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ORIGINAL RESEARCH ARTICLE

Risk of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Addition of SGLT2 Inhibitors Versus Sulfonylureas to Baseline GLP-1RA Therapy

Editorial, see p 780

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BACKGROUND: Several glucagon-like peptide receptor agonists (GLP-1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have demonstrated cardiovascular benefit in type 2 diabetes in large randomized controlled trials in patients with established cardiovascular disease or multiple risk factors. However, few trial participants were on both agents, and it remains unknown whether the addition of SGLT2i to GLP-1RA therapy has further cardiovascular benefits.

METHODS: Patients adding either SGLT2i or sulfonylureas to baseline GLP-1RA were identified within 3 US claims datasets (2013–2018) and were 1:1 propensity score–matched, adjusting for >95 baseline covariates. The primary outcomes were a composite cardiovascular end point (comprising myocardial infarction, stroke, and all-cause mortality) and heart failure hospitalization. Adjusted hazard ratios (HRs) and 95% CIs were estimated in each dataset and pooled through fixed-effects meta-analysis.

RESULTS: Among 12 584 propensity score–matched pairs (mean [SD] age, 58.3 [10.9] years; 48.2% male) across the 3 datasets, there were 107 composite cardiovascular end point events (incidence rate per 1000 person-years, 9.9 [95% CI, 8.1–11.9]) among SGLT2i initiators compared with 129 events (incidence rate, 13.0 [95% CI, 10.9–15.3]) among sulfonylurea initiators, corresponding to an adjusted pooled HR of 0.76 (95% CI, 0.59–0.98); this decrease in composite cardiovascular end point was driven by numeric decreases in the risk of myocardial infarction (HR, 0.71 [95% CI, 0.51–1.003]) and all-cause mortality (HR, 0.68 [95% CI, 0.40–1.14]) but not stroke (HR, 1.05 [95% CI, 0.62–1.79]). For the outcome of heart failure hospitalization, there were 141 events (incidence rate, 13.0 [95% CI, 11.0–15.2]) among SGLT2i initiators versus 206 events (incidence rate, 20.8 [95% CI, 18.1–23.8]) among sulfonylurea initiators, corresponding to an adjusted pooled HR of 0.65 (95% CI, 0.50–0.82).

CONCLUSIONS: Risk of residual confounding cannot be fully excluded. Individual therapeutic agents within each class may have different magnitudes of effect. In this large real-world cohort of patients with diabetes already on GLP-1RA, addition of SGLT2i conferred greater cardiovascular benefit compared with addition of sulfonylurea. The magnitude of the cardiovascular risk reduction was comparable with the benefit seen in cardiovascular outcome trials of SGLT2i versus placebo, where baseline GLP-1RA use was minimal.

Key Words: glucagon-like peptide receptors ■ heart failure ■ myocardial infarction ■ sodium-glucose transporter 2 inhibitors ■ stroke

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Clinical Perspective

What Is New?

- Given their orthogonal effects on cardiovascular health, it has been postulated that the addition of sodium-glucose cotransporter-2 inhibitors (SGLT2i) to baseline glucagon-like peptide receptor agonist (GLP-1RA) therapy may confer additional cardiovascular benefits; however, there were few participants using both agents in randomized clinical trials.
- Patients adding either SGLT2i or sulfonylureas were identified within 3 US observational datasets of patients with type 2 diabetes already on GLP-1RA.
- Compared with initiation of sulfonylureas, the addition of SGLT2i conferred greater cardiovascular benefit; the magnitude of this benefit was comparable with that observed in cardiovascular outcome trials of SGLT2i versus placebo where baseline GLP-1RA use was minimal.

What Are the Clinical Implications?

- Because major cardiovascular events occur at significantly higher rates in patients with type 2 diabetes, strategies that reduce the incidence of such events are relevant in guiding patient care.
- Short-term trials have demonstrated that the combination of SGLT2i and GLP-1RA results in clinically relevant improvements in glycemic control with acceptable tolerability. This study provides the evidentiary support for adding SGLT2i to existing GLP-1RA therapy to reduce cardiovascular events in patients with diabetes in routine clinical care.

Atherosclerotic cardiovascular disease and heart failure (HF) are the primary contributors to mortality and morbidity among patients with type 2 diabetes; therefore, reducing these events is the cornerstone of disease management.[1] Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a newer class of medications that lower serum glucose by inhibiting its reabsorption in the proximal convoluted tubule.[2] In several large randomized cardiovascular outcome trials, SGLT2i have demonstrated their efficacy in reducing HF hospitalizations[3–5] and, for empagliflozin and canagliflozin, the composite of cardiovascular death, myocardial infarction (MI), and stroke.[3,5] Reductions in cardiovascular events occurred early after randomization, often within the first 6 months of SGLT2i therapy initiation, before anticipated times when change would occur in the underlying coronary atherosclerotic burden.

There is growing interest in the use of SGLT2i in conjunction with other therapies with established cardiovascular benefits—most notably, glucagon-like peptide receptor agonists (GLP-1RA)—where several within-class agents (liraglutide, dulaglutide, and semaglutide) have demonstrated benefit on the composite of cardiovascular death, MI, and stroke.[6–8] The putative mechanisms by which SGLT2i and GLP-1RA exert their cardiovascular benefit appear to be complementary in nature based on the orthogonal molecular mechanisms of action and the different time courses over which improved cardiovascular outcomes are manifest in the trials. However, the combined use of these 2 drug classes in cardiovascular outcome trials was rare. The prevalence of baseline SGLT2i in GLP-1RA–related cardiovascular trials ranged from no use (several trials finished patient recruitment before SGLT2i became available) to 5.3%; likewise, prevalence of GLP-1RA use in SGLT2i-related cardiovascular trials ranged from 2.5% to 4.4%.[3–5]

To assess whether the addition of SGLT2i to GLP-1RA reduced cardiovascular events compared with GLP-1RA alone, we used 3 US-based insurance claims datasets to identify a cohort of diabetic patients adding SGLT2i to their baseline GLP-1RA therapy compared with patients adding sulfonylureas. Sulfonylureas were used as the comparator group because they are not associated with a cardiovascular benefit, can be used in conjunction with GLP-1RA (unlike dipeptidyl peptidase-4 inhibitors), and are more widely prescribed in clinical practice compared with other glucose-lowering therapies such as thiazolidinediones or α-glucosidase inhibitors. We hypothesized that given their orthogonal pharmacodynamic effects on cardiovascular risk, adding SGLT2i to existing GLP-1RA therapy would result in greater reductions in cardiovascular events compared with the addition of agents without established cardiovascular benefits.

METHODS

All supporting data are available in the article and its Data Supplement.

Data Sources

Data were collected from 3 US-based insurance claims databases. Two were commercial claims databases generalizable to ≈50% of the US population enrolled in an employer-based insurance program: Optum Clinformatics Data Mart Database (April 2013 to June 2018) and IBM MarketScan (April 2013 to December 2017). The Medicare components of Optum provide data for patients enrolled in Medicare Advantage plans and MarketScan for patients enrolled in supplemental Medicare plans. The third data source was Medicare fee-for-service data (Parts A/B/D, April 2013 to December 2016), comprising all patients >65 years of age with a diagnosis of type 2 diabetes. For each study participant, the data source included information on patient demographics, medical and pharmacy enrollment status, inpatient and outpatient medical service utilization, and outpatient pharmacy dispensing information.

The study was approved by the Brigham and Women's Hospital's Institutional Review Board and the appropriate data use agreements were in place for all databases.

Study Population and Exposure Definition

In each database, we identified a cohort of patients with type 2 diabetes initiating an SGLT2i (canagliflozin, dapagliflozin, or empagliflozin; exposure group) or a second-generation sulfonylurea (glipizide, glyburide, glimepiride; active comparator group) without evidence of previous use of either of the 2 classes in the 6-month period before the date of cohort entry (defined as date of SGLT2i or sulfonylurea initiation). Patients were required to have previously filled a prescription for a GLP-1RA therapy (exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, or semaglutide) with the days' supply sufficient to overlap the cohort entry date when the initial SGLT2i or sulfonylurea prescription was filled. Patients younger than 18 years (or 65 years in Medicare fee-for-service); those with evidence of gestational or type 1 diabetes, cancer, end-stage renal disease, or human immunodeficiency virus infection; or those who had nursing home admission or hospice care were excluded from analysis (see Figure I in the Data Supplement for study design).

Baseline Covariates

We assessed >95 baseline covariates that were measured in the 6-month period before and including the day of cohort entry. These covariates included demographics and calendar time (eg, age, sex, and calendar year of cohort entry), complications of diabetes (eg, diabetic neuropathy, nephropathy, retinopathy), oral and injectable antidiabetic therapy (eg, metformin, insulin, dipeptidyl peptidase-4 inhibitors), cardiovascular conditions (eg, myocardial infarction, stroke, HF), cardiovascular medications (eg, dispensing of β-blockers, loop diuretics, statins), noncardiovascular comorbid conditions (eg, diagnosis of chronic kidney disease, chronic obstructive pulmonary disease, psychiatric conditions), noncardiovascular medications (eg, dispensing of anticonvulsants, antidepressants), and measures of burden of comorbidities and healthcare utilization (eg, combined comorbid index,[9] number of hospitalizations, number of medications). Hemoglobin A1C (available for a subset of patients in MarketScan and Optum data but not in Medicare; not included in the propensity score) was used to assess the presence of adequate therapeutic equipoise between the SGLT2 and sulfonylurea arms before propensity score matching and to assess potential residual confounding after propensity score matching. There were no other missing data in our study.

Follow-Up and Study End Points

Separately for each study outcome, patients began contributing to follow-up time on the day after cohort entry up until the first occurrence of one of the following: end of pharmacy or health care eligibility; medication discontinuation, defined as 60-day gap in therapy of SGLT2i (among SGLT2i initiators), sulfonylureas (among sulfonylurea initiators), or GLP-1RA (among both groups); medication switching or augmentation (patients in SGLT2i arm initiating sulfonylureas and vice versa); end of study data (December 2016 for Medicare, December 2017 for MarketScan, and June 2018 for Optum); or the occurrence of that outcome.

The 2 primary outcomes of interest were a composite cardiovascular end point comprising MI hospitalization, stroke hospitalization, or all-cause mortality and HF hospitalizations (see Table I in the Data Supplement for outcome definitions). Analysis of each of the 2 primary outcomes was conducted independently of the other. In previous validation studies, the positive predictive value of these outcomes was >80%.[10–12] Information on mortality was available in Medicare fee-for-service through the vital status file, whereas it was limited to in-hospital deaths in MarketScan. For Optum, mortality data were informed from 4 sources: Centers for Medicare and Medicaid Services, Social Security Administration Master Death Files, in-hospital deaths, and death as a reason for insurance discontinuation.

Primary Analyses

To mitigate the risk of confounding, new initiators of SGLT2i were matched to those initiating sulfonylureas on their estimated propensity score, which used multivariable logistic regression to model the probability of adding a SGLT2i versus adding a sulfonylurea. Variables were included in the model without selection. A greedy-matching approach was used with a maximum caliper width of 0.01 on the propensity score.[13] We assessed the performance of propensity scores in confounding control by examining the distribution of the baseline covariates before and after propensity score matching by exposure group, using a threshold of 10% in the standardized difference as a metric for a meaningful imbalance.[14] Thereafter, using a primary as-treated analysis, where patients were censored on treatment discontinuation or switching, we estimated the rates of the primary composite endpoints among patients exposed to both SGLT2i and GLP-1RA and among patients exposed to both sulfonylureas and GLP-1RA, by calculating the number of outcome events and incidence rates (IRs). Cox proportional hazard models were used to estimate the hazard ratios (HRs) with 95% CIs and included exposure status as the independent variable; for nonfatal endpoints, we accounted for the competing risk of death by estimating cause-specific hazard functions.[15] Analyses were performed separately in each data source and pooled through inverse-variance fixed effects meta-analysis,[16] as random effects pooling performs poorly when applied in the setting of few databases.[17] Kaplan-Meier curves were generated to visualize the cumulative incidence of the outcome over time and log-rank tests were used to compare the survival distribution in the 2 groups. All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Sensitivity, Subgroup, and Secondary Analysis

Frist, to assess the robustness of the primary findings, we conducted sensitivity analysis pertaining to exposure-related censoring criteria, where instead of censoring patients at the time of treatment switching or discontinuation, we instead carried the index exposure forward to mimic an intention-to-treat approach. Second, we estimated the average treatment

effects using the stabilized inverse probability of treatment weights based on the propensity score in lieu of the propensity score–matching approach.[18] Third, we examined the heterogeneity of treatment effect within the subgroups of patients with and without established cardiovascular disease, defined as history of MI, ischemic or hemorrhagic stroke, HF, coronary atherosclerosis and other forms of chronic ischemic heart disease (including unstable angina), transient ischemic attacks, and peripheral vascular disease. Last, we restricted our analysis to a subgroup of patients treated with an SGLT2i with proven benefit on major adverse cardiovascular events (ie, empagliflozin and canagliflozin) compared with the only sulfonylurea tested for cardiovascular safety in a trial setting (ie, glimepiride). In all subgroups, the propensity score was reestimated, and patients were rematched on their newly estimated propensity score using the same caliper width as in the primary analysis.

We also examined several secondary outcomes including the individual components of the composite cardiovascular end point (MI, stroke, all-cause mortality) and the composite of the 2 primary outcomes. We also assessed the association with a control outcome with an expected null finding (ie, administration of the influenza vaccination during follow-up).

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

RESULTS

After applying the inclusion and exclusion criteria, we identified a cohort of 32 221 patients who added SGLT2i and 26 894 who added sulfonylureas to existing GLP-1RA therapy. Table 1 shows select pooled baseline characteristics of the cohort before and after propensity score matching across the 3 databases (see Tables II through IV in the Data Supplement for information on all baseline characteristics before and after propensity score matching by database; Table V in the Data Supplement lists the clinical characteristics of unmatched patients). Before matching, patients in the SGLT2i and sulfonylurea group differed with respect to some baseline characteristics (defined as standardized difference >10%). Patients in the SGLT2i arm were younger, more obese, and more likely to use insulin and to have diabetes-related complications. Fewer than 20% of patients in either group had evidence of existing cardiovascular disease. After 1:1 propensity score matching on >95 covariates, there were 25 168 patients, 12 584 in each group; the baseline characteristics were well-balanced with no standardized difference >10%. Hemoglobin A1C values were similar between the 2 groups even before propensity score matching, implying good therapeutic equipoise between the SGLT2 and sulfonylureas, and remained well-balanced after propensity score matching. The mean (SD) age of the matched cohort was 58.3 (10.0) years and 48.2% were male. Canagliflozin (61.6%), liraglutide (60.3%), and glimepiride (54.9%) were the most commonly used agents within their respective classes (Table VI in the Data Supplement).

Primary Analysis

Before propensity score matching, there were 258 events for the composite cardiovascular end point (IR per 1000 person-years, 9.5) among SGLT2i initiators (mean follow-up, 11.3 months) compared with 374 events (IR, 14.6) among sulfonylurea initiators (10.1 months), corresponding to an unadjusted pooled HR of 0.70 (95% CI, 0.60–0.82).

In the propensity score–matched cohort, there were 107 composite cardiovascular end point events (IR, 9.9) among patients who initiated a SGLT2i (10.4 months) compared with 129 events (IR, 13.0) among patients who initiated a sulfonylurea (9.4 months), corresponding to a pooled adjusted HR of 0.76 (95% CI, 0.59–0.98). Table 2 shows the pooled number of events, IRs, and HRs for the primary analysis before and after propensity score matching across the 3 databases (see Table VII in the Data Supplement for database-specific information on number of events and IRs).

Before matching, there were 324 HF hospitalizations (IR, 11.9) in the SGLT2i group (11.3 months) compared with 581 HF hospitalizations (IR, 22.9) in the sulfonylurea group (10.1 months; unadjusted pooled HR, 0.57 [95% CI, 0.47–0.68]). After propensity score matching, there were 141 (IR, 13.0; 10.3 months) versus 206 (IR, 20.8; 9.4 months) HF hospitalizations, corresponding to a pooled adjusted HR of 0.64 (95% CI, 0.50–0.82).

The pooled cumulative incidence of the primary composite cardiovascular and HF hospitalization outcomes in the propensity score matched cohort over time along with the corresponding *P* values for the log-rank test are shown in the Figure. The Kaplan-Meier curves for the outcome of HF hospitalization separated earlier (within the first 3 months; *P* value for log-rank test <0.001) compared with the composite cardiovascular outcome (after the 5th month; *P*=0.0403).

Sensitivity, Subgroup, and Secondary Analysis

Findings for the sensitivity analysis using intention-to-treat and inverse probability of treatment weights approach were consistent with primary analysis for both primary outcomes (Table 3; see Table VIII in the Data Supplement for information on number of events and database-specific estimates). There was no evidence of

Table 1. Select Pooled Baseline Characteristics Before and After Propensity Score Matching*

Variable	Before matching			After matching		
	SGLT2i (n=32 221)	Sulfonylurea (n=26 894)	Standardized mean difference, %	SGLT2i (n=12 584)	Sulfonylurea (n=12 584)	Standardized mean difference, %
Age, y	56.3 (10.6)	59.1 (10.9)	26.0	58.3 (10.9)	58.4 (11.1)	0.9
Male	16 326 (50.7)	13 198 (49.1)	3.2	6079 (48.3)	6039 (48.0)	0.6
Diabetic severity						
Diabetic neuropathy	4754 (14.8)	3085 (11.5)	9.7	1747 (13.9)	1686 (13.4)	1.4
Diabetic retinopathy	2285 (7.1)	1577 (5.9)	5.0	867 (6.9)	843 (6.7)	0.8
Diabetic nephropathy	2153 (6.7)	1786 (6.6)	0.2	938 (7.5)	926 (7.4)	0.4
Insulin	13 515 (41.9)	5472 (20.3)	48.0	3233 (25.7)	3148 (25.0)	1.6
Metformin	23 679 (73.5)	18 199 (67.7)	12.8	8872 (70.5)	8850 (70.3)	0.4
Hemoglobin A1c†	8.4 (1.7)	8.4 (1.7)	0.3	8.4 (1.8)	8.4 (1.7)	0.4
Cardiovascular characteristics						
Cardiovascular disease	6014 (18.7)	5268 (19.6)	2.3	2577 (20.5)	2579 (20.5)	0.0
Stroke	277 (0.9)	261 (1.0)	1.2	139 (1.1)	139 (1.1)	0.0
Recent myocardial infarction	168 (0.5)	127 (0.5)	0.7	63 (0.5)	63 (0.5)	0.0
Heart failure	890 (2.8)	918 (3.4)	3.8	406 (3.2)	430 (3.4)	1.1
Other ischemic heart disease	3624 (11.2)	3166 (11.8)	1.6	1499 (11.9)	1546 (12.3)	1.1
Transient ischemic attack	178 (0.6)	163 (0.6)	0.7	84 (0.7)	72 (0.6)	1.2
Peripheral vascular disease	999 (3.1)	853 (3.2)	0.4	435 (3.5)	434 (3.4)	0.0
Atrial fibrillation	991 (3.1)	1049 (3.9)	4.5	480 (3.8)	488 (3.9)	0.3
Angiotensin-converting enzyme inhibitors	13 484 (41.8)	11 176 (41.6)	0.6	5267 (41.9)	5313 (42.2)	0.7
β-Blockers	9662 (30.0)	8258 (30.7)	1.6	4001 (31.8)	3969 (31.5)	0.5
Loop diuretics	2802 (8.7)	2803 (10.4)	5.9	1295 (10.3)	1302 (10.3)	0.2
Antiplatelet	2331 (7.2)	2004 (7.5)	0.8	925 (7.4)	945 (7.5)	0.6
Anticoagulant	1220 (3.8)	1188 (4.4)	3.2	569 (4.5)	581 (4.6)	0.5
Statins	22 401 (69.5)	17 392 (64.7)	10.3	8529 (67.8)	8506 (67.6)	0.4
Other characteristics						
Obesity	8691 (27.0)	4708 (17.5)	22.9	2972 (23.6)	3040 (24.2)	1.3
Smoking	1865 (5.8)	1266 (4.7)	4.8	758 (6.0)	755 (6.0)	0.1
Combined comorbidity score	0.4 (1.4)	0.4 (1.5)	0.1	0.5 (1.5)	0.5 (1.5)	0.0

Values are mean (SD) or n (%). SGLT2 indicates sodium-glucose cotransporter-2 inhibitor.

*Select pooled baseline characteristics after 1:1 propensity score matching. See Tables I through IV in the Data Supplement for information on all baseline covariates before and after propensity score matching for each database.

†Available for 15% of patients.

effect modification by CVD for either of the primary outcomes (*P* value for heterogeneity = 0.61 for composite cardiovascular end point and 0.59 for HF hospitalizations). For the empagliflozin and canagliflozin versus glimepiride analysis, the point estimates were consistent with the primary analysis for both outcomes.

On the basis of the secondary outcome analyses (Table 4; see Table IX in the Data Supplement for information on number of events and database-specific estimates), the composite cardiovascular end point was primarily driven by numeric decreases in MI (pooled adjusted HR, 0.71 [95% CI, 0.51–1.003]) and all-cause mortality (pooled adjusted HR, 0.68 [95% CI, 0.40–1.14]) but not stroke (pooled adjusted HR, 1.05 [95% CI, 0.62–1.79]). For the combined composite cardiovascular/HF hospitalization outcome, the pooled adjusted HR was 0.69 (95% CI, 0.55–0.87). There was no association between SGLT2i and the control outcome of influenza vaccination (HR, 0.97 [95% CI, 0.92–1.01]).

DISCUSSION

Given their distinct mechanistic and pharmacodynamic profiles relating to cardiovascular risk, it has been postulated—but untested in previous clinical trials or observational studies—that the addition of SGLT2i therapy in

Table 2. Risk of Composite Cardiovascular End Point and Heart Failure Hospitalization Before and After Propensity Score Matching

Variable	Before matching		After matching	
	SGLT2i (n=32 221)	Sulfonylurea (n=26 894)	SGLT2i (n=12 584)	Sulfonylurea (n=12 584)
Composite cardiovascular end point*				
Events (incidence rate)†	258 (9.5)	374 (14.6)	107 (9.9)	129 (13.0)
Mean follow-up, mo	11.3	10.1	10.4	9.4
Database-specific hazard ratio (95% CI)‡				
Optum	0.64 (0.49–0.84)		0.76 (0.51–1.13)	
MarketScan	0.77 (0.59–1.01)		0.71 (0.43–1.18)	
Medicare	0.69 (0.51–0.93)		0.81 (0.52–1.26)	
Pooled hazard ratio (95% CI)§	0.70 (0.60–0.82)		0.76 (0.59–0.98)	
Heart failure hospitalizations				
Events (incidence rate)†	324 (11.9)	581 (22.9)	141 (13.0)	206 (20.8)
Mean follow-up, mo	11.3	10.1	10.3	9.4
Database-specific hazard ratio (95% CI)‡				
Optum	0.58 (0.45–0.75)		0.79 (0.56–1.11)	
MarketScan	0.48 (0.38–0.61)		0.51 (0.33–0.79)	
Medicare	0.66 (0.52–0.84)		0.61 (0.42–0.87)	
Pooled hazard ratio (95% CI)§	0.57 (0.47–0.68)		0.64 (0.50–0.82)	

SGLT2 indicates sodium-glucose cotransporter-2 inhibitor.

*Defined as the composite of myocardial infarction hospitalizations, stroke hospitalizations, and all-cause mortality.

†Events and incidence rates are pooled across the 3 databases. Incidence rates are per 1000 person-years of follow-up. See Table V in the Data Supplement for database-specific number of events and rates.

‡Hazard ratios were adjusted through 1:1 propensity score matching constructed using >95 variables.

§Analysis was stratified within each database and fixed-effects meta-analysis was used to pool.

patients using GLP-1RA would result in a greater reduction in the risk of cardiovascular events compared with adding a different glucose-lowering agent. Using real-world data generated from 3 US-based insurance claims datasets, this study demonstrates for the first time that the initiation of SGLT2i is associated with reductions in the risk of a composite cardiovascular end point outcome (comprising MI, stroke, and all-cause mortality) and HF hospitalizations compared with the initiation of sulfonylureas in patients with existing GLP-1RA therapy.

This study has important clinical implications. Strategies that reduce the incidence of cardiovascular events are relevant in guiding the care of patients with type 2 diabetes because major cardiovascular events occur at significantly higher rates[19] and are the primary cause of excess mortality among patients with type 2 diabetes.[20–22] This study shows that adding SGLT2i to GLP-1RA reduces major cardiovascular events and HF hospitalizations. The randomized trials of SGLT2i included patients with established cardiovascular disease or multiple risk factors. In contrast, this study population includes real-world patients with and without previous cardiovascular disease or additional risk factors, supporting benefit across the spectrum of established cardiovascular disease. We observed nonstatistically significant reductions in MI and all-cause mortality but not stroke, with point estimates similar to those seen in the randomized clinical trials.[3,5] Furthermore, the Kaplan-Meier curves for HF hospitalizations separated early, and within 6 months of therapy initiation, similar to published trials[3–5] and observational studies.[23] Findings from this study support that not only do SGLT2i reduce cardiovascular events in patients using GLP-1RA therapy, but that the magnitudes of these reductions are similar to what was observed in cardiovascular trials with SGLT2i, where GLP-1RA use was minimal.[24]

Whereas no previous study has examined the cardiovascular benefits of combining SGLT2i and GLP-1RA, 2 short-term clinical trials have demonstrated clinically relevant improvements in glycemic control with acceptable tolerability. DURATION-8 (Phase 3 28-Week Study With 24-Week and 52-Week Extension Phases to Evaluate Efficacy and Safety of Exenatide Once Weekly and Dapagliflozin Versus Exenatide and Dapagliflozin Matching Placebo) was a 28-week randomized clinical trial that showed that coinitiation of SGLT2i (dapagliflozin) and GLP-1RA (exenatide) was superior to either agent alone and to placebo in reducing hemoglobin A1C, blood pressure, and body weight.[25] AWARD-10 (A Study of Dulaglutide [LY2189265] in Participants With Type 2 Diabetes Mellitus) was a 24-week randomized trial that assessed the effect of using GLP-1RA (dulaglutide) and any SGLT2i and found superior

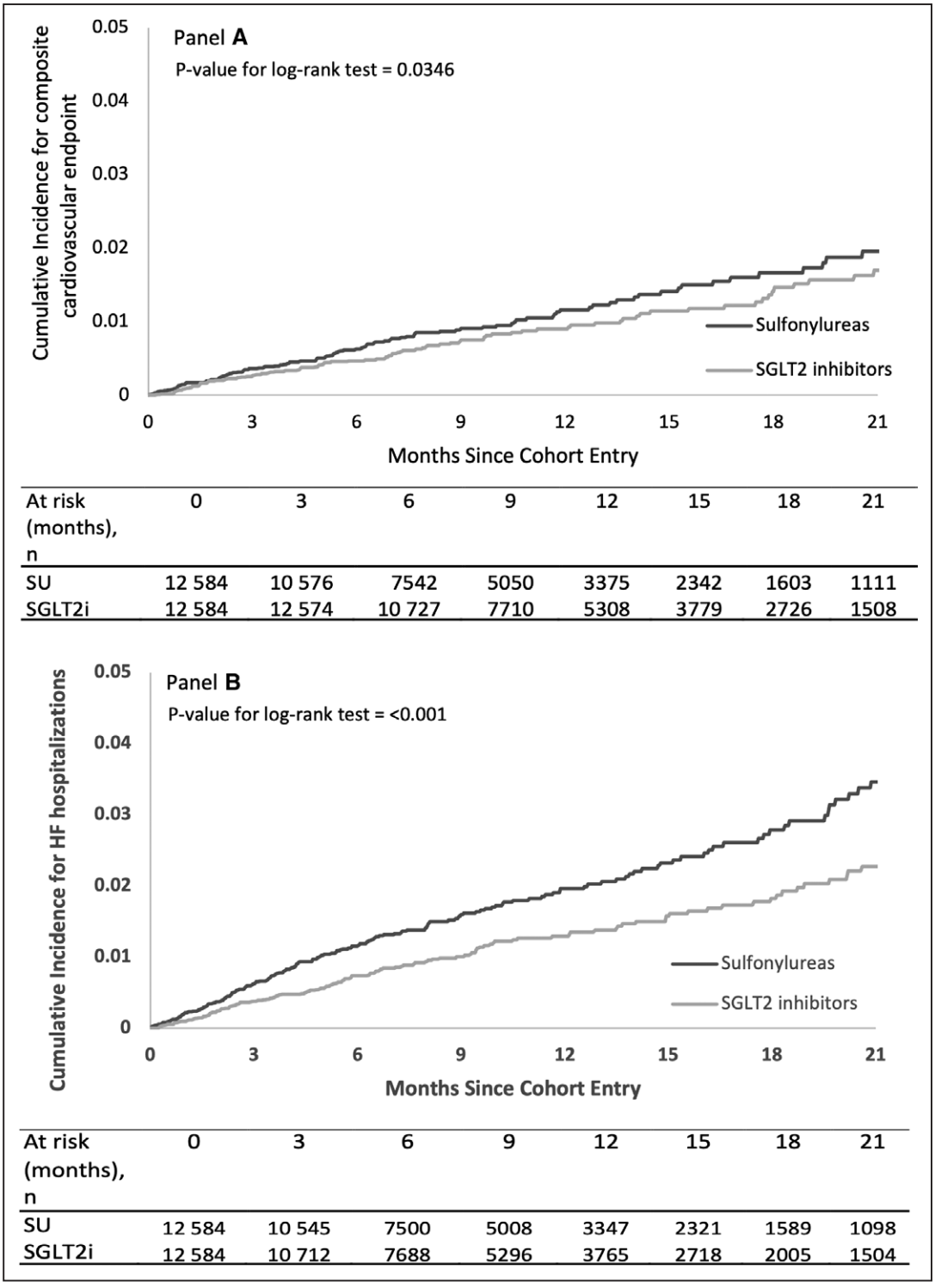

Figure. Propensity score matched Kaplan-Meier curves for cumulative incidence of the primary outcomes.
Propensity score matched Kaplan-Meier curves for cumulative incidence of composite cardiovascular end point, defined as myocardial infarction or stroke hospitalizations or all-cause mortality (see text for details; **A**), and heart failure (HF) admissions (**B**) for patients initiating sodium-glucose cotransporter-2 inhibitor (SGLT2i) or sulfonylureas (SU) with existing glucagon-like peptide receptor agonist therapy.

reductions in hemoglobin A1C with the combination compared with placebo.[26] Together these studies support additive glucose-lowering effects, but do not elucidate their cardiovascular effects.

In routine clinical care, there may be several barriers to adding SGLT2i in patients using GLP-1RA therapy. These include high drug costs associated with the use of 2 branded products (to date, neither agent has a

Table 3. Risk of the Primary Outcomes in Propensity Score–Matched Cohorts, Sensitivity, and Subgroup Analyses

Variable	Total no. of patients	Events (incidence rates)*		Hazard ratio (95% CI)†
		SGLT2i	Sulfonylurea	
Composite cardiovascular end point‡				
Primary analysis	25 168	107 (9.9)	129 (13.0)	0.76 (0.59–0.98)
Intention-to-treat analysis	25 168	214 (11.1)	269 (14.1)	0.80 (0.67–0.96)
Inverse probability of treatment weights analysis	59 115	215 (9.7)	309 (13.5)	0.73 (0.61–0.87)
Subgroup: no cardiovascular disease	19 928	75 (8.8)	77 (9.8)	0.87 (0.53–1.40)
Subgroup: cardiovascular disease	4976	37 (18.1)	50 (25.2)	0.74 (0.48–1.13)
Select active ingredients§	15 420	69 (10.0)	82 (13.0)	0.77 (0.54–1.12)
Heart failure hospitalizations				
Primary analysis	25 168	274 (14.3)	358 (18.9)	0.64 (0.50–0.82)
Intention-to-treat analysis	25 168	260 (13.5)	343 (18.1)	0.74 (0.57–0.96)
Inverse probability of treatment weights analysis	59 115	275 (12.4)	491 (21.6)	0.59 (0.51–0.68)
Subgroup: no cardiovascular disease	19 928	55 (6.4)	72 (9.1)	0.64 (0.38–1.09)
Subgroup: cardiovascular disease	4976	98 (48.5)	130 (67.1)	0.76 (0.59–0.98)
Select active ingredients§	15 420	95 (13.8)	135 (21.6)	0.66 (0.51–0.86)

SGLT2i indicates sodium-glucose cotransporter-2 inhibitor.

*Events and incidence rates are pooled across the 3 databases. Incidence rates are per 1000 person-years of follow-up. See Table V in the Data Supplement for database-specific number of events and rates.

†Hazard ratios were adjusted through 1:1 propensity score matching constructed using >95 variables and are for SGLT2i vs sulfonylurea (referent). See text for details. Analysis was stratified within each database and fixed effects meta-analysis were used to pool. See Table VIII in the Data Supplement in the supplement for information on number of events and database-specific estimates.

‡Defined as the composite of myocardial infarction hospitalizations, stroke hospitalizations, and all-cause mortality (see text for details).

§Restricted to 2 SGLT2i (empagliflozin and canagliflozin) versus glimepiride. See text for details.

generic approved), long-term adherence to a complicated glucose-lowering regimen consisting of oral and injectable therapies, and an unwillingness among some patients to use injectable therapies; the recent approval of oral semaglutide may alleviate some, but not all, of these concerns. In addition, GLP1-RA use may be limited by gastrointestinal intolerance, among other adverse effects; SGLT2i may be associated with unique adverse reactions, including diabetic ketoacidosis and genital infections,[5,27–30] which require consideration in deciding whether to prescribe an SGLT2i.

This study took several steps to mitigate the potential for confounding by restricting analysis to new users and adjusting for more than 95 pertinent variables. By pooling data from 3 US-based insurance claims, this investigation included >12 000 matched pairs; patients were sourced from routine clinical care (ie, no enrichment strategies were used), ensuring wide generalizability of the study findings across age groups and in patients with employer-sponsored health plans and patients in Medicare fee-for-service and managed care plans. Moreover, estimates were consistent across a range of sensitivity (eg, intention-to-treat analysis) and subgroup analyses highlighting the robustness of the study findings. Information on medication dispensing, rather than prescribing data, were available for all 3 databases, reducing the opportunity for exposure misclassification.

There are some limitations to this study. Owing to the observational nature of the design, our study is susceptible to residual confounding because of lack of randomization. For instance, patients initiating sulfonylureas were different from those initiating SGLT2i and therefore we were able to match fewer than half of the patients in the sulfonylurea arm (the smaller of the 2 groups). Furthermore, although we measured and adjusted for several potential confounders and their proxies, information on important diabetes-related variables such as duration of diabetes or cardiovascular risk factors such as body mass index or blood pressure were unavailable. However, previous studies have shown that balance in these unmeasured characteristics can be achieved with the use of claims-based proxies in administrative claims data.[31] Furthermore, the requirement of use of GLP-1RA in both groups may have reduced imbalance among unmeasured covariates. After adjustments for previous cardiovascular events and conditions, severity of diabetes, other comorbidities (eg, chronic kidney disease), and treatments for cardiovascular conditions and diabetes, we do not expect these factors to be substantially imbalanced between the 2 treatment groups. Second, treatment initiation was defined using a 180-day period, so that some patients may have been exposed to the treatment before this time window. Third, therapeutics were assessed by drug class and therefore individual agents may have

Table 4. Risk of the Secondary Outcomes in Propensity Score Matched Cohorts

Variable	Events (incidence rate)*		Hazard ratio (95% CI)†
	SGLT2i	Sulfonylurea	
Primary outcomes	107 (9.9)	129 (13.0)	0.76 (0.59–0.98)
Composite cardiovascular end point	107 (9.9)	129 (13.0)	0.76 (0.59–0.98)
Heart failure hospitalizations	141 (13.0)	206 (20.8)	0.64 (0.50–0.82)
Secondary outcomes			
Composite cardiovascular end point plus heart failure hospitalizations	216 (20.0)	290 (29.4)	0.69 (0.55–0.87)
Myocardial infarction or stroke hospitalizations	88 (8.1)	100 (10.0)	0.80 (0.60–1.06)
Myocardial infarction hospitalizations	60 (5.5)	76 (7.6)	0.71 (0.51–1.00)
Stroke hospitalizations	30 (2.8)	26 (2.6)	1.05 (0.62–1.79)
All-cause mortality	25 (2.3)	34 (3.4)	0.68 (0.40–1.14)
Influenza vaccination‡	3954 (528)	3980 (503)	0.97 (0.92–1.01)

SGLT2i indicates sodium-glucose cotransporter-2 inhibitor.

*Events and incidence rates are pooled across the 3 databases. Incidence rates are per 1000 person-years of follow-up. See Table V in the Data Supplement for database-specific number of events and rates.

†Hazard ratios were adjusted through 1:1 propensity score matching constructed using >95 variables and are for SGLT2i vs sulfonylurea (referent). See text for details. Analysis was stratified within each database and fixed effects meta-analysis were used to pool. See Table IX in the Data Supplement for information on number of events and database-specific estimates.

‡Administration of influenza vaccine was a negative control outcome. See text for details.

contributed disproportionately to findings. To account for this, we conducted a subgroup analysis of patients using empagliflozin and canagliflozin versus glimepiride, which produced similar findings.

In conclusion, in this large real-world cohort of 25 168 propensity score matched patients with diabetes on GLP-1RA, the addition of SGLT2i conferred additional cardiovascular benefit. This study offers important clinical information by increasing understanding of the cardiovascular benefits of adding SGLT2i to existing GLP-1RA therapy and provides support for SGLT2i use in this setting. These findings have relevant implications for preventing further cardiovascular morbidity and mortality in patients with diabetes.

ARTICLE INFORMATION

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Supplemental Materials

Data Supplement Figure I
Data Supplement Tables I–IX

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