ORIGINAL RESEARCH

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Sodium–Glucose Cotransporter-2 Inhibitors Versus Glucagon-like Peptide-1 Receptor Agonists and the Risk for Cardiovascular Outcomes in Routine Care Patients With Diabetes Across Categories of Cardiovascular Disease

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Background: Both sodium–glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have shown cardiovascular benefits in placebo-controlled trials of patients with type 2 diabetes (T2D) and established cardiovascular disease (CVD).

Objective: To evaluate whether SGLT2 inhibitors and GLP-1 RAs are associated with differential cardiovascular benefit among T2D patients with and without CVD.

Design: Population-based cohort study.

Setting: Medicare and 2 U.S. commercial claims data sets (April 2013 to December 2017).

Participants: 1:1 propensity score–matched adult T2D patients with and without CVD (52 901 and 133 139 matched pairs) initiating SGLT2 inhibitor versus GLP-1 RA therapy.

Measurements: Primary outcomes were myocardial infarction (MI) or stroke hospitalization and hospitalization for heart failure (HHF). Pooled hazard ratios (HRs) and rate differences (RDs) per 1000 person-years were estimated, with 95% CIs, controlling for 138 preexposure covariates.

Results: The initiation of SGLT2 inhibitor versus GLP-1 RA therapy was associated with a slightly lower risk for MI or stroke in patients with CVD (HR, 0.90 [95% CI, 0.82 to 0.98]; RD, −2.47 [CI, −4.45 to −0.50]) but similar risk in those without CVD (HR, 1.07 [CI, 0.97 to 1.18]; RD, 0.38 [CI, −0.30 to 1.07]). The initiation of SGLT2 inhibitor versus GLP-1 RA therapy was associated with reductions in HHF risk regardless of baseline CVD in patients with CVD (HR, 0.71 [CI, 0.64 to 0.79]; RD, −4.97 [CI, −6.55 to −3.39]) and in those without CVD (HR, 0.69 [CI, 0.56 to 0.85]; RD, −0.58 [CI, −0.91 to −0.25]).

Limitation: Treatment selection was not randomized.

Conclusion: Use of SGLT2 inhibitors versus GLP-1 RAs was associated with consistent reductions in HHF risk among T2D patients with and without CVD, although the absolute benefit was greater in patients with CVD. There were no large differences in risk for MI or stroke among T2D patients with and without CVD.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes (T2D), and patients with T2D are at substantially elevated risk for heart failure (1–5). Although there are promising data suggesting that CVD-related morbidity and mortality from diabetes are improving, these trends lag reductions seen in patients without diabetes (2, 6). Large cardiovascular outcome trials have provided evidence that 2 classes of glucose-lowering medications—glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium–glucose cotransporter-2 (SGLT2) inhibitors—can lead to clinically important reductions in myocardial infarction (MI), stroke, hospitalization for heart failure (HHF), and cardiovascular death (7–15).

A recent meta-analysis of placebo-controlled cardiovascular outcome trials reported that GLP-1 RAs reduced the risk for major adverse cardiovascular events (MACE), a composite of MI, stroke, and cardiovascular death, by 12% (hazard ratio [HR], 0.88 [95% CI, 0.82 to 0.94]) (16). A similar reduction in MACE of 11% was seen in another meta-analysis of placebo-controlled cardiovascular outcome trials on SGLT2 inhibitors (HR, 0.89 [CI, 0.83 to 0.96]) (17). Those same meta-analyses reported a more substantial reduction in the risk for HHF with SGLT2 inhibitors (HR, 0.69 [CI, 0.61 to 0.79]) than with GLP-1 RAs (HR, 0.91 [CI, 0.83 to 0.99]) (16, 17). Current guidelines recommend that physicians consider either SGLT2 inhibitors or GLP-1 RAs as therapies for patients with diabetes and atherosclerotic CVD and recommend SGLT2 inhibitors for patients with a history of heart failure (4, 18, 19). However, the lack of randomized trials directly comparing GLP-1 RAs with SGLT2 inhibitors for cardiovascular

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event prevention in patients with T2D means that clinicians and patients have to decide which drug to use without any studies comparing the 2 classes.

To address this lack of evidence, we sought to use real-world data to assess the relative benefits of SGLT2 inhibitors and GLP-1 RAs in routine care populations. Our primary objective was to do a head-to-head comparison of SGLT2 inhibitors versus GLP-1 RAs with regard to the risk for MACE and HHF, accounting for baseline CVD, in a population-based cohort of patients with T2D.

Methods

Data Source

Data were collected from 2 commercial U.S. health insurance data sets (Optum's deidentified Clinformatics Data Mart database and IBM MarketScan database) and Medicare fee-for-service Parts A, B, and D. (For information on the data sources, see the Data Sources section in the **Supplement**, available at Annals.org.)

The institutional review board of Mass General Brigham approved the study (#2011P002580). A licensing agreement was in place.

Study Population and Exposure Definition

The study population included patients aged 18 years or older in Optum and MarketScan and patients aged 66 years or older in Medicare fee-for-service who initiated treatment with a SGLT2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin) or a GLP-1 RA (albiglutide, dulaglutide, exenatide, or liraglutide) between 1 April 2013 (consistent with the release of the first SGLT2 inhibitor in the United States) and 31 December 2017. Cohort entry was the day of the first filled prescription of any of the drugs above, defined as no use of either a SGLT2 inhibitor or GLP-1 RA in the previous year among patients who had 12 or more months of continuous enrollment before cohort entry. Patients who started treatment with a SGLT2 inhibitor or GLP-1 RA on the date of cohort entry were excluded. A recorded diagnosis of T2D was required during the year before drug initiation. Patients were excluded if they had a diagnosis of type 1 or secondary diabetes, cancer, end-stage renal disease or renal replacement therapy, HIV, solid 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 MI, coronary revascularization, unstable angina, ischemic or hemorrhagic stroke, transient ischemic attack, and heart failure in the 60 days before cohort entry (**Supplement Table 1** and **Appendix Figure**, available at Annals.org). Within the overall study population, we identified patients with and without baseline CVD, defined as a diagnosis of MI, angina, coronary atherosclerosis or other forms of chronic ischemic heart disease, coronary procedure, congestive heart failure, ischemic stroke, peripheral artery disease or surgery, or lower extremity amputation, recorded in the 12 months before cohort entry.

Follow-up for study outcomes began on the day after cohort entry and continued in an "as-treated" approach until treatment discontinuation, switch to or augmentation with 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 2017), whichever came first. We extended the exposure effect window until 90 days after the expiration of the last prescription's supply (20).

Study Outcomes

The primary outcomes included a composite cardiovascular outcome—that is, hospitalization for acute MI or ischemic or hemorrhagic stroke and HHF. In prior studies, the positive predictive values of claims-based algorithms for MI, stroke, and HHF were at least 84% (21–24). Secondary outcomes were MI; ischemic or hemorrhagic stroke; all-cause mortality; and a composite outcome of MI, ischemic or hemorrhagic stroke, or all-cause mortality (see **Supplement Table 2** for definitions, available at Annals.org).

Patient Characteristics

Baseline patient characteristics were measured during the 12 months before and including the date of cohort entry. Covariates of interest included demographic characteristics (age, sex, and race), census region (Northeast, Midwest, South, and West), calendar time (in quarters), 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 measured a claims-based frailty index (25). Patient characteristics were defined using International Classification of Diseases, Ninth Revision or 10th Revision diagnosis or procedure codes; CPT (Current Procedural Terminology), 4th edition codes; and pharmacy National Drug Codes. Laboratory test results, which were available for approximately 13% of the population, were also measured at baseline. The complete list of baseline patient characteristics is reported in **Supplement Tables 3** to **5** (available at Annals.org).

Statistical Analysis

Analyses were stratified by subgroup of patients with and without CVD and in the overall population. Baseline characteristics were compared by treatment group. To control for confounding, we calculated an exposure propensity score (PS), separately in each CVD stratum, as the predicted probability of receiving treatment with a SGLT2 inhibitor versus a GLP-1 RA, conditional on 138 baseline characteristics using a multivariable logistic regression model (26). All prespecified variables were included in the PS model, and no further selection was done (**Supplement Tables 6** and **7**, available at Annals.org). Because laboratory test results were available only for a subset of the population, they were not included in the PS model. Within each CVD stratum, patients were 1:1 PS matched using the nearest neighbor method with a maximum caliper of 0.01 of the PS (27). Postmatching covariate balance between treatments was assessed by the calculation of standardized differences for each covariate, with meaningful imbalances set at values greater than 0.1 (28). The balance in laboratory test results in the population subset with this information available was also inspected after PS matching to assess the potential

for residual confounding by unmeasured factors not included in the PS model. For all outcomes, we calculated PS-matched numbers of events and incidence rates as well as HRs using Cox proportional hazards models and rate differences (RDs), each with 95% CIs. The HRs and RDs with their 95% CIs were estimated in each data source and pooled across the data sources using a fixed-effects meta-analysis because random-effects pooling can be biased in the context of few databases (29). The presence of effect measure modification across the 2 categories of baseline CVD was evaluated on the relative and absolute risk scale using the Wald test for homogeneity (30). For primary end points, we also obtained cumulative incidence function plots and compared cumulative incidence of outcomes between treatment groups with the Gray nonparametric test to account for competing risk for death.

We conducted sensitivity analyses to test the robustness of the primary findings. To assess potential exposure misclassification, we extended the exposure effect window until 60 days after the expiration of the last prescription's supply. To address potential informative censoring, we carried forward the exposure to the first-used medication for 183 or 365 days without considering drug treatment discontinuation or switching, mimicking an "intention-to-treat" approach (31). To explore the presence of potential residual confounding due to geographic variation in clinical care, we reestimated the PS, replacing the 4 census regions of the primary analysis with 50 states and 1 federal district. Finally, to assess the presence of potential unmeasured confounding, we assessed the association of SGLT2 inhibitors with other outcomes shown previously to be related or expected to be unrelated to this drug. Specifically, we assessed the risk for diabetic ketoacidosis, for which we expected an increased risk associated with the initiation of SGLT2 inhibitors (32), and the risk for herpes zoster virus reactivation, for which we expected a null finding (see **Supplement Table 2** for definitions).

All analyses were done using Aetion Evidence Platform, version 4.10, with R, version 3.2 (R Foundation for Statistical Computing) (33), and SAS, version 9.4 (SAS Institute).

Role of the Funding Source

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

RESULTS

Study Cohort and Patient Characteristics

The overall study population included 156 825 patients with baseline CVD (82 625 patients initiating SGLT2 inhibitor therapy and 74 200 initiating GLP-1 RA therapy) and 400 284 patients without baseline CVD (227 792 patients initiating SGLT2 inhibitor therapy and 172 492 initiating GLP-1 RA therapy), for a total of 557 109 patients (310 417 patients initiating SGLT2 inhibitor therapy and 246 692 initiating GLP-1 RA therapy) (**Appendix Figure**). After 1:1 PS matching stratified by baseline CVD status, we identified 105 802 patients with baseline CVD and 266 278 without baseline CVD, for a total of 372 080 patients initiating SGLT2 inhibitor or GLP-1 RA therapy (**Table 1**).

Although reasonably well balanced in baseline patient characteristics compared with patients receiving a GLP-1 RA before PS matching, patients receiving a SGLT2 inhibitor were less frequently female and had a slightly lower burden of comorbidities, as measured by the combined comorbidity score (34) (**Supplement Tables 3** to **5**). They were less likely to have diabetes-related complications (nephropathy, neuropathy, and retinopathy) and history of chronic kidney disease, to use insulin at baseline, or to have seen an endocrinologist, and they were more likely to be on baseline treatment with metformin and dipeptidyl peptidase-4 inhibitors. All differences in patient characteristics were well balanced after PS matching. Laboratory results, which were available in a subset of the population and therefore not included in the PS adjustment, were also balanced. The average age in the overall population was 61 years (67 and 58 years in patients with and without CVD, respectively) and 51% of study participants were female (44% and 54% in patients with and without CVD, respectively); 28% had a history of CVD, 61% received metformin on the day of cohort entry (57% and 63% in patients with and without CVD, respectively), and 21% received insulin (27% and 19% in patients with and without CVD, respectively) during the previous year (**Table 1** and **Supplement Tables 3** to **5**). Canagliflozin and liraglutide were the most frequently initiated agents within the SGLT2 inhibitor and GLP-1 RA classes (approximately 60% and 50%, respectively) (**Supplement Table 8**, available at Annals.org).

After PS matching, the median follow-up time on treatment was approximately 7 months for both exposure groups. More than 100 000 patients had greater than 1-year follow-up (more than 25 000 with CVD and more than 5000 without CVD) and more than 35 000 had greater than 2-year follow-up (more than 9000 with CVD and more than 25 000 without CVD). Most patients were censored due to treatment discontinuation (approximately 40% to 45%) or end of the study period, that is 31 December 2017 (approximately 30%) (**Supplement Table 9**, available at Annals.org).

Absolute and Relative Risks of Primary and Secondary Outcomes

After PS matching, we identified 21.3 versus 23.8 events per 1000 person-years for the composite cardiovascular outcome of hospitalization for MI or stroke in patients with CVD receiving a SGLT2 inhibitor versus a GLP-1 RA (HR, 0.90 [CI, 0.82 to 0.98]; RD, −2.47 [CI, −4.45 to −0.50] per 1000 person-years) and 7.2 versus 6.8 events in patients without CVD (HR, 1.07 [CI, 0.97 to 1.18]; RD, 0.38 [CI, −0.30 to 1.07] per 1000 person-years), with evidence of effect heterogeneity on both the relative and the absolute scale (**Table 2**). For the HHF outcome, there were 12.0 versus 16.9 events per 1000 person-years in patients with CVD receiving a SGLT2 inhibitor versus a GLP-1 RA (HR, 0.71 [CI, 0.64 to 0.79]; RD,

Table 1. Selected Baseline Characteristics of Patients Initiating SGLT2 Inhibitor Versus GLP-1 RA Therapy After 1:1 Propensity Score Matching

Baseline Characteristics	History of CVD*			No History of CVD			Overall Population		
	SGLT2 Inhibitor (*n* = 52 901)	GLP-1 RA (*n* = 52 901)	Standardized Difference	SGLT2 Inhibitor (*n* = 133 139)	GLP-1 RA (*n* = 133 139)	Standardized Difference	SGLT2 Inhibitor (*n* = 186 040)	GLP-1 RA (*n* = 186 040)	Standardized Difference
Demographic characteristics									
Mean age (SD), *y*	67.43 (9.49)	67.44 (9.50)	0.00	58.09 (11.89)	58.11 (11.89)	0.00	60.74 (12.02)	60.76 (12.03)	0.00
Female, *n* (%)	23 221 (43.9)	23 182 (43.8)	0.00	72 052 (54.1)	71 772 (53.9)	0.00	95 273 (51.2)	94 954 (51.0)	0.00
Race/ethnicity, *n* (%)†									
White	30 703 (78.5)	30 664 (78.4)	0.00	47 811 (73.2)	47 513 (72.8)	0.01	78 514 (75.2)	78 177 (74.9)	0.01
Black	3317 (8.5)	3294 (8.4)	0.00	6664 (10.2)	6713 (10.3)	0.00	9981 (9.6)	10 007 (9.6)	0.00
Asian	1024 (2.6)	1082 (2.8)	−0.01	1849 (2.8)	1887 (2.9)	−0.01	2873 (2.8)	2969 (2.8)	0.00
Hispanic	2310 (5.9)	2270 (5.8)	0.00	6030 (9.2)	6144 (9.4)	−0.01	8340 (8.0)	8414 (8.1)	0.00
Other	1738 (4.4)	1782 (4.6)	−0.01	2942 (4.5)	3039 (4.7)	−0.01	4680 (4.5)	4821 (4.6)	0.00
Burden of comorbidities									
Mean combined comorbidity score (SD)	1.87 (2.15)	1.87 (2.13)	0.00	0.36 (1.22)	0.36 (1.21)	0.00	0.79 (1.69)	0.79 (1.67)	0.00
Mean frailty score (SD)	0.20 (0.06)	0.20 (0.06)	0.00	0.14 (0.04)	0.14 (0.04)	0.00	0.16 (0.05)	0.16 (0.05)	0.00
Diabetes-related conditions, *n* (%)									
Diabetic nephropathy	7658 (14.5)	7654 (14.5)	0.00	10 217 (7.7)	10 171 (7.6)	0.00	17 875 (9.6)	17 825 (9.6)	0.00
Diabetic retinopathy	7122 (13.5)	7122 (13.5)	0.00	9792 (7.4)	9859 (7.4)	0.00	16 914 (9.1)	16 981 (9.1)	0.00
Diabetic neuropathy	16 179 (30.6)	16 178 (30.6)	0.00	19 916 (15.0)	19 937 (15.0)	0.00	36 095 (19.4)	36 115 (19.4)	0.00
Diabetes with peripheral circulatory disorders	3303 (6.2)	3276 (6.2)	0.00	1817 (1.4)	1797 (1.3)	0.01	5120 (2.8)	5073 (2.7)	0.01
Diabetic foot	2378 (4.5)	2360 (4.5)	0.00	1635 (1.2)	1626 (1.2)	0.00	4013 (2.2)	3986 (2.1)	0.01
Lower extremity amputation	642 (1.2)	634 (1.2)	0.00	0 (0.0)	0 (0.0)	-	642 (0.3)	634 (0.3)	0.00
Hypoglycemia	5607 (10.6)	5581 (10.5)	0.00	8138 (6.1)	8147 (6.1)	0.00	13 745 (7.4)	13 728 (7.4)	0.00
Hyperglycemia	18 020 (34.1)	17 915 (33.9)	0.00	40 528 (30.4)	40 078 (30.1)	0.01	58 548 (31.5)	57 993 (31.2)	0.01
Diabetic ketoacidosis	280 (0.5)	281 (0.5)	0.00	451 (0.3)	451 (0.3)	0.00	731 (0.4)	732 (0.4)	0.00
Diabetes treatment									
Mean antidiabetic drugs at cohort entry (SD), *n*	2.49 (0.98)	2.49 (0.99)	0.00	2.40 (0.97)	2.40 (0.98)	0.00	2.43 (0.98)	2.43 (0.98)	0.00
No previous use of diabetes treatment, *n* (%)‡	2567 (4.9)	2591 (4.9)	0.00	8665 (6.5)	8726 (6.6)	0.00	11 232 (6.0)	11 317 (6.1)	0.00

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Table 1–Continued

Baseline Characteristics	History of CVD*			No History of CVD			Overall Population		
	SGLT2 Inhibitor (*n* = 52 901)	GLP-1 RA (*n* = 52 901)	Standardized Difference	SGLT2 Inhibitor (*n* = 133 139)	GLP-1 RA (*n* = 133 139)	Standardized Difference	SGLT2 Inhibitor (*n* = 186 040)	GLP-1 RA (*n* = 186 040)	Standardized Difference
Monotherapy, *n* (%)	2203 (4.2)	2183 (4.1)	0.01	6708 (5.0)	6613 (5.0)	0.00	8911 (4.8)	8796 (4.7)	0.00
Long-term use of insulin, *n* (%)§	8357 (15.8)	8432 (15.9)	0.00	10 018 (7.5)	10 069 (7.6)	0.00	18 375 (9.9)	18 501 (9.9)	0.00
Diabetes drug on the day of entry to the cohort, *n* (%)									
Metformin	29 977 (56.7)	30 019 (56.7)	0.00	83 625 (62.8)	83 632 (62.8)	0.00	113 602 (61.1)	113 651 (61.1)	0.00
Sulfonylureas	17 864 (33.8)	17 831 (33.7)	0.00	39 892 (30.0)	39 748 (29.9)	0.00	57 756 (31.0)	57 579 (30.9)	0.00
Dipeptidyl peptidase-4 inhibitors	12 190 (23.0)	12 425 (23.5)	−0.01	26 639 (20.0)	26 751 (20.1)	0.00	38 829 (20.9)	39 176 (21.1)	0.00
Glitazones	3556 (6.7)	3505 (6.6)	0.00	9251 (6.9)	9238 (6.9)	0.00	12 807 (6.9)	12 743 (6.8)	0.00
Insulin	14 031 (26.5)	14 030 (26.5)	0.00	25 643 (19.3)	25 455 (19.1)	0.01	39 674 (21.3)	39 485 (21.2)	0.00
Lifestyle factors, *n* (%)									
Obesity	21 256 (40.2)	21 196 (40.1)	0.00	45 749 (34.4)	45 443 (34.1)	0.01	67 005 (36.0)	66 639 (35.8)	0.00
Overweight	3448 (6.5)	3458 (6.5)	0.00	5927 (4.5)	5932 (4.5)	0.00	9375 (5.0)	9390 (5.0)	0.00
Smoking	12 506 (23.6)	12 413 (23.5)	0.00	14 757 (11.1)	14 761 (11.1)	0.00	27 263 (14.7)	27 174 (14.6)	0.00
Other comorbidities at baseline, *n* (%)									
Acute myocardial infarction	2160 (4.1)	2115 (4.0)	0.01	0 (0.0)	0 (0.0)	–	2160 (1.2)	2115 (1.1)	0.01
Old myocardial infarction	5149 (9.7)	5105 (9.7)	0.00	0 (0.0)	0 (0.0)	–	5149 (2.8)	5105 (2.7)	0.01
Unstable angina	3249 (6.1)	3218 (6.1)	0.00	0 (0.0)	0 (0.0)	–	3249 (1.7)	3218 (1.7)	0.00
Stable angina	7000 (13.2)	6937 (13.1)	0.00	0 (0.0)	0 (0.0)	–	7000 (3.8)	6937 (3.7)	0.01
Other chronic ischemic heart disease	34 642 (65.5)	34 536 (65.3)	0.00	0 (0.0)	0 (0.0)	–	34 642 (18.6)	34 536 (18.6)	0.00
Coronary revascularization	2384 (4.5)	2326 (4.4)	0.00	0 (0.0)	0 (0.0)	–	2384 (1.3)	2326 (1.3)	0.00
Heart failure	11 822 (22.3)	11 760 (22.2)	0.00	0 (0.0)	0 (0.0)	–	11 822 (6.4)	11 760 (6.3)	0.00
Atrial fibrillation	7910 (15.0)	7874 (14.9)	0.00	3306 (2.5)	3243 (2.4)	0.01	11 216 (6.0)	11 117 (6.0)	0.00
Ischemic stroke	11 574 (21.9)	11 574 (21.9)	0.00	0 (0.0)	0 (0.0)	–	11 574 (6.2)	11 574 (6.2)	0.00
Transient ischemic attack	2267 (4.3)	2249 (4.3)	0.00	623 (0.5)	601 (0.5)	0.00	2890 (1.6)	2850 (1.5)	0.01
Peripheral arterial disease or surgery	13 935 (26.3)	13 965 (26.4)	0.00	0 (0.0)	0 (0.0)	–	13 935 (7.5)	13 965 (7.5)	0.00
Hypertension	48 686 (92.0)	48 671 (92.0)	0.00	96 154 (72.2)	95 954 (72.1)	0.00	144 840 (77.9)	144 625 (77.7)	0.00
Hyperlipidemia	47 736 (90.2)	47 737 (90.2)	0.00	100 934 (75.8)	100 834 (75.7)	0.00	148 670 (79.9)	148 571 (79.9)	0.00
Chronic obstructive pulmonary disease	8491 (16.1)	8483 (16.0)	0.00	5426 (4.1)	5415 (4.1)	0.00	13 917 (7.5)	13 898 (7.5)	0.00
Pneumonia	3029 (5.7)	3034 (5.7)	0.00	2803 (2.1)	2812 (2.1)	0.00	5832 (3.1)	5846 (3.1)	0.00
Obstructive sleep apnea	12 930 (24.4)	12 993 (24.6)	0.00	20 113 (15.1)	20 007 (15.0)	0.00	33 043 (17.8)	33 000 (17.7)	0.00

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Table 1–Continued

Baseline Characteristics	History of CVD*			No History of CVD			Overall Population		
	SGLT2 Inhibitor (*n* = 52 901)	GLP-1 RA (*n* = 52 901)	Standardized Difference	SGLT2 Inhibitor (*n* = 133 139)	GLP-1 RA (*n* = 133 139)	Standardized Difference	SGLT2 Inhibitor (*n* = 186 040)	GLP-1 RA (*n* = 186 040)	Standardized Difference
Osteoarthritis	14 110 (26.7)	13 983 (26.4)	0.01	21 034 (15.8)	21 017 (15.8)	0.00	35 144 (18.9)	35 000 (18.8)	0.00
Chronic kidney disease	9328 (17.6)	9474 (17.9)	−0.01	8492 (6.4)	8707 (6.5)	0.00	17 820 (9.6)	18 181 (9.8)	−0.01
Stage 3-4 chronic kidney disease	6040 (11.4)	6065 (11.5)	0.00	4962 (3.7)	5070 (3.8)	−0.01	11 002 (5.9)	11 135 (6.0)	0.00
Proteinuria	2954 (5.6)	2899 (5.5)	0.00	5076 (3.8)	5119 (3.8)	0.00	8030 (4.3)	8018 (4.3)	0.00
Acute kidney injury	2640 (5.0)	2652 (5.0)	0.00	1271 (1.0)	1336 (1.0)	0.00	3911 (2.1)	3988 (2.1)	0.00
Edema‖	8370 (15.8)	8340 (15.8)	0.00	7666 (5.8)	7703 (5.8)	0.00	16 036 (8.6)	16 043 (8.6)	0.00
Other medication use, *n* (%)									
Angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers	42 603 (80.5)	42 565 (80.5)	0.00	96 080 (72.2)	96 015 (72.1)	0.00	138 683 (74.5)	138 580 (74.5)	0.00
B-blockers	33 085 (62.5)	33 047 (62.5)	0.00	31 129 (23.4)	30 975 (23.3)	0.00	64 214 (34.5)	64 022 (34.4)	0.00
Calcium-channel blockers	18 075 (34.2)	18 126 (34.3)	0.00	30 339 (22.8)	30 464 (22.9)	0.00	48 414 (26.0)	48 590 (26.1)	0.00
Thiazides	8261 (15.6)	8212 (15.5)	0.00	16 960 (12.7)	16 690 (12.5)	0.01	25 221 (13.6)	24 902 (13.4)	0.01
Loop diuretics	13 851 (26.2)	13 820 (26.1)	0.00	9207 (6.9)	9170 (6.9)	0.00	23 058 (12.4)	22 990 (12.4)	0.00
Mineralocorticoid receptor antagonists	3658 (6.9)	3660 (6.9)	0.00	3000 (2.3)	2996 (2.3)	0.00	6658 (3.6)	6656 (3.6)	0.00
Nitrates	9210 (17.4)	9123 (17.2)	0.01	1054 (0.8)	1057 (0.8)	0.00	10 264 (5.5)	10 180 (5.5)	0.00
Digoxin	1895 (3.6)	1937 (3.7)	−0.01	655 (0.5)	665 (0.5)	0.00	2550 (1.4)	2602 (1.4)	0.00
Statins	43 228 (81.7)	43 167 (81.6)	0.00	86 439 (64.9)	86 267 (64.8)	0.00	129 667 (69.7)	129 434 (69.6)	0.00
Antiplatelets	14 077 (26.6)	14 084 (26.6)	0.00	2777 (2.1)	2815 (2.1)	0.00	16 854 (9.1)	16 899 (9.1)	0.00
Anticoagulants	6725 (12.7)	6647 (12.6)	0.00	3671 (2.8)	3674 (2.8)	0.00	10 396 (5.6)	10 321 (5.5)	0.00
Measures of health care use									
Mean hospitalizations (SD), *n*	0.25 (0.60)	0.25 (0.62)	0.00	0.05 (0.26)	0.05 (0.26)	0.00	0.11 (0.40)	0.11 (0.41)	0.00
Length of stay within prior 30 d, *n* (%)	0.08 (0.80)	0.09 (0.85)	−0.01	0.02 (0.35)	0.02 (0.36)	0.00	0.04 (0.52)	0.04 (0.55)	0.00
Length of stay within prior 31–365 d, *n* (%)	1.12 (3.82)	1.12 (4.05)	0.00	0.20 (1.33)	0.21 (1.51)	−0.01	0.46 (2.37)	0.46 (2.54)	0.00
Mean emergency department visits (SD), *n*	0.76 (1.89)	0.76 (1.93)	0.00	0.25 (0.97)	0.25 (0.93)	0.00	0.40 (1.32)	0.40 (1.32)	0.00
Mean internal medicine visits (SD), *n*	18.12 (21.75)	18.02 (21.64)	0.00	12.19 (14.45)	12.18 (14.69)	0.00	13.88 (17.06)	13.84 (17.16)	0.00
Internal medicine visit within prior 30 d, *n* (%)	34 819 (65.8)	34 776 (65.7)	0.00	85 573 (64.3)	85 710 (64.4)	0.00	120 392 (64.7)	120 486 (64.8)	0.00
Mean endocrinologist visits (SD), *n*	2.04 (7.06)	2.07 (7.30)	0.00	1.45 (5.18)	1.44 (5.35)	0.00	1.62 (5.78)	1.62 (5.98)	0.00
Endocrinologist visit within prior 30 d, *n* (%)	8849 (16.7)	8898 (16.8)	0.00	19305 (14.5)	19166 (14.4)	0.00	28154 (15.1)	28064 (15.1)	0.00

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Table 1–Continued

Baseline Characteristics	History of CVD*			No History of CVD			Overall Population		
	SGLT2 Inhibitor (*n* = 52 901)	GLP-1 RA (*n* = 52 901)	Standardized Difference	SGLT2 Inhibitor (*n* = 133 139)	GLP-1 RA (*n* = 133 139)	Standardized Difference	SGLT2 Inhibitor (*n* = 186 040)	GLP-1 RA (*n* = 186 040)	Standardized Difference
Mean cardiologist visits (SD), *n*	5.71 (8.94)	5.71 (9.66)	0.00	0.59 (2.36)	0.59 (2.37)	0.00	2.05 (5.66)	2.04 (5.99)	0.00
Cardiologist visit within prior 30 d, *n* (%)	9656 (18.3)	9664 (18.3)	0.00	3885 (2.9)	3833 (2.9)	0.00	13541 (7.3)	13497 (7.3)	0.00
Mean electrocardiograms (SD), *n*	1.93 (2.58)	1.93 (2.69)	0.00	0.50 (1.04)	0.49 (1.05)	0.01	0.90 (1.76)	0.90 (1.81)	0.00
Eechocardiograms and other cardiac imaging, *n* (%)	1.29 (2.63)	1.28 (2.60)	0.00	0.16 (0.67)	0.16 (0.67)	0.00	0.48 (1.60)	0.48 (1.58)	0.00
Mean distinct prescriptions (SD), *n*	15.73 (6.56)	15.69 (6.36)	0.01	11.99 (5.66)	11.97 (5.37)	0.00	13.06 (6.17)	13.03 (5.91)	0.00
Mean distinct prescriptions of brand medications (SD), *n*	4.02 (2.45)	4.02 (2.44)	0.00	3.03 (1.87)	3.03 (1.83)	0.00	3.31 (2.10)	3.31 (2.07)	0.00
Mean out-of-pocket pharmacy costs (SD), $	919.71 (915.66)	919.37 (905.51)	0.00	731.34 (735.48)	728.92 (727.12)	0.00	784.90 (795.45)	783.08 (786.70)	0.00
Mean HbA_{1c} tests ordered (SD), *n*	2.69 (1.50)	2.69 (1.53)	0.00	2.36 (1.33)	2.36 (1.34)	0.00	2.46 (1.39)	2.45 (1.41)	0.01
Mean microalbuminuria tests ordered (SD), *n*	0.96 (1.09)	0.95 (1.10)	0.01	0.87 (0.94)	0.87 (0.94)	0.00	0.90 (0.99)	0.90 (0.99)	0.00
Mean metabolic or renal/creatinine tests ordered (SD), *n*	3.40 (2.61)	3.39 (2.69)	0.00	2.14 (1.79)	2.14 (1.81)	0.00	2.50 (2.13)	2.49 (2.17)	0.00
Mean lipid tests (SD), *n*	2.21 (1.82)	2.21 (2.01)	0.00	1.83 (1.53)	1.83 (1.64)	0.00	1.93 (1.63)	1.94 (1.76)	−0.01
Laboratory test results¶									
Mean HbA_{1c} (SD), %	8.85 (2.12)	8.85 (2.15)	0.00	8.97 (2.18)	8.97 (2.29)	0.00	8.95 (2.17)	8.94 (2.26)	0.00
Patients with HbA_{1c} results available, *n* (%)	5790 (10.94)	5728 (10.83)	0.00	19 380 (14.56)	18 793 (14.12)	0.01	25 170 (13.53)	24 521 (13.18)	0.01
Mean eGFR (SD), *mL/min/1.73 m²*	76.41 (20.89)	74.24 (22.28)	0.10	86.84 (20.52)	85.56 (22.02)	0.06	84.44 (21.07)	82.91 (22.59)	0.07
Patients with eGFR results available, *n* (%)	5931 (11.21)	5856 (11.07)	0.00	19 833 (14.9)	19 127 (14.4)	0.01	25 764 (13.8)	24 983 (13.4)	0.01
Mean UACR (SD), *mg/g*	131.59 (448.33)	150.78 (640.08)	−0.03	79.32 (381.20)	89.10 (385.45)	−0.03	91.61 (398.60)	103.86 (460.14)	−0.03
Patients with UACR results available, *n* (%)	2704 (5.11)	2672 (5.05)	0.00	8796 (6.61)	8492 (6.38)	0.01	11 500 (6.18)	11 164 (6.00)	0.01
Mean total cholesterol (SD)									
mmol/L	4.46 (1.30)	4.47 (1.30)	−0.01	4.80 (1.36)	4.79 (1.35)	0.01	4.72 (1.36)	4.72 (1.34)	0.00
mg/dL	172.40 (50.34)	172.98 (50.34)	−0.01	185.73 (52.73)	185.33 (52.09)	0.01	182.68 (52.49)	182.49 (51.95)	0.00
Patients with total cholesterol results available, *n* (%)	5610 (10.60)	5441 (10.29)	0.01	18 878 (14.18)	18 209 (13.68)	0.01	24 488 (13.16)	23 650 (12.71)	0.01
Mean LDL level (SD)									
mmol/L	2.37 (1.07)	2.37 (1.05)	0.00	2.65 (1.11)	2.64 (1.09)	0.02	2.59 (1.11)	2.57 (2.57)	0.01
mg/dL	91.59 (41.41)	91.48 (40.43)	0.00	102.65 (42.87)	101.95 (42.20)	0.02	100.08 (42.79)	99.52 (42.03)	0.01

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Table 1–Continued

Baseline Characteristics	History of CVD*			No History of CVD			Overall Population		
	SGLT2 Inhibitor (*n* = 52 901)	GLP-1 RA (*n* = 52 901)	Standardized Difference	SGLT2 Inhibitor (*n* = 133 139)	GLP-1 RA (*n* = 133 139)	Standardized Difference	SGLT2 Inhibitor (*n* = 186 040)	GLP-1 RA (*n* = 186 040)	Standardized Difference
Patients with LDL results available, *n* (%)	5474 (10.35)	5327 (10.07)	0.01	18058 (13.56)	17650 (13.26)	0.01	23532 (12.65)	22977 (12.35)	0.01
Mean HDL level (SD)									
mmol/L	1.16 (0.40)	1.16 (0.40)	0.00	1.20 (0.41)	1.20 (0.43)	0.00	1.19 (0.41)	1.19 (0.42)	0.00
mg/dL	44.75 (15.43)	44.80 (15.58)	0.00	46.27 (16.00)	46.27 (16.50)	0.00	45.92 (15.88)	45.93 (16.31)	0.00
Patients with HDL results available, *n* (%)	5538 (10.47)	5362 (10.14)	0.01	18 593 (13.97)	17 978 (13.50)	0.01	24 131 (12.97)	23 340 (12.55)	0.01
Mean triglyceride level (SD)									
mmol/L	2.30 (1.74)	2.33 (1.72)	−0.02	2.36 (1.89)	2.36 (1.85)	0.00	2.35 (1.86)	2.35 (1.82)	0.00
mg/dL	203.61 (153.67)	206.34 (152.71)	−0.02	209.45 (167.43)	209.23 (163.55)	0.00	208.11 (164.39)	208.56 (161.12)	0.00
Patients with triglyceride results available, *n* (%)	5568 (10.53)	5376 (10.16)	0.01	18 723 (14.06)	17 972 (13.50)	0.02	24 291 (13.06)	23 348 (12.55)	0.02

CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA_{1c}: hemoglobin A_{1c}; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SGLT2 = sodium–glucose cotransporter-2; UACR = urine albumin–creatinine ratio.
* Defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral arterial disease or surgery, or lower extremity amputation.
† Only available in Medicare fee for service and the Optum Clinformatics.
‡ Defined as patients without any use of glucose-lowering medications during the 12 mo before cohort entry.
§ Based on International Classification of Diseases coding.
‖ Localized, generalized, or unspecified edema.
¶ Only available in Optum Clinformatics and IBM MarketScan.

−4.97 [CI, −6.55 to −3.39] per 1000 person-years) and 1.3 versus 1.9 events per 1000 person-years in patients without CVD (HR, 0.69 [CI, 0.56 to 0.85]; RD, −0.58 [CI, −0.91 to −0.25] per 1000 person-years), with evidence of effect heterogeneity on the absolute scale only. Cumulative incidence function plots comparing the cumulative incidence of the composite cardiovascular outcome and HHF among patients receiving SGLT2 inhibitors versus GLP-1 RAs were consistent with these findings (**Figure 1**). The proportional hazards assumption, which was assessed by testing the significance of the interaction term between exposure and time, was not violated.

Among patients with CVD, the initiation of SGLT2 inhibitor versus GLP-1 RA therapy was associated with a decrease in the risk for hospitalization for MI (HR, 0.83 [CI, 0.74 to 0.93]; RD, −2.64 [CI, −4.21 to −1.08] per 1000 person-years) and in the risk for a composite outcome of MI, stroke, or all-cause mortality (HR, 0.90 [CI, 0.84 to 0.97]; RD, −3.61 [CI, −6.05 to −1.19] per 1000 person-years), with no benefit among patients without CVD and evidence of effect heterogeneity on both the relative and the absolute scale (**Figure 2**; **Supplement Table 10**, available at Annals.org). There was no difference in the risk for all-cause mortality in those who received SGLT2 inhibitors versus GLP-1 RAs, although a decrease in risk was seen among patients with CVD receiving a SGLT2 inhibitor (HR, 0.88 [CI, 0.79 to 0.99]; RD, −1.74 [CI, −3.27 to −0.21] per 1000 person-years), with evidence of effect heterogeneity on the absolute scale.

Sensitivity Analyses

Primary and secondary findings remained consistent when we extended the exposure effect window until 60 days after the expiration of the last prescription's supply and when we carried forward the exposure to the first-used medication without considering discontinuation or switching of the drug treatment (**Supplement Figure 1** and **Supplement Table 11**, available at Annals.org), although estimates moved closer to the null when we carried forward the exposure to the first-used medication for 365 days. The analysis adjustment for 50 states and 1 federal district also yielded results consistent with the primary analysis. The known association between SGLT2 inhibitors and the risk for diabetic ketoacidosis and the expected null association with the risk for herpes zoster virus reactivation were correctly estimated among patients with and without history of CVD (**Supplement Figure 1** and **Supplement Table 11**).

DISCUSSION

In this population-based study of more than 370 000 patients with diabetes, including more than 100 000 with

Table 2. Number of Events, Incidence Rates, and Relative and Absolute Measures of Association for Primary Outcomes in 1:1 Propensity Score–Matched Patients Initiating SGLT2 Inhibitor Versus GLP-1 RA Therapy, by History of CVD*, and in the Overall Populations

Population (1:1 propensity score-matched patients)	Events, *n* (Incidence Rate per 1000 Person-Years)		SGLT2 Inhibitor Versus GLP-1 RA			
	SGLT2 Inhibitor	GLP-1 RA	Hazard Ratio (95% CI)	*P* Value for Homogeneity	Rate Difference per 1000 Person-Years (95% CI)	*P* Value for Homogeneity
Composite cardiovascular outcome†						
History of CVD (*n* = 105 802)	979 (21.29)	1023 (23.76)	0.90 (0.82 to 0.98)	0.003	−2.47 (−4.45 to −0.50)	<0.001
No history of CVD (*n* = 266 278)	868 (7.16)	738 (6.78)	1.07 (0.97 to 1.18)		0.38 (−0.30 to 1.07)	
Overall population (*n* = 372 080)	1847 (11.05)	1761 (11.59)	0.97 (0.91 to 1.03)	-	−0.54 (−1.28 to 0.20)	-
Hospitalization for heart failure						
History of CVD (*n* = 105 802)	553 (11.95)	731 (16.92)	0.71 (0.64 to 0.79)	0.52	−4.97 (−6.55 to −3.39)	<0.001
No history of CVD (*n* = 266 278)	160 (1.32)	207 (1.9)	0.69 (0.56 to 0.85)		−0.58 (−0.91 to −0.25)	
Overall population (*n* = 372 080)	713 (4.25)	938 (6.16)	0.70 (0.64 to 0.77)	-	−1.91 (−2.41 to −1.41)	-

CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium–glucose cotransporter-2.
* History of cardiovascular disease is defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral arterial disease or surgery, or lower extremity amputation.
† Hospitalization for myocardial infarction or ischemic or hemorrhagic stroke.

established CVD, we found that initiating SGLT2 inhibitor versus GLP-1 RA therapy was associated with no differences in the risk for the primary outcome of hospitalization for MI or stroke. When we stratified according to history of CVD at baseline, we again saw that rates of MI and stroke were similar in patients without history of CVD prescribed SGLT2 inhibitors and GLP-1 RAs, although there was a 10% decrease in risk (2.5 fewer events per 1000 person-years) among patients initiating SGLT2 inhibitor versus GLP-1 RA therapy. The initiation of SGLT2 inhibitor versus GLP-1 RA therapy was associated with an approximately 30% reduction in the risk for the primary HHF outcome in all included patients, regardless of the presence or absence of CVD at baseline. This benefit was substantially greater among patients with CVD (5.0 fewer HHF events per 1000 person-years) compared with those without CVD (0.6 fewer HHF events per 1000 person-years). Finally, we did not find meaningful differences in the risk for all-cause mortality in those who initiated SGLT2 inhibitor versus GLP-1 RA therapy, although a decrease in risk was seen among patients with CVD who received SGLT2 inhibitors.

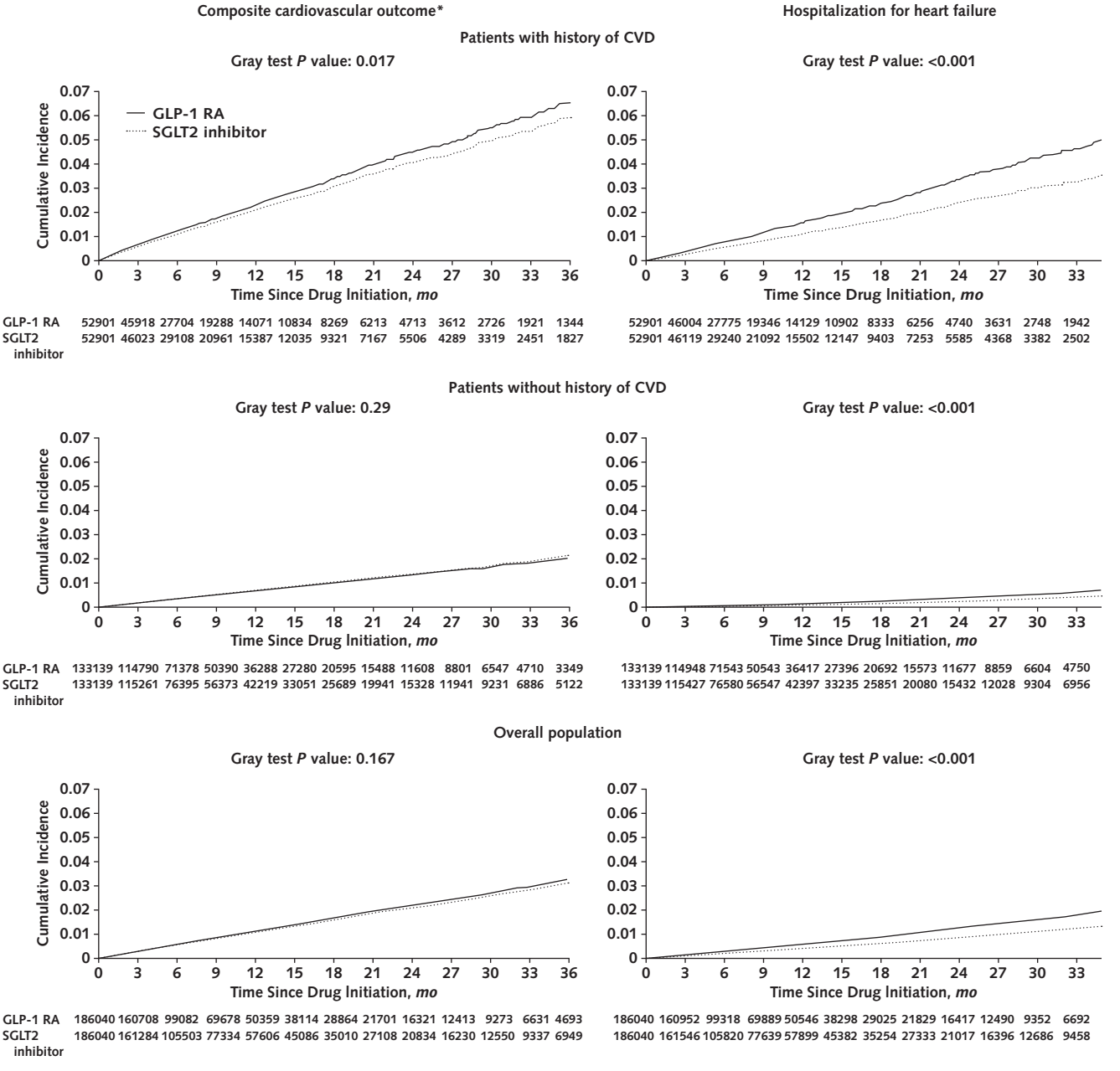
We believe these data are clinically relevant for many reasons. First, both SLGT2 inhibitors and GLP-1 RAs are recommended by guidelines and expert consensus documents as therapies for the prevention of MI, stroke, and cardiovascular death in patients with established CVD (4, 5, 18, 19, 35). Although both classes have been compared with placebo in large cardiovascular outcome trials, to date, no randomized clinical trials exist or are planned to allow for the direct comparison of the 2 classes. Little incentive exists for industry to conduct such trials in the future, and any potential trial would require several years to complete, delaying the answer to a question that is currently relevant in clinical practice. Thus, we believe these data represent the first comprehensive attempt to make such a comparison, albeit in an observational rather than experimental context. Our findings are consistent with the guidelines that recommend that in patients with established CVD, a SGLT2 inhibitor with demonstrated cardiovascular benefit offers similar efficacy with respect to preventing MI or stroke as the GLP-1 RA drugs with cardiovascular benefit (4, 5, 18, 19, 35). The data suggest that SGLT2 inhibitors may have a small incremental benefit in preventing hospitalization for MI or stroke compared with GLP-1 RAs among patients with established CVD within the time frame of this study, although features related to the study, including potential unmeasured confounding, potential ascertainment bias, and the large sample size, merit cautious acceptance of this finding.

Second, whether SGLT2 inhibitors and GLP-1 RAs lead to similar reductions in the risk for MACE among those without baseline CVD has been a controversial topic. Early trials of both classes of agents excluded patients without established CVD (7, 8, 36). More recent trials have included patients with risk factors but no established CVD (11, 13), and meta-analyses have suggested that the MACE prevention benefits are confined to those with established CVD compared with just cardiovascular risk factors (16, 17, 37). Here, we report no difference in the effects of SGLT2 inhibitors and GLP-1 RAs on the risk for hospitalization for MI or stroke in patients without established CVD. These observations are for a lower-risk population, as the observed incidence of MI and stroke hospitalization among those without established CVD in our population was substantially lower than that seen among those with established CVD. Because our study focused on the direct comparison of SGLT2 inhibitors to GLP-1 RAs, we are unable to test whether these 2 classes offered a benefit compared with other non-SGLT2 inhibitors or non–GLP-1 RA glucose-lowering therapies in this lower-risk population.

Third, when compared with GLP-1 RAs, SGLT2 inhibitors were associated with a substantial 30% reduction in the risk for HHF. This finding is consistent with the effects of SGLT2 inhibitors on HHF in cardiovascular outcome

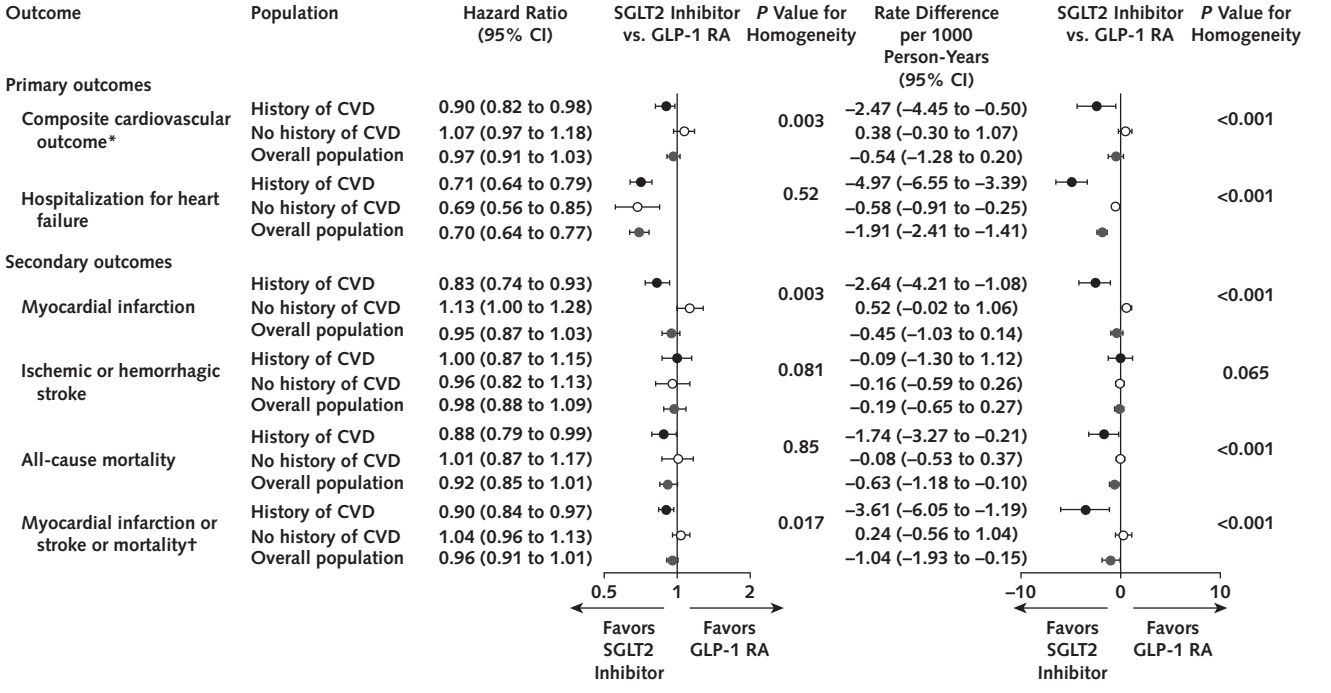
trials and in real-world comparisons to other glucose-lowering drugs (7, 10, 11, 15, 38, 39). Indeed, SGLT2 inhibitors have been shown to reduce HHF and all-cause mortality in patients with heart failure with reduced ejection fraction regardless of the presence or absence of T2D (14, 40). The effects of GLP-1 RAs on the risk for HHF in large randomized trials suggest the possibility of a modest, statistically significant benefit when compared with placebo (HR, 0.91 [CI, 0.83 to 0.99]) (16), so the data presented here represent the first direct comparison of SGLT2 inhibitors to GLP-1 RAs for HHF. Our data suggest that the benefits of SGLT2 inhibitors for HHF are substantially greater than those from GLP-1 RAs. The reductions in HHF seen with SGLT2 inhibitors versus GLP-1 RAs were present regardless of whether patients did (HR, 0.71 [CI, 0.64 to 0.79]) or did not (HR, 0.69 [CI, 0.56 to

Figure 1. Cumulative incidence function plots for primary outcomes comparing propensity score–matched patients initiating SGLT2 inhibitor versus GLP-1 RA therapy, by history of CVD, and overall.



History of CVD is defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral artery disease or surgery, or lower extremity amputation. CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium–glucose cotransporter-2.* Hospitalization for myocardial infarction or ischemic or hemorrhagic stroke.

Figure 2. Primary and secondary outcomes in 1:1 propensity score–matched patients initiating SGLT2 inhibitor versus GLP-1 RA therapy, by history of cardiovascular disease, and overall.



History of cardiovascular disease is defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral artery disease or surgery, or lower extremity amputation. CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium–glucose cotransporter-2.

* Hospitalization for myocardial infarction or ischemic or hemorrhagic stroke.

† Hospitalization for myocardial infarction, ischemic or hemorrhagic stroke, or all-cause mortality.

0.85]) have CVD at baseline, although the benefit was substantially greater on an absolute risk scale among patients with CVD versus those without CVD (5.0 vs. 0.6 fewer HHF events per 1000 person-years).

Fourth, we noted no difference in the risk for all-cause mortality between GLP-1 RAs and SGLT2 inhibitors, although a small incremental benefit in preventing death was seen among patients with CVD initiating SGLT2 inhibitor therapy. Although our mortality data are limited and are available in reasonable numbers only from Medicare subscribers, they nonetheless suggest that large differences in effectiveness between the 2 therapies can be excluded with respect to all-cause mortality.

The observed absence of large differences in the risk for the primary cardiovascular outcome and the composite outcome of MI, stroke, or all-cause mortality among patients without CVD initiating SGLT2 inhibitor or GLP-1 RA therapy and the substantial decrease in the risk for HHF associated with the use of SGLT2 inhibitors have important implications with respect to clinical decision making. Specifically, our findings suggest that the initiation of SGLT2 inhibitor therapy versus GLP-1 RA therapy in patients with T2D who have no established CVD at baseline may have greater cardiovascular benefit. Our study has several limitations. First, although we adjusted for a large number of baseline characteristics through PS matching, residual confounding by some unmeasured or not fully measured characteristics in claims (for example, hemoglobin A_{1c} level, diabetes duration, body mass index, estimated glomerular filtration rate, and ejection fraction) cannot be entirely excluded. However, in a previous study, we showed that a new user, active comparator cohort study design paired with the adjustment for a large number of claims-based confounder proxies ensured sufficient balance in many characteristics typically unmeasured in claims data (41). This was confirmed in the current study by the achieved balance in important laboratory test results after PS adjustment in the subset of the population with this information available, despite not being included in the PS models. When we quantified the bias associated with the observed residual difference for an acknowledged risk factor for cardiovascular events, for example, kidney function as measured by estimated glomerular filtration rate, between patients initiating SGLT2 inhibitor therapy and patients initiating GLP-1 RA therapy, we found that adjusted effect estimates were fairly robust even under scenarios of strong residual association between decrease in estimated glomerular filtration rate and the primary cardiovascular outcomes (42) (**Supplement Figure 2**, available at Annals.org). After PS adjustment for 138 potential confounders, including claims-based measures of kidney disease and health care use variables suggestive of care

targeting kidney function, such strong association seems unlikely. In addition, we used data collected before the large dissemination of the evidence showing cardiovascular benefits of SGLT2 inhibitors and GLP-1 RAs and their large uptake among patients with CVD (43), thus limiting chances of confounding. Finally, we were able to replicate the known association between SGLT2 inhibitors and the risk for a "positive control"–that is, diabetic ketoacidosis–which is known to occur with SGLT2 inhibitors but not with GLP-1 RAs, and the expected null association with the "falsification end point" of herpes zoster virus reactivation, which is not known to associate with either SGLT2 inhibitor or GLP-1 RA therapy.

Second, because of the reduction in HHF risk with SGLT2 inhibitors, more patients receiving GLP-1 RAs, who had a HHF during follow-up, may have had increased opportunity to be diagnosed with type 2 MI. However, our study definition of hospitalization for MI only included type 1 MI, limiting the chances of detection bias. Third, we were unable to evaluate cardiovascular death or all-cause mortality as the primary outcome because information on cause of death was not available and the completeness of all-cause mortality varied across the available administrative data, with complete information available only in the Medicare database. Fourth, because of the limited number of initiators for each of the individual SGLT2 inhibitors or GLP-1 RAs during the study period, we were unable to do a real-world evaluation of the effectiveness of individual SGLT2 inhibitors or GLP-1 RA agents among patients with and without CVD. Moreover, the current investigation did not include initiators of more recently marketed SGLT2 inhibitors or GLP-1 RAs, including semaglutide, a GLP-1 RA that showed large benefit with respect to atherosclerotic cardiovascular events in placebo-controlled cardiovascular outcome trials (9), and ertugliflozin, a SGLT2 inhibitor that showed more limited benefit (44). The inclusion of these agents could further reduce the difference in risk for hospitalization for MI or stroke seen among patients with established CVD receiving SGLT2 inhibitors and GLP-1 RAs and potentially increase the difference in risk for MI or stroke seen among patients without CVD. Fifth, because this investigation was based on the use of SGLT2 inhibitors or GLP-1 RAs in routine care, the median follow-up (that is, time on treatment) was shorter compared with cardiovascular outcome trials, 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 allowed us to generate results with high precision, despite a shorter duration of time on treatment.

In conclusion, this population-based study of 370 000 patients with T2D supports the hypothesis that SGLT2 inhibitors and GLP-1 RAs do not largely differ with respect to the risk for hospitalization for MI or stroke, regardless of whether patients have or do not have established CVD at the time of drug initiation. However, SGLT2 inhibitors seem to be associated with a consistent decrease in the risk for HHF in both patients with and without CVD, although the absolute decrease in risk seems to be substantially greater among patients with CVD. These real-world clinical data support the existing guidelines, which suggest that SGLT2 inhibitors and GLP-1 RAs offer similar benefits in atherosclerotic CVD prevention to patients with T2D and that SGLT2 inhibitors offer greater efficacy in HHF prevention.

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

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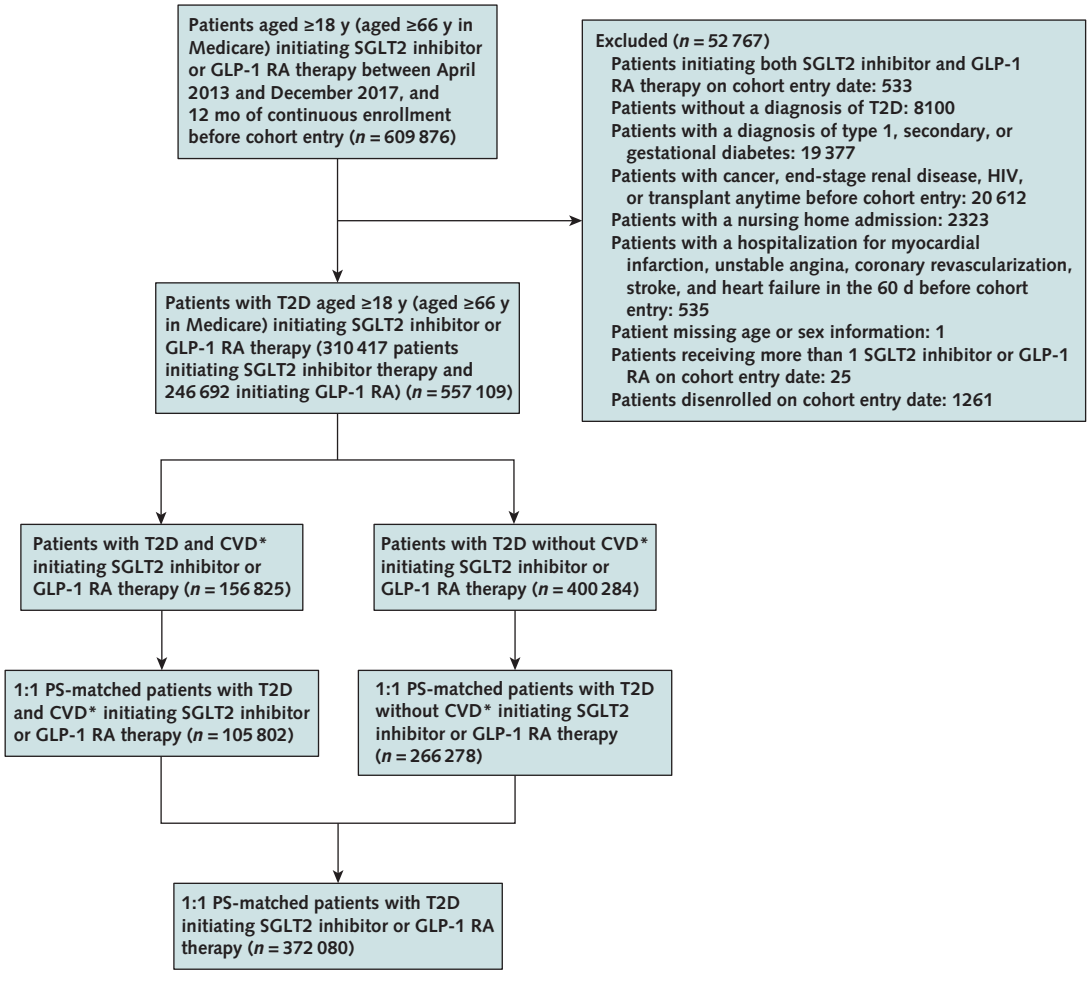
Collection and assembly of data: E. Patorno.

Appendix Figure. Consort diagram of patients initiating SGLT2 inhibitor versus GLP-1 RA therapy.



CVD = cardiovascular disease; GLP-1 RA = glucagon-like peptide-1 receptor agonist; PS = propensity score; SGLT2 = sodium–glucose cotransporter-2; T2D = type 2 diabetes.

* Defined as history of myocardial infarction, angina, coronary atherosclerosis and other forms of chronic ischemic heart disease, coronary procedure, heart failure, ischemic stroke, peripheral artery disease or surgery, or lower extremity amputation.