	45047	31962	20073	13579	9557	6963	4966	3359	2281	1567	1021

	0	3	6	9	12	15	18	21	24	27	30
SGLT2i	45047	32789	22216	15526	11170	8327	6180	4488	3208	2308	1531
GLP-1RA	45047	31982	20091	13596	9564	6980	4983	3367	2292	1578	1031

History of cardiovascular disease[2]

C Major adverse cardiovascular event

Log-rank test p-value: 0.1320; HR (95% CI): 0.90 (0.78, 1.03)

D Hospitalization for heart failure

Log-rank test p-value: <0.0001; HR (95% CI): 0.69 (0.57, 0.83)

	0	3	6	9	12	15	18	21	24	27	30
GLP-1RA	20654	14473	8987	6058	4295	3119	2203	1481	976	657	412
SGLT2i	20654	14883	9898	6840	4895	3642	2736	1936	1345	942	626

	0	3	6	9	12	15	18	21	24	27	30
SGLT2i	20654	14900	9950	6884	4928	3677	2761	1963	1363	954	634
GLP-1RA	20654	14479	8981	6060	4295	3128	2217	1486	978	658	418

No history of cardiovascular disease

E Major adverse cardiovascular event

Log-rank test p-value: 0.1083; HR (95% CI): 1.17 (0.97, 1.43)

F Hospitalization for heart failure

Log-rank test p-value: 0.0312; HR (95% CI): 0.64 (0.43, 0.96)

	0	3	6	9	12	15	18	21	24	27	30
SGLT2i	24329	17863	12209	8589	6240	4654	3447	2486	1771	1278	848
GLP-1RA	24329	17387	11008	7477	5190	3764	2666	1809	1246	848	556

	0	3	6	9	12	15	18	21	24	27	30
SGLT2i	24329	17894	12245	8617	6270	4683	3475	2512	1785	1288	858
GLP-1RA	24329	17411	11037	7502	5202	3773	2675	1819	1252	855	561

Figure 1—Cumulative incidence for composite cardiovascular outcome and HHF comparing PS-matched SGLT2i vs. GLP-1RA initiators overall and by history of CVD. [1]Hospitalization for myocardial infarction, ischemic or hemorrhagic stroke, or cardiovascular mortality. [2]History of CVD is defined as history of myocardial infarction, unstable angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral arterial disease or surgery, or lower-extremity amputation. Data are *n* unless otherwise indicated.

to quantify the risk of fractures and severe UTI in a vulnerable older population while also reporting precise estimates of the increased risk of DKA and LLA, and a reduction in the risk of AKI, compared with GLP-1RA. Our study also quantified the risk of genital infections among older patients routinely treated with SGLT2i vs. GLP-1RA; while this is an adverse event of lesser severity compared with other safety outcomes, e.g., DKA, its

occurrence may deter patients from continuing SGLT2i therapy despite its potential benefits.

This study has limitations. First, while we balanced 140 baseline characteristics between treatment groups through PS matching, residual confounding by some unmeasured (e.g., hemoglobin A_{1c} level, diabetes duration, BMI, estimated glomerular filtration rate, ejection fraction) or not fully measured (e.g., obesity)

characteristic(s) in claims, cannot be entirely ruled out. However, a previous new-user active comparator cohort study with use of claims data linked to electronic health records showed sufficient balance in many of these characteristics after adjustment for claims-based proxies of diabetes severity and duration (39). Second, due to the limited use of SGLT2i or GLP-1RA agents besides canagliflozin and liraglutide, respectively, in

Table 3—Number of events, person-time, and incidence rates for safety outcomes in 1:1 PS-matched initiators of SGLT2i versus GLP-1RA

Safety outcomes	SGLT2i (N = 45,047)	GLP-1RA (N = 45,047)	SGLT2i vs. GLP-1RA HR (95% CI)	SGLT2i vs. GLP-1RA RD/1,000 PY (95% CI)
DKA	79 (2.37)	50 (1.65)	1.46 (1.02, 2.07)	0.72 (0.02, 1.41)
Bone fracture*	181 (5.43)	175 (5.80)	0.94 (0.76, 1.16)	−0.36 (−1.53, 0.81)
LLA	104 (3.12)	67 (2.22)	1.44 (1.06, 1.96)	0.90 (0.10, 1.70)
GIs	2,623 (82.31)	753 (25.23)	3.34 (3.08, 3.62)	57.08 (53.45, 60.70)
AKI	1,268 (38.49)	1,352 (45.54)	0.85 (0.79, 0.92)	−7.05 (−10.27, −3.83)
Severe UTI†	147 (4.41)	161 (5.33)	0.83 (0.67, 1.04)	−0.92 (−2.01, 0.17)

Data are N events (incidence rate/1,000 person-years) unless otherwise indicated. GIs, genital infections; PY, person-years. *Humerus, wrist, hip, and pelvis fracture. †UTI requiring hospitalization.
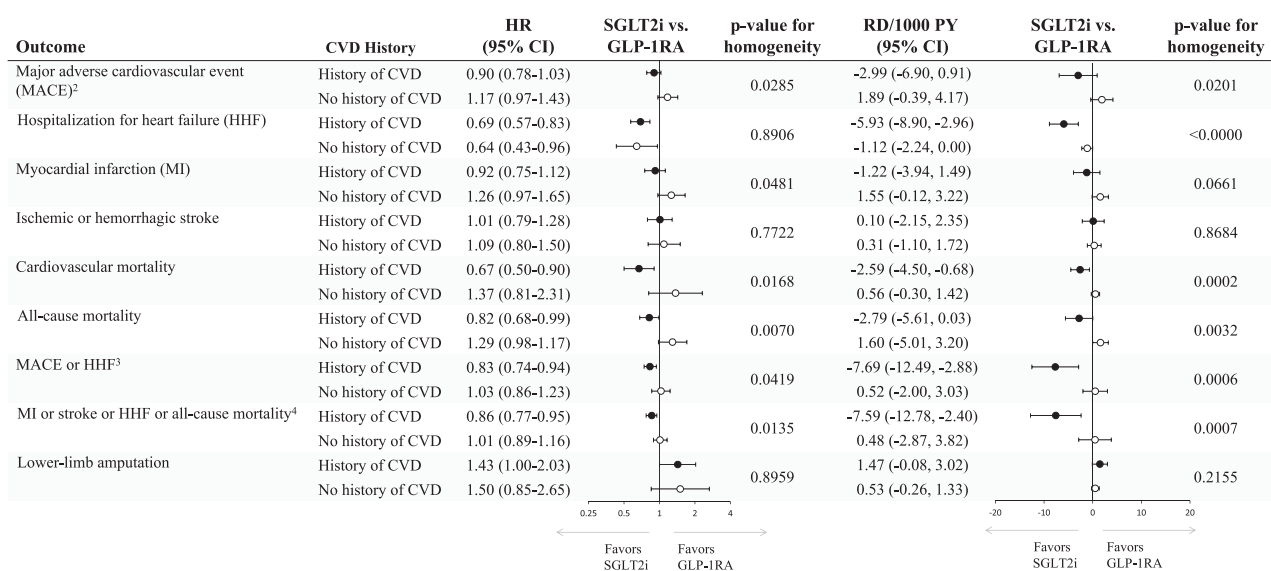
the U.S. during the study period, we were unable to perform a real-world evaluation of the effectiveness and safety of more recently marketed SGLT2i or GLP-1RA agents. Third, as this investigation was based on the use of SGLT2i or GLP-1RA in routine care, the mean study follow-up (i.e., time on treatment) was shorter compared with CVOTs, which have substantial measures in place to improve medication adherence. Randomized controlled trials generally require long follow-up to accumulate sufficient events for powered analyses. The size of our study population (~90,000 patients) allowed us to generate results with high precision, despite a shorter duration of follow-up. Assuming no time-varying hazards, as

confirmed in our analyses, these results should be generalizable to longer-term findings. Nevertheless, long-term clinical trials powered to assess cardiovascular events would be needed to confirm the risk-benefit profile of SGLT2i versus GLP-1RA. Fourth, the current study did not specifically address the safety signals associated with the use of GLP-1RA, including acute pancreatitis and acute gallbladder or biliary disease (40), which may also be taken into consideration in the assessment of the benefit-risk balance of SGLT2i and GLP-1RA. Lastly, our study population did not include older commercially insured or Medicare Advantage patients, who are more likely to have differential socioeconomic

status, medication adherence, and risk factors for outcomes. However, the biological effect of SGLT2i on health outcomes is unlikely to differ by insurance status; thus, our results may generalize to other older populations besides Medicare Fee-for-Service.

Conclusion

Overall, in a large population-based cohort study of ~90,000 older adults with T2D, the initiation of SGLT2i versus GLP-1RA was associated with a similar occurrence of MACE, 3.2 fewer HHF events, 0.7 more DKA, 0.9 more LLA, 57.1 more genital infection, and 7.1 fewer AKI events over 1,000 person-years. SGLT2i appeared to be associated with greater

Outcome	CVD History	HR (95% CI)	SGLT2i vs. GLP-1RA	p-value for homogeneity	RD/1000 PY (95% CI)	SGLT2i vs. GLP-1RA	p-value for homogeneity
Major adverse cardiovascular event (MACE)[2]	History of CVD	0.90 (0.78-1.03)		0.0285	-2.99 (-6.90, 0.91)		0.0201
	No history of CVD	1.17 (0.97-1.43)			1.89 (-0.39, 4.17)		
Hospitalization for heart failure (HHF)	History of CVD	0.69 (0.57-0.83)		0.8906	-5.93 (-8.90, -2.96)		<0.0000
	No history of CVD	0.64 (0.43-0.96)			-1.12 (-2.24, 0.00)		
Myocardial infarction (MI)	History of CVD	0.92 (0.75-1.12)		0.0481	-1.22 (-3.94, 1.49)		0.0661
	No history of CVD	1.26 (0.97-1.65)			1.55 (-0.12, 3.22)		
Ischemic or hemorrhagic stroke	History of CVD	1.01 (0.79-1.28)		0.7722	0.10 (-2.15, 2.35)		0.8684
	No history of CVD	1.09 (0.80-1.50)			0.31 (-1.10, 1.72)		
Cardiovascular mortality	History of CVD	0.67 (0.50-0.90)		0.0168	-2.59 (-4.50, -0.68)		0.0002
	No history of CVD	1.37 (0.81-2.31)			0.56 (-0.30, 1.42)		
All-cause mortality	History of CVD	0.82 (0.68-0.99)		0.0070	-2.79 (-5.61, 0.03)		0.0032
	No history of CVD	1.29 (0.98-1.17)			1.60 (-5.01, 3.20)		
MACE or HHF[3]	History of CVD	0.83 (0.74-0.94)		0.0419	-7.69 (-12.49, -2.88)		0.0006
	No history of CVD	1.03 (0.86-1.23)			0.52 (-2.00, 3.03)		
MI or stroke or HHF or all-cause mortality[4]	History of CVD	0.86 (0.77-0.95)		0.0135	-7.59 (-12.78, -2.40)		0.0007
	No history of CVD	1.01 (0.89-1.16)			0.48 (-2.87, 3.82)		
Lower-limb amputation	History of CVD	1.43 (1.00-2.03)		0.8959	1.47 (-0.08, 3.02)		0.2155
	No history of CVD	1.50 (0.85-2.65)			0.53 (-0.26, 1.33)		

Favors SGLT2i — Favors GLP-1RA

Figure 2—Cardiovascular effectiveness and safety outcomes in subgroups of 1:1 PS-matched initiators of SGLT2i vs. GLP-1RA by history of CVD. History of CVD is defined as history of myocardial infarction, unstable angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral arterial disease or surgery, or lower-extremity amputation. Patients with CVD, 41,308; patients without CVD, 48,658. [2]Hospitalization for myocardial infarction, ischemic or hemorrhagic stroke, or cardiovascular mortality. [3]Hospitalization for myocardial infarction, ischemic or hemorrhagic stroke, cardiovascular mortality, or HHF. [4]Hospitalization for myocardial infarction, ischemic or hemorrhagic stroke, all-cause mortality, or HHF. PY, person-years.

cardiovascular benefit than GLP-1RA among older patients with history of CVD, with less benefit in those without history of CVD.

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