ORIGINAL RESEARCH

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Sodium–Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections

A Population-Based Cohort Study

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Background: Prior studies evaluating risk for severe urinary tract infections (UTIs) with sodium–glucose cotransporter-2 (SGLT-2) inhibitors have reported conflicting findings.

Objective: To assess whether patients initiating use of SGLT-2 inhibitors were at increased risk for severe UTI events compared with those initiating use of dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor (GLP-1) agonists.

Design: Population-based cohort study.

Setting: 2 large, U.S.-based databases of commercial claims (March 2013 to September 2015).

Participants: Within each database, 2 cohorts were created and matched 1:1 on propensity score. Patients were aged 18 years or older, had type 2 diabetes mellitus, and were initiating use of SGLT-2 inhibitors versus DPP-4 inhibitors (cohort 1) or GLP-1 agonists (cohort 2).

Measurements: The primary outcome was a severe UTI event, defined as a hospitalization for primary UTI, sepsis with UTI, or pyelonephritis; the secondary outcome was outpatient UTI treated with antibiotics. Hazard ratios (HRs) were estimated in each propensity score–matched cohort, with adjustment for more than 90 baseline characteristics.

Results: After 1:1 matching on propensity score, 123 752 patients were identified in cohort 1 and 111 978 in cohort 2 in the 2 databases. In cohort 1, persons newly receiving SGLT-2 inhibitors had 61 severe UTI events (incidence rate [IR] per 1000 person-years, 1.76), compared with 57 events in the DPP-4 inhibitor group (IR, 1.77) (HR, 0.98 [95% CI, 0.68 to 1.41]). In cohort 2, those receiving SGLT-2 inhibitors had 73 events (IR, 2.15), compared with 87 events in the GLP-1 agonist group (IR, 2.96) (HR, 0.72 [CI, 0.53 to 0.99]). Findings were robust across sensitivity analyses; within several subgroups of age, sex, and frailty; and for canagliflozin and dapagliflozin individually. In addition, SGLT-2 inhibitors were not associated with increased risk for outpatient UTIs (cohort 1: HR, 0.96 [CI, 0.89 to 1.04]; cohort 2: HR, 0.91 [CI, 0.84 to 0.99]).

Limitation: Generalizability of the study findings may be limited to patients with commercial insurance.

Conclusion: In a large cohort of patients seen in routine clinical practice, risk for severe and nonsevere UTI events among those initiating SGLT-2 inhibitor therapy was similar to that among patients initiating treatment with other second-line antidiabetic medications.

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Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are a newer class of antidiabetic medications that reduce serum glucose by inhibiting its reabsorption in the proximal tubule (1). In addition to decreasing serum glucose, they exert a beneficial effect on cardiometabolic markers, such as blood pressure (2), and have reduced cardiovascular events and mortality in both randomized and nonexperimental studies (3–6).

Because SGLT-2 inhibitors increase the availability of glucose in the urinary tract, they provide substrate for bacteria to grow (7, 8). Accordingly, they have been previously linked to infections of the genitourinary tract (2, 9). Although SGLT-2 inhibitors have consistently been shown to increase risk for genital infections (9, 10), their association with urinary tract infections (UTIs) is less clear, and prior meta-analyses have reported conflicting findings (2, 11, 12). Most UTIs caused by SGLT-2 inhibitors are of mild to moderate severity (13), but in 2015 the U.S. Food and Drug Administration revised labels for all SGLT-2 inhibitors to add a warning about severe UTIs. This warning was prompted by postmarketing reports of sepsis with UTI and pyelonephritis in patients using these agents (14).

The relationship between SGLT-2 inhibitor use and risk for severe UTI remains unclear, and prior evidence comes either from postmarketing reports—which have limited validity (15)—or from clinical trials—which despite pooling leave substantial uncertainty for such a rare outcome. For example, a recent meta-analysis of 72 clinical trials found only 17 cases of sepsis with UTI in the SGLT-2 inhibitor group (0.67 events per 1000 patients) (11).

Using 2 large databases of U.S. commercial claims, we aimed to assess whether initiation of SGLT-2 inhibitor therapy was associated with increased risk for severe UTIs compared with initiation of treatment using 2 alternative nongliflozin classes of antidiabetic medication among patients with type 2 diabetes mellitus.

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Methods

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

Data Sources

The study used data sourced from IBM MarketScan ("MarketScan") and Optum Clinformatics Data Mart ("Optum"), both of which are U.S. databases of patients with employer-based insurance. In addition, Optum provides data for patients with managed-care Medicare through UnitedHealthcare plans, and MarketScan provides data for patients with supplemental Medicare coverage. Data elements of interest include patient demographic characteristics, medical and pharmacy enrollment status, inpatient and outpatient medical services (International Classification of Diseases, Ninth Revision, Clinical Modification, and CPT-4 [Current Procedural Terminology, Fourth Edition] codes), and outpatient pharmacy dispensing (including drug names, strength, units dispensed, and days' supply).

Study Population and Exposure Definition

Within each database, a separate cohort was created for each pairwise comparison of SGLT-2 inhibitors versus an alternative nongliflozin class, and cohort entry was restricted to between March 2013 (to coincide with approval of the first SGLT-2 inhibitor in the United States) and September 2015. Cohort membership required patients to be new users of the study medications of interest (defined as no use in the 180-day washout window), be aged 18 years or older at cohort entry, and have a recorded diagnosis of type 2 diabetes mellitus at any time before initiating use of the study drug. Patients with evidence of nursing home or hospice care, gestational diabetes, type 1 diabetes mellitus, cancer, HIV, or renal insufficiency (chronic kidney disease, acute renal failure, or end-stage renal disease); those with high risk for UTI (for example, hydronephrosis, vesicoureteral reflux, spinal cord injuries, or catheter use); and those with a history of UTI were excluded from the analysis (**Appendix Table 1** [available at Annals.org] gives a complete list of exclusion criteria).

The first cohort comprised patients initiating use of an SGLT-2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin; empagliflozin–linagliptin combination was not considered in cohort 1 [**Appendix Table 2** lists included products]) or a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin, saxagliptin, linagliptin, or alogliptin) without evidence of prior use of either SGLT-2 or DPP-4 inhibitors. Similarly, the second cohort included patients initiating use of an SGLT-2 inhibitor or a glucagon-like peptide-1 receptor (GLP-1) agonist (albiglutide, dulaglutide, exenatide, or liraglutide) without prior use of either SGLT-2 inhibitors or GLP-1 agonists. Patients meeting the inclusion criteria could contribute to each cohort only once, but the same patient could be included in both cohorts (**Appendix Figure 1** [available at Annals.org] shows the study design).

Propensity Score Matching

All analyses were done using SAS, version 9.4 (SAS Institute). To mitigate risk for confounding, new users of SGLT-2 inhibitors were matched to patients receiving a nongliflozin agent (DPP-4 inhibitors in cohort 1 and GLP-1 agonists in cohort 2) on their estimated propensity score, which used logistic regression with 91 baseline covariates (PROC LOGISTIC) to model the probability of initiating SGLT-2 inhibitor therapy. These baseline covariates were measured in the 180-day period before cohort entry and included demographic variables (such as age and sex), microvascular and macrovascular complications of diabetes (such as diabetic neuropathy and myocardial infarction), insulin use and other antidiabetic therapy, risk factors for UTI (such as use of oral steroids or broad-spectrum antibiotics, history of mycotic infections, and use of disease-modifying antirheumatic drugs), comorbid conditions (such as chronic obstructive pulmonary disease), a claims-based frailty index (which uses claims data to create an aggregate measure of frailty in which higher scores correspond to higher risk for death and disability [16, 17]), measures of health care use (such as number of emergency department visits), and markers for a healthy user (such as immunization status). A 1:1 propensity score–matched cohort was created in each comparison using nearest-neighbor matching within a maximum caliper width of 0.01.

Follow-up and Study End Point

Patients contributed follow-up time from the day after cohort entry until occurrence of any of the following: end of health care or pharmacy eligibility, switching to a comparator class, discontinuation of therapy (defined as a 30-day treatment gap after the last prescription), end of study data (30 September 2015), or occurrence of the outcome.

The primary study end point was the occurrence of a severe UTI event (composite of primary UTI hospitalizations, hospitalizations with sepsis and UTI, and hospitalizations with pyelonephritis). A primary UTI hospitalization required the presence of diagnosis codes related to UTI (cystitis, ureteritis, or pyelonephritis: 590.xx, 595.xx, 597.xx, or 599.0x) in the primary discharge diagnosis field. A hospitalization with sepsis and UTI required the co-occurrence of discharge codes related to UTI (590.xx, 595.xx, 597.xx, or 599.0x) and those related to sepsis (bacteremia, septicemia, sepsis, or septic shock: 785.52, 790.7, 955.8x, or 995.9x) at any discharge diagnosis position, whereas a hospitalization with pyelonephritis required codes related to pyelonephritis (590.xx) at any discharge diagnosis position.

In addition to examining the individual components of the primary composite outcome, we examined the following 2 secondary outcomes: any UTI-related hospitalization (UTI-related codes in any position) and treated outpatient UTI (which required evidence of outpatient antibiotic dispensing and outpatient diagnosis codes related to UTI). **Appendix Table 1** defines all outcomes.

Statistical Analysis

Primary Analysis

We assessed the performance of the propensity score by cross-tabulating the baseline covariates before and after propensity score matching by exposure group; we used a threshold of 10% in the standardized difference as a meaningful imbalance between the 2

Table 1. Selected Pooled Baseline Characteristics After Propensity Score Matching*

Characteristic	SGLT-2 vs. DPP-4 Inhibitors (Cohort 1)			SGLT-2 Inhibitors vs. GLP-1 Agonists (Cohort 2)		
	SGLT-2 (*n* = 61 876)	DPP-4 (*n* = 61 876)	Standardized Difference, %	SGLT-2 (*n* = 55 989)	GLP-1 (*n* = 55 989)	Standardized Difference, %
Male sex, *n* (%)	33 502 (54.1)	33 645 (54.4)	0.5	27 686 (49.4)	27 715 (49.5)	0.1
Mean age (SD), *y*	54.7 (9.9)	54.7 (10.2)	0.2	54.5 (10.1)	54.4 (10.1)	1.4
Diabetic severity						
Ocular complications, *n (%)*	2469 (4.0)	2453 (4.0)	0.1	2519 (4.5)	2466 (4.4)	0.5
Neurologic complications, *n (%)*	4567 (7.4)	4634 (7.5)	0.4	5126 (9.2)	5093 (9.1)	0.2
Other or unspecified complications, *n (%)*	4292 (6.9)	4235 (6.8)	0.4	4381 (7.8)	4392 (7.8)	0.1
Mean hemoglobin A_{1c} level (SD), %†	8.8 (1.8)	8.8 (1.9)	0.1	8.7 (1.8)	8.8 (1.9)	0.1
Antidiabetic therapy, *n* (%)						
Metformin	48 319 (78.1)	48 480 (78.4)	0.6	42 599 (76.1)	42 586 (76.1)	0.1
DPP-4 inhibitors	–	–	–	17 046 (30.4)	17 113 (30.6)	0.3
GLP-1 agonists	4915 (7.9)	4270 (6.9)	4.0	–	–	–
Insulin	12 067 (19.5)	11 838 (19.1)	0.9	18 237 (32.6)	18 117 (32.4)	0.5
Sulfonylureas	22 052 (35.6)	22 208 (35.9)	0.5	20 850 (37.2)	20 720 (37.0)	0.5
Risk factors for UTI, *n* (%)						
Use of broad-spectrum antibiotics	14 487 (23.4)	14 393 (23.3)	0.4	13 648 (24.4)	13 489 (24.1)	0.7
Use of oral steroids	6353 (10.3)	6263 (10.1)	0.5	5796 (10.4)	5833 (10.4)	0.2
Use of nonbiologic DMARDs	519 (0.8)	509 (0.8)	0.2	473 (0.8)	481 (0.9)	0.2
Use of biologic DMARDs	381 (0.6)	389 (0.6)	0.2	386 (0.7)	391 (0.7)	0.1
Mycotic infections	3402 (5.5)	3377 (5.5)	0.2	3453 (6.2)	3439 (6.1)	0.1
	Value			Value		
Propensity score diagnostics						
AUC						
Optum	0.52			0.51		
MarketScan	0.52			0.51		
Average standardized difference, %	0.4			0.3		

AUC = area under the curve; DMARD = disease-modifying antirheumatic drug; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.
* Selected pooled variables are shown; Appendix Tables 3 to 6 (available at Annals.org) show baseline characteristics before and after propensity score matching, stratified by database and cohort. Appendix Table 7 (available at Annals.org) is analogous to this table but before propensity score matching.
† Available for 10% of the pooled sample and not included in the propensity score model.

groups (18) and examined the c-statistic for the logistic regression model (values closer to 0.50 indicate less imbalance in the covariates between the 2 groups) (19). Hemoglobin A_{1c} levels (available for 10% of the pooled population; not included in the propensity score) were used to assess the presence of adequate therapeutic equipoise between the SGLT-2 group and their nongliflozin counterparts before propensity score matching and to assess potential residual confounding after propensity score matching. No other data were missing in our study.

In the propensity score–matched cohorts, we estimated risk for a severe UTI event for patients receiving SGLT-2 inhibitors versus nongliflozin agents by calculating numbers of events, incidence rates (IRs), and hazard ratios (HRs) (PROC PHREG) with Wald 95% CIs. Analyses were done in each database, and estimates were pooled through inverse-variance fixed-effects meta-analysis (20). Kaplan–Meier curves (PROC LIFETEST) were generated to visualize the risk for the outcome over time, and log-rank tests were used to compare the survival distribution in the 2 groups.

Sensitivity and Subgroup Analyses

We did several sensitivity analyses to assess the robustness of the study findings. First, because severe UTI events may be rare and to preserve power by including more patients, we altered the propensity score specification using a variable-ratio, parallel, balanced matching technique (21). We also used a propensity score–based fine-stratification approach (50 strata) (22). Second, we varied study specifications pertaining to exposure-related censoring criteria and maximum length of follow-up. Specifically, in addition to the as-treated analysis—where we censored patients at the time of treatment discontinuation or switching—we carried the index exposure forward to mimic an intention-to-treat approach. For both approaches, we also varied the maximum follow-up duration to 3 months, 6 months, 12 months, and the end of study data.

We tested for the presence of effect modification in several relevant subgroups. First, we restricted the analysis to patients without evidence of antibiotic use, disease-modifying antirheumatic drug use, or infections in the baseline period (defined as 180 days be-

fore cohort entry). Second, we stratified the analysis by sex to reflect the differences in incidence and severity of UTIs (23). Third, because older patients may have a higher baseline risk for UTIs and develop more severe symptoms (24), we also stratified the analysis by age (using 60 years as the threshold to reflect the distribution of older patients in our study population). Fourth, because high frailty is likely associated with higher risk for severe infections, we stratified the analysis by frailty using tertiles of a claims-based frailty index to group patients into low, moderate, and high frailty.

Finally, we examined the association between individual SGLT-2 inhibitors and risk for severe UTI events, although this analysis was limited to canagliflozin and dapagliflozin because not enough patients were exposed to empagliflozin during the study period. For the dapagliflozin analysis, cohort entry was restricted to after February 2014 to reflect the U.S. market approval date.

Within each subgroup, the propensity score was reestimated and patients were rematched on the newly estimated score using 1:1 nearest-neighbor matching within a caliper width of 0.01.

Role of the Funding Source

This study was funded by internal funds of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. The authors had complete control over design, analysis, and the decision to submit the manuscript for publication.

RESULTS

Across the 2 databases, cohort 1 comprised 270 762 patients who started to use an SGLT-2 inhibitor and 440 970 patients who started to use a DPP-4 inhibitor and cohort 2 comprised 273 617 patients who started to use an SGLT-2 inhibitor and 211 701 who started to use a GLP-1 agonist. After the inclusion and exclusion criteria were applied, cohort 1 comprised 86 665 new users of SGLT-2 inhibitors and 136 741 new users of DPP-4 inhibitors and cohort 2 comprised 107 289 new users of SGLT-2 inhibitors and 67 871 new users of GLP-1 agonists who were eligible for propensity score matching. From these, we created cohorts of 123 752 patients (cohort 1) and 111 978 patients (cohort 2) who were matched 1:1 on propensity score (**Appendix Figures 2** and **3** [available at Annals.org] show the CONSORT [Consolidated Standards of Reporting Trials] flow diagram).

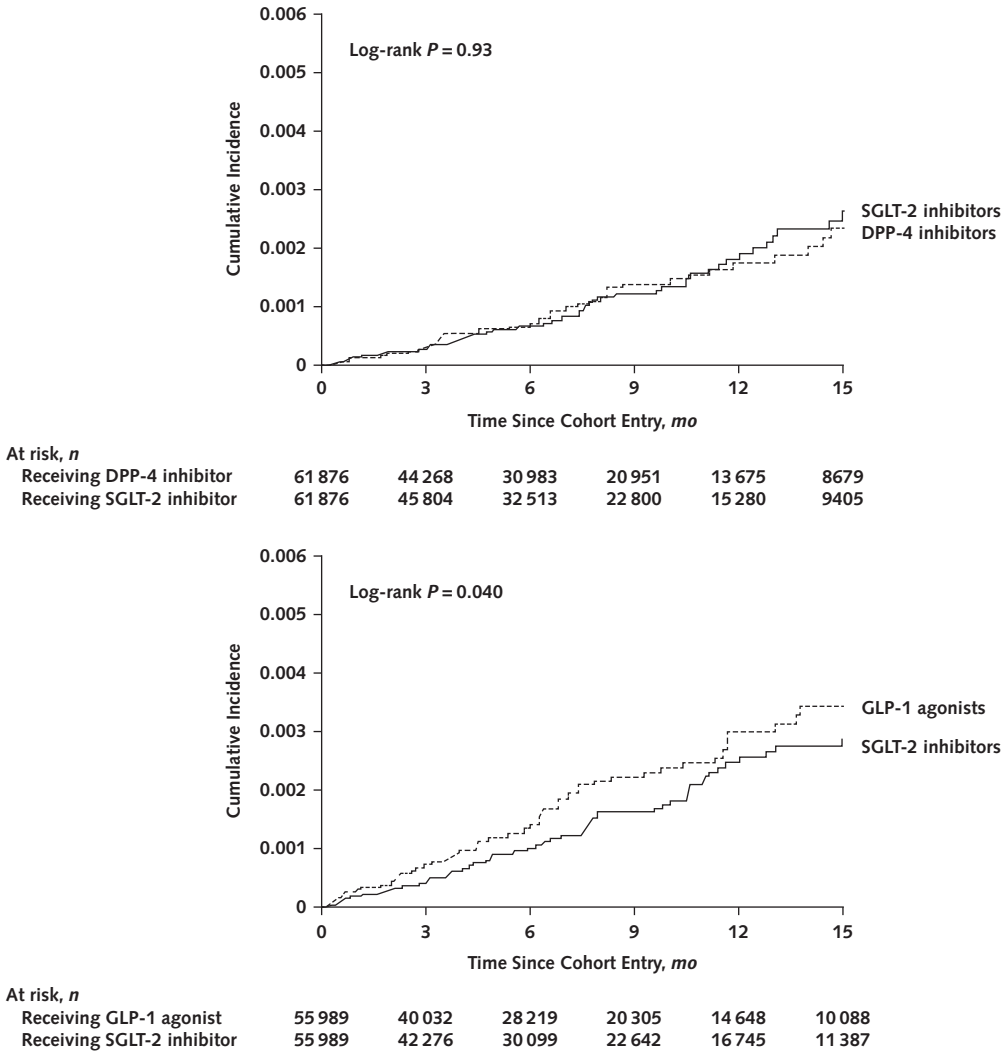
Appendix Tables 3 to **6** (available at Annals.org) show the baseline characteristics of patients before and after propensity score matching (stratified by database and cohort). **Appendix Table 7** (available at Annals.org) and **Table 1** show selected pooled baseline characteristics before and after propensity score matching, respectively. Before matching, new users of SGLT-2 inhibitors in cohort 1 were more likely to be younger, have more diabetes-related complications, and have a history of insulin or GLP-1 agonist use; patients in the SGLT-2 inhibitor group in cohort 2 were more likely to

Table 2. Risk for a Severe UTI Event Associated With SGLT-2 Inhibitors Before and After Propensity Score Matching*

Variable	Before Propensity Score Matching				After Propensity Score Matching			
	SGLT-2 vs. DPP-4 Inhibitors (Cohort 1)		SGLT-2 Inhibitors vs. GLP-1 Agonists (Cohort 2)		SGLT-2 vs. DPP-4 Inhibitors (Cohort 1)		SGLT-2 Inhibitors vs. GLP-1 Agonists (Cohort 2)	
	SGLT-2 (*n* = 21 976)	DPP-4 (*n* = 38 993)	SGLT-2 (*n* = 26 519)	GLP-1 (*n* = 18 402)	SGLT-2 (*n* = 16 147)	DPP-4 (*n* = 16 147)	SGLT-2 (*n* = 14 645)	GLP-1 (*n* = 14 645)
Optum Clinformatics								
Events, *n*	19	63	27	19	12	14	19	15
Mean follow-up, *d*	192	235	194	201	195	188	208	187
Incidence rate†	1.64	2.51	1.92	1.88	1.39	1.68	2.27	2.00
HR (95% CI)	0.65 (0.39–1.08)		1.01 (0.56–1.81)		0.82 (0.38–1.77)		1.14 (0.58–2.24)	
	SGLT-2 (*n* = 64 689)	DPP-4 (*n* = 97 748)	SGLT-2 (*n* = 80 759)	GLP-1 (*n* = 49 480)	SGLT-2 (*n* = 45 729)	DPP-4 (*n* = 45 729)	SGLT-2 (*n* = 41 344)	GLP-1 (*n* = 41 344)
MarketScan								
Events, *n*	70	143	85	93	49	43	54	72
Mean follow-up, *d*	205	237	205	207	208	191	225	193
Incidence rate†	1.93	2.25	1.88	3.32	1.88	1.79	2.12	3.30
HR (95% CI)	0.86 (0.65–1.14)		0.56 (0.42–0.75)		1.03 (0.69–1.56)		0.64 (0.45–0.91)	
	SGLT-2 (*n* = 86 665)	DPP-4 (*n* = 136 741)	SGLT-2 (*n* = 107 278)	GLP-1 (*n* = 67 882)	SGLT-2 (*n* = 61 876)	DPP-4 (*n* = 61 876)	SGLT-2 (*n* = 55 989)	GLP-1 (*n* = 55 989)
Pooled								
Events, *n*	89	206	112	112	61	57	73	87
Mean follow-up, *d*	202	236	202	205	204	190	221	191
Incidence rate†	1.86	2.33	1.89	2.93	1.76	1.77	2.15	2.96
HR (95% CI)‡	0.80 (0.63–1.03)		0.63 (0.48–0.82)		0.98 (0.68–1.41)		0.72 (0.53–0.99)	

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; HR = hazard ratio; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.
* Outcome defined as a composite of primary UTI hospitalizations, hospitalizations with sepsis and UTI, and hospitalizations with pyelonephritis; see text and Appendix figures and tables for definitions.
† Per 1000 person-years of follow-up.
‡ Estimates were pooled across the 2 databases using fixed-effects meta-analysis.

Figure. Propensity score–matched Kaplan–Meier curves for cumulative incidence of severe urinary tract infection events in the pooled cohort of patients.



DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2.

be male and have a history of DPP-4 inhibitor use but were less likely to have used insulin during the baseline period.

After 1:1 propensity score matching, the baseline characteristics were well balanced between the 2 groups in both cohorts and no standardized differences exceeded 10%. After matching, the average standardized difference decreased from 6.9% to 0.5% in cohort 1 and from 5.1% to 0.3% in cohort 2; c-statistics (where values closer to 0.5 indicate better balance) also decreased after matching from 0.80 to 0.52 for cohort 1 and from 0.70 to 0.51 for cohort 2. Hemoglobin A_{1c} values were similar between the 2 groups in both cohorts even before propensity score matching, implying good therapeutic equipoise between the SGLT-2 and nongliflozin groups, and they remained well balanced after matching.

Analysis of Primary and Secondary Outcomes

Table 2 shows pooled and database-specific estimates for the primary analysis (Appendix Tables 8 and 9 [available at Annals.org] give further information on follow-up time and censoring reasons). In cohort 1 before propensity score matching, the SGLT-2 inhibitor group had 89 cases of severe UTI events among 86 665 patients, corresponding to an IR of 1.86 cases per 1000 person-years of follow-up; the DPP-4 inhibitor group had 206 events among 136 741 patients (IR, 2.33 cases per 1000 person-years), corresponding to an unadjusted HR of 0.80 (95% CI, 0.63 to 1.03). After propensity score matching (n = 61 876 matched pairs), the SGLT-2 inhibitor group had 61 severe UTI events (IR, 1.76 cases per 1000 person-years) compared with 57 in the DPP-4 inhibitor group (IR, 1.77 cases per 1000 person-years), corresponding to an adjusted HR of 0.98

(CI, 0.68 to 1.41). The **Figure** shows the cumulative incidence of severe UTIs since the start of study drug use pooled across both cohorts as Kaplan–Meier plots. **Appendix Figures 4** and **5** (available at Annals.org) show database-specific plots. The *P* value for the log-rank test was 0.93 in cohort 1.

In cohort 2, the SGLT-2 inhibitor group had 112 events among 107 278 patients (IR, 1.89 cases per 1000 person-years) compared with 112 events among 67 882 patients in the GLP-1 agonist group (IR, 2.93 cases per 1000 person-years) (unadjusted HR, 0.63 [CI, 0.48 to 0.82]). After matching (n = 55 989 matched pairs), the SGLT-2 inhibitor group had 73 events (IR, 2.15 cases per 1000 person-years) and the GLP-1 agonist group 87 events (IR, 2.96 cases per 1000 person-years) (HR, 0.72 [CI, 0.53 to 0.99]). The *P* value for the log-rank test was 0.040.

Findings were consistent for all secondary outcomes (**Table 3** and **Appendix Table 10**, available at Annals.org; **Appendix Table 11** [available at Annals.org] gives the IRs of the secondary outcomes). Sodium–glucose cotransporter-2 inhibitors were not associated with an increase in risk for any UTI hospitalizations in cohort 1 (HR, 0.68 [CI, 0.54 to 0.87]) or cohort 2 (HR, 0.78 [CI, 0.62 to 0.99]). Likewise, SGLT-2 inhibitors were not associated with an increase in risk for treated outpatient UTIs in cohort 1 (HR, 0.96 [CI, 0.89 to 1.04]) or cohort 2 (HR, 0.91 [CI, 0.84 to 0.99]).

Sensitivity and Subgroup Analyses

Study findings were consistent across a range of sensitivity and subgroup analyses (**Table 4**; **Appendix Figures 6** and **7** [available at Annals.org] show database-specific estimates). Changing the propensity score matching approach from a 1:1 to a variable-ratio match did not appreciably change the point estimates; findings were also similar using fine stratification based on propensity score. Further, findings from the intention-to-treat analysis were similar to those from the as-treated analysis regardless of the maximum duration of follow-up considered.

Risk for the outcome also did not vary meaningfully in either cohort across the several subgroups of sex, age, and baseline frailty; among those at low risk for severe UTI events; or for individual SGLT-2 inhibitors.

DISCUSSION

Because of their pharmacodynamic properties, SGLT-2 inhibitors have been postulated to increase risk for severe UTI events; however, to our knowledge this association has not been previously studied in a routine care setting. This study examined data from 2 large commercial claims databases and found that compared with patients initiating use of a DPP-4 inhibitor or GLP-1 agonist, those initiating use of an SGLT-2 inhibitor for the management of type 2 diabetes mellitus had a similar rate of severe or nonsevere UTI events. Study findings were consistent across a range of predefined sensitivity analyses; within several subgroups of age, sex, and frailty; and for individual SGLT-2 agents.

This study has important clinical implications. Patients with diabetes have a higher frequency and severity of UTIs (25, 26); thus, antidiabetic agents that increase risk for such infections may decrease quality of life, predisposing patients to therapy discontinuation and poor glycemic control. In addition, uroseptic and pyelonephritic infections have been found to contribute to patient mortality, making the study findings relevant in guiding the care of patients with diabetes. Further, patients who may be good candidates to receive SGLT-2 inhibitors for diabetes control but who have a history of recurrent UTIs may be precluded from being prescribed these agents; because UTIs are highly prevalent in patients with diabetes, this could exclude a substantial number of patients from receiving an entire class of medications that has been shown to decrease risk for major cardiovascular events and death.

Our study did not find an increase in risk for UTI events among new users of SGLT-2 inhibitors, but some evidence suggested a lower risk for UTIs with these agents (vs. GLP-1 agonists) in 1 database (MarketScan). However, we caution against overinterpreting these results, because additional sources of uncertainty—possibly

Table 3. Risk for Secondary Outcomes Associated With SGLT-2 Inhibitors in a Propensity Score–Matched Analysis*

Outcome	HR (95% CI) for SGLT-2 vs. DPP-4 Inhibitors (Cohort 1)	HR (95% CI) for SGLT-2 Inhibitors vs. GLP-1 Agonists (Cohort 2)
Primary outcome†	0.98 (0.68–1.41)	0.72 (0.53–0.99)
Individual components of the primary outcome		
Hospitalizations with sepsis and UTI	1.11 (0.68–1.82)	0.54 (0.36–0.82)
Hospitalizations with pyelonephritis	0.74 (0.45–1.21)	0.65 (0.42–1.00)
Primary UTI hospitalizations	0.81 (0.46–1.43)	0.86 (0.52–1.43)
Other secondary outcomes		
UTI hospitalizations‡	0.68 (0.54–0.87)	0.78 (0.62–0.99)
Treated outpatient UTIs§	0.96 (0.89–1.04)	0.91 (0.84–0.99)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; HR = hazard ratio; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.
* See text and Appendix Table 1 for outcome definitions and Appendix Table 8 for database-specific estimates.
† Defined as the composite of hospitalizations with sepsis and UTI, hospitalizations with pyelonephritis, and primary UTI hospitalizations. See text for details.
‡ At any diagnosis position.
§ Required evidence of outpatient antibiotic dispensing and outpatient diagnosis codes related to UTI.

Table 4. Sensitivity and Subgroup Analyses

Variable	HR (95% CI) for SGLT-2 vs. DPP-4 Inhibitors (Cohort 1)	HR (95% CI) for SGLT-2 Inhibitors vs. GLP-1 Agonists (Cohort 2)
Sensitivity analyses		
Propensity score specification*		
1:1 nearest-neighbor†	0.98 (0.68–1.41)	0.72 (0.53–0.99)
1:n variable-ratio	0.88 (0.59–1.31)	0.68 (0.46–1.00)
Fine stratification	0.79 (0.61–1.02)	0.74 (0.55–0.98)
Intention-to-treat analysis		
3 mo	1.00 (0.50–1.98)	0.49 (0.28–0.86)
6 mo	0.83 (0.52–1.34)	0.62 (0.41–0.92)
12 mo	0.82 (0.58–1.17)	0.64 (0.47–0.88)
Any duration	0.85 (0.63–1.16)	0.67 (0.51–0.88)
As-treated analysis		
3 mo	0.93 (0.46–1.89)	0.54 (0.31–0.95)
6 mo	0.97 (0.58–1.65)	0.70 (0.46–1.06)
12 mo	0.99 (0.66–1.47)	0.76 (0.54–1.06)
Any duration†	0.98 (0.68–1.41)	0.72 (0.53–0.99)
Subgroup analysis‡		
Exclusion criteria		
No major risk factors§	0.92 (0.55–1.51)	0.64 (0.41–1.01)
Active ingredient		
Canagliflozin	0.83 (0.57–1.21)	0.66 (0.47–0.92)
Dapagliflozin	0.57 (0.29–1.14)	0.52 (0.28–0.97)
Sex		
Male	0.66 (0.37–1.20)	0.72 (0.40–1.29)
Female	0.77 (0.51–1.17)	0.76 (0.53–1.10)
Age		
<60 y	0.78 (0.49–1.25)	0.75 (0.47–1.20)
≥60 y	1.09 (0.64–1.84)	0.79 (0.51–1.23)
Frailty‖		
Low	1.00 (0.46–2.15)	1.12 (0.58–2.16)
Medium	0.60 (0.33–1.09)	0.59 (0.31–1.10)
High	0.84 (0.49–1.43)	0.64 (0.40–1.02)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; HR = hazard ratio; SGLT-2 = sodium–glucose cotransporter-2.
* 1:1 nearest-neighbor matching was the primary analysis. A parallel, balanced, variable-ratio matching approach was also used. Fine stratification used 50 strata.
† Primary analysis.
‡ Propensity score was reestimated within each subgroup, and patients were rematched on the new reestimated score. Estimates were pooled across the 2 databases using fixed-effects meta-analysis. Appendix Figures 6 and 7 give database-specific estimates.
§ Patients without evidence of any use of antibiotics or disease-modifying antirheumatic drugs and without any history of infections were included for analysis.
‖ Patients were stratified into 3 groups on the basis of their estimated frailty score; see text for details.

including chance findings, bias due to differential surveillance, and residual confounding caused by differences in access policies—may have affected our final point estimates and corresponding confidence bounds.

Although prior literature on SGLT-2 inhibitors and UTIs overall has been inconsistent and an older meta-analysis with fewer clinical trials alluded to a higher UTI risk (2), our findings are consistent with a recently published meta-analysis of 72 trials that did not find an elevated risk for severe or nonsevere UTI events, sepsis with UTI (HR, 1.41 [CI, 0.57 to 3.48]), pyelonephritis (HR, 0.78 [CI, 0.52 to 1.18]), or overall UTI events (severe and nonsevere) (HR, 1.03 [CI, 0.96 to 1.11]) (11). A network meta-analysis by Li and colleagues (9) examined individual SGLT-2 inhibitors and similarly did not find an elevated risk for UTI (with a possible exception of dapagliflozin at higher doses). A small observational study of 1977 new users of SGLT-2 inhibitors in Australia also did not find a meaningful increase in 6-month risk for overall UTIs (HR, 0.90 [CI, 0.66 to 1.24]) (27).

Prior data examining the effect of SGLT-2 inhibitors on severe UTI events have come from randomized trials. Although randomized trials are the gold standard to assess pharmaceutical efficacy, they are often inadequately powered to detect differences in rare events, such as uroseptic or pyelonephritic events. Our study, which included more than 55 000 new users of SGLT-2 inhibitors matched on propensity score in each pairwise comparison, took several steps to decrease bias by characteristics associated with both treatment selection and risk for severe UTI events—that is, confounding by indication. We assessed this risk in 2 large, U.S.-based, commercial claims databases against 2 other comparable classes of antidiabetic medications and did several sensitivity and subgroup analyses to test the robustness of our primary findings. The data included in the study predate the drug safety communication released by the U.S. Food and Drug Administration in December 2015 that revised labels for SGLT-2 products to include a warning about serious UTIs (14); this may mitigate concerns about selective physician prescribing after this time.

Our study has several limitations. As an observational study, it is susceptible to residual confounding

due to the lack of randomization. For example, although we excluded patients at higher risk for a severe UTI (thereby increasing the therapeutic equipoise between the groups) and adjusted for more than 90 potential confounders in the propensity score model, we could not directly account for some important variables like duration of diabetes and body mass index. Similarly, hemoglobin A_{1c} results were available for a small proportion (10%) of our sample, which limited our ability to directly adjust for diabetes severity and glycemic control. Good balance across comparison groups for these unmeasured characteristics can be achieved by use of claims-based proxies in studies based on databases of health care use (28). Further, treatment initiation was defined using a 180-day period; thus, patients may have been exposed to the treatment before this window. Finally, our findings are generalizable to a commercial insurance population (approximately 55% of the United States) and to patients meeting the study inclusion criteria (that is, patients without high risk for or history of UTI). Future studies should validate our findings in other populations, especially older adults who may be particularly susceptible to severe UTI events.

In this large population-based cohort study of patients with type 2 diabetes mellitus, SGLT-2 inhibitor use was not associated with an increase in risk for serious—or nonserious—UTIs. On the basis of our findings, other factors beyond risk for UTI events should be considered in decisions about whether to prescribe SGLT-2 therapy for patients with diabetes in routine care settings.

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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: C.V. Dave, S. Schneeweiss, A. Tong.

Appendix Table 1. Outcome and Exclusion Criteria Definitions

Variable	Measurement
Outcomes	
Sepsis with UTI	Within the same inpatient discharge: 1 code related to sepsis (any position) 038.xx (septicemia), 790.7 (bacteremia), 995.9x (sepsis), 785.52 (septic shock) PLUS 1 code related to UTI (any position) 599.0x, 595.xx (cystitis), 590.xx (pyelonephritis), 597.xx (ureteritis)
Primary UTI hospitalization	Inpatient discharge code (must be present in the primary diagnosis) 599.0x, 595.xx (cystitis), 590.xx (pyelonephritis), 597.xx (ureteritis)
Pyelonephritis hospitalization	Inpatient discharge code (any position) 590.xx (pyelonephritis)
Any UTI hospitalization	Inpatient discharge code (any position) 599.0x, 595.xx (cystitis), 590.xx (pyelonephritis), 597.xx (ureteritis)
Outpatient UTI	Outpatient dispensing for 1 of the following antibiotics: sulfamethoxazole, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, or nitrofurantoin PLUS Outpatient diagnosis of UTI within 1 wk of antibiotic dispensing ICD-9 diagnosis codes: 599.0x, 595.xx (cystitis), 590.xx (pyelonephritis), 597.xx (ureteritis) PLUS No hospitalization related to a severe UTI event within 1 wk
Exclusion criteria	
Gestational diabetes	648.0x
DM type II	Patients excluded if no evidence of DM type II at any time before therapy initiation 250.xx (except 250.x1 and 250.x3)
DM type I	250.x1 and 250.x3
End-stage renal disease	ICD-9 diagnosis codes: 585.5x, 585.6x, 996.81, V42.0x, V45.1x, V45.12, V56.0x, V56.1x, V56.2x, V56.31, V56.32, V56.8x HCPCS + CPT-4 codes: 50360, 50365, 50380, 90935, 90937, 90940, 90945, 90947, 90989, 90993, 99512, 99559
Cancer	140.xx-208.xx (except 173.xx, 210.xx-229.xx)
HIV	042.xx, 079.53
UTI	599.0x, 595.xx (cystitis), 590.xx (pyelonephritis), 597.xx (ureteritis)
Sepsis	Inpatient diagnosis 038.xx, 790.7, 995.9x, 785.52
Antibiotics (UTI-related)	Sulfamethoxazole, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, nitrofurantoin
Acute glomerulonephritis	580.xx
Chronic glomerulonephritis	582.xx
Acute kidney failure	584.xx
Chronic kidney disease	585.xx
Renal complications of diabetes	250.4x
Urinary catheter use	HCPCS/CPT procedure codes: 51701, 51702, 51703, P9612 ICD-9 diagnostic codes: 996.64, 996.31, V53.6x, V43.5x ICD-9 procedure code: 57.94
Spinal cord injury	952.xx, 953.xx
Hydronephrosis	591.xx
Enlarged prostate	600.xx
Obstructive defects of renal pelvis and ureter	753.2x
Organ transplant	ICD-9 diagnosis codes: V42.xx (except V42.0x), V58.44, 996.8x ICD-9 procedure codes: 33.5x, 33.6x, 37.51, 41.0x, 46.97, 50.5x, 52.8x, 55.6x HCPCS/CPT procedure codes: 32851, 32852, 32853, 32854, 33935, 33945, 38240, 38241, 44135, 44136, 47135, 47136, 48554, 48556, 50360, 50365
Graft-versus-host disease	279.5x
Other immune disorders	279.xx (except 279.5x)
Neutropenia	288.0x
Calcineurin inhibitors	Tacrolimus, cyclosporine (not topical)
Vesicoureteral reflux	593.7x
Calculus of kidney, ureter, and lower urinary tract	592.xx, 594.xx
Neurogenic bladder	596.54

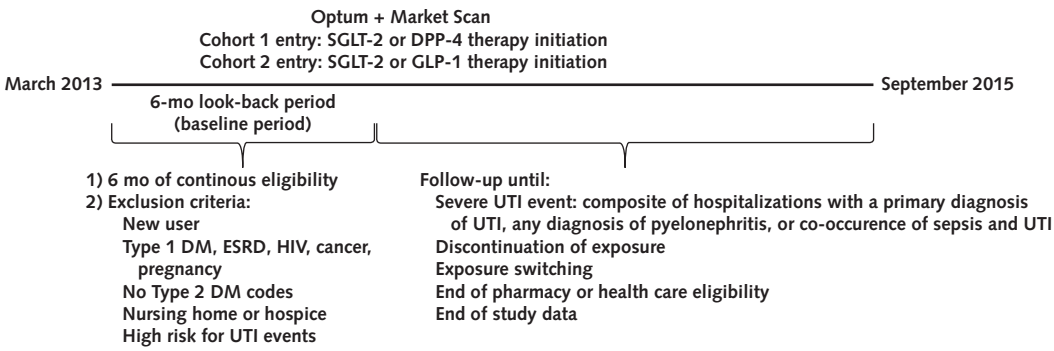
CPT = Current Procedural Terminology; DM = diabetes mellitus; HCPCS = Healthcare Common Procedure Coding System; ICD-9 = International Classification of Diseases, Ninth Revision; UTI = urinary tract infection.

Appendix Table 2. List of Drugs Included in the Study

Drug Class	Included Drugs
SGLT-2 inhibitors	Canagliflozin, canagliflozin–metformin, dapagliflozin, dapagliflozin–metformin, empagliflozin, empagliflozin–metformin, empagliflozin–linagliptin (empagliflozin–linagliptin for cohort 2 [SGLT-2 inhibitors vs. GLP-1 agonists] only)
DPP-4 inhibitors	Alogliptin, alogliptin–metformin, alogliptin–pioglitazone, linagliptin, linagliptin–metformin, saxagliptin, saxagliptin–metformin, sitagliptin, sitagliptin–metformin
GLP-1 agonists	Albiglutide, dulaglutide, exenatide, liraglutide

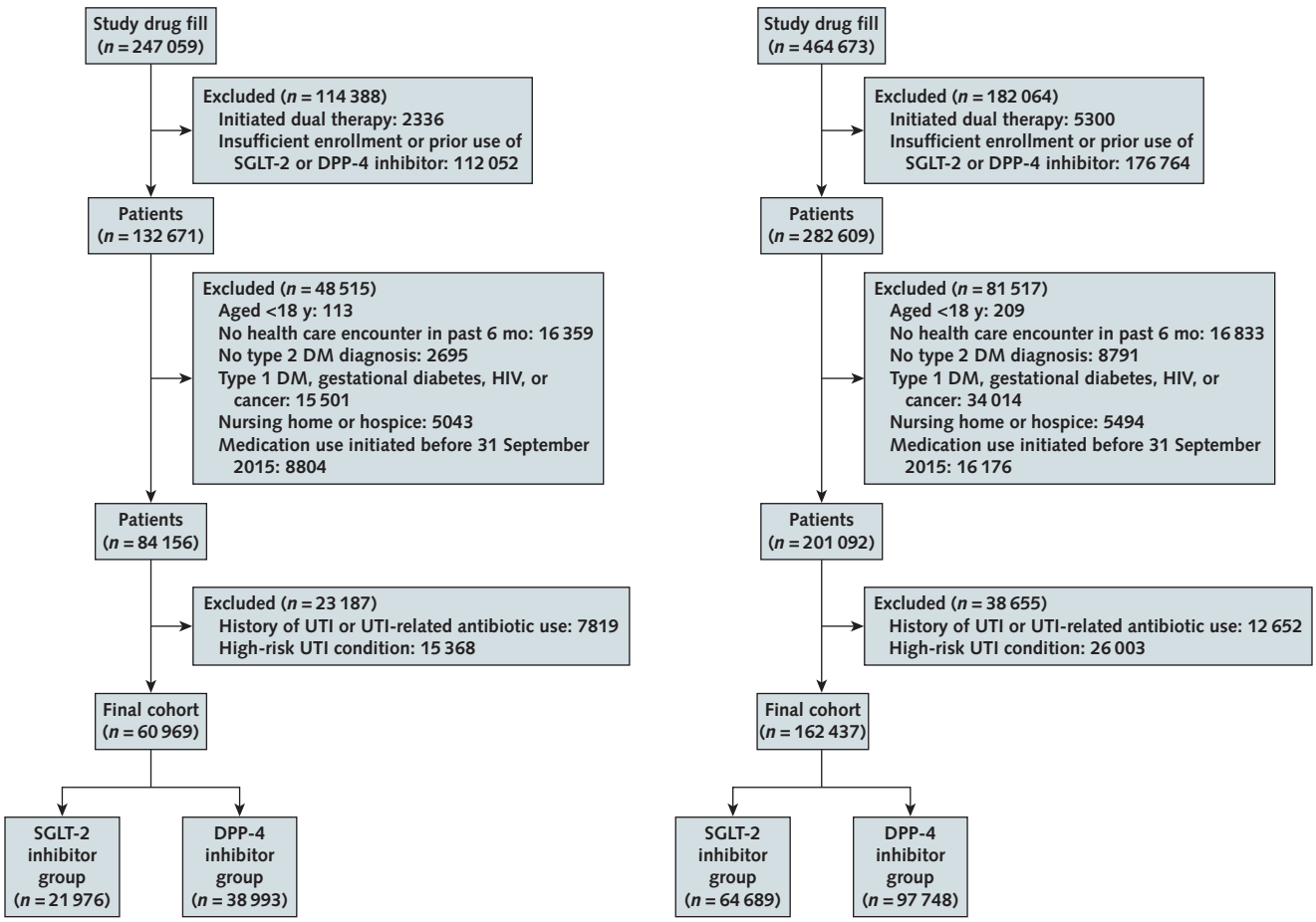
DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Figure 1. Study design.



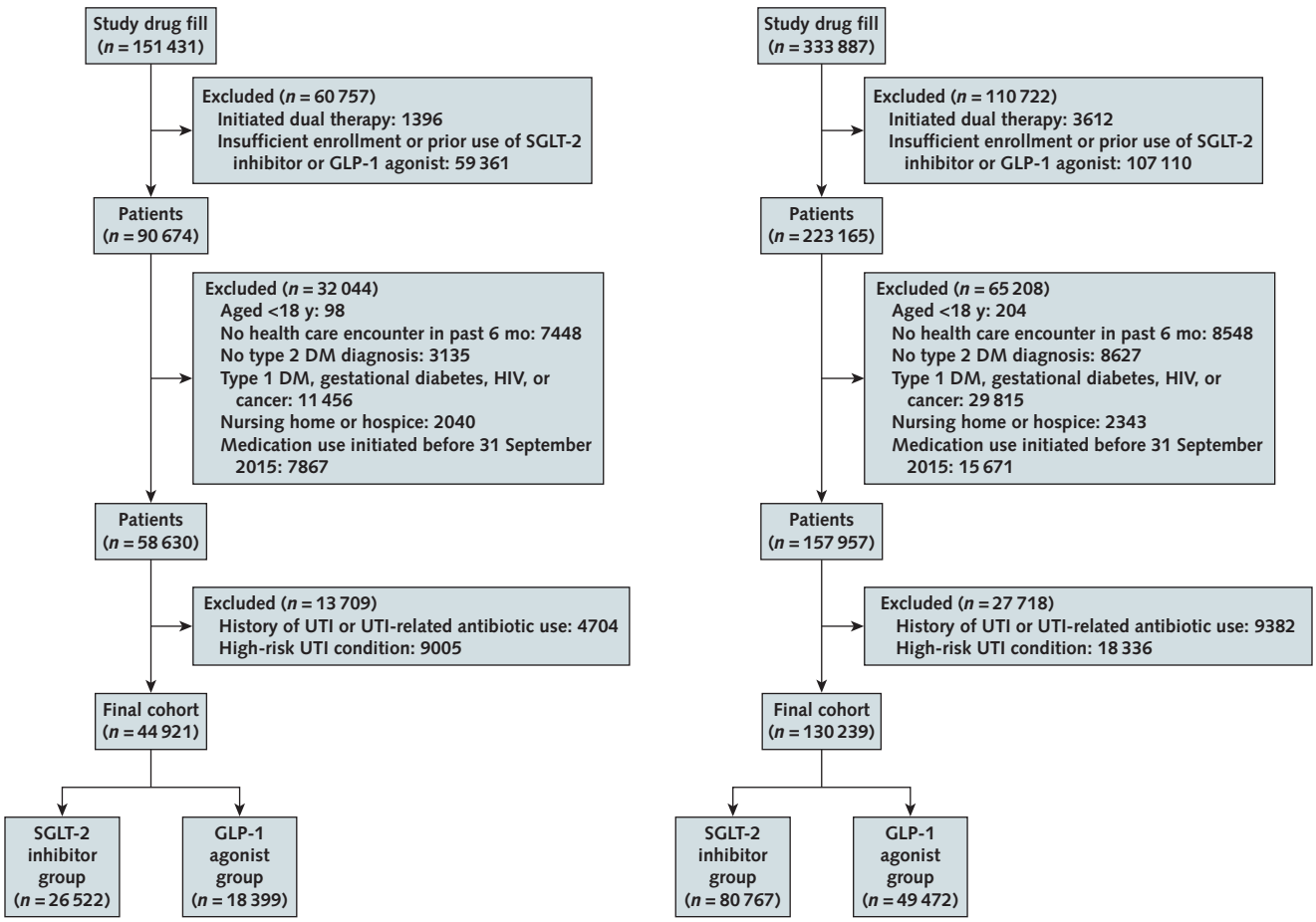
Cohorts 1 and 2 had similar inclusion and exclusion criteria, with a few key differences. In cohort 1 (SGLT-2 vs. DPP-4 inhibitors), patients were included if they newly initiated use of either an SGLT-2 inhibitor or a DPP-4 inhibitor (did not have a history of use of either SGLT-2 or DPP-4 inhibitors in the baseline period). We did not consider patients initiating use of empagliflozin–linagliptin (an SGLT-2 inhibitor–DPP-4 inhibitor combination product) in cohort 1. Use of a GLP-1 agonist was permitted and adjusted for in the propensity score. In cohort 2 (SGLT-2 inhibitors vs. GLP-1 agonists), patients were included if they newly initiated use of either an SGLT-2 inhibitor or a GLP-1 agonist (did not have a history of use of either SGLT-2 inhibitors or GLP-1 agonists in the baseline period). Use of a DPP-4 inhibitor was permitted and adjusted for in the propensity score. DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase-4; ESRD = end-stage renal disease; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.

Appendix Figure 2. CONSORT flow diagram for cohort 1 (SGLT-2 vs. DPP-4 inhibitors) for Optum (*left*) and MarketScan (*right*).



CONSORT = Consolidated Standards of Reporting Trials; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase-4; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.

Appendix Figure 3. CONSORT flow diagram for cohort 2 (SGLT-2 inhibitors vs. GLP-1 agonists) for Optum (*left*) and MarketScan (*right*).



CONSORT = Consolidated Standards of Reporting Trials; DM = diabetes mellitus; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium-glucose cotransporter-2; UTI = urinary tract infection.

Appendix Table 3. Distribution of Baseline Covariates Before Propensity Score Matching: Cohort 1 (SGLT-2 vs. DPP-4 Inhibitors)

Covariate	Optum			MarketScan			Combined		
	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %
Male	20 917 (53.6)	12 335 (56.1)	5	53 439 (54.7)	34 326 (53.1)	3.2	74 356 (54.4)	46 661 (53.8)	1.1
Age Decile 1	3537 (9.1)	2559 (11.6)	8.5	9607 (9.8)	6638 (10.3)	1.4	13 144 (9.6)	9197 (10.6)	3.3
Age Decile 2	3446 (8.8)	2649 (12.1)	10.5	9225 (9.4)	7010 (10.8)	4.6	12 671 (9.3)	9659 (11.1)	6.2
Age Decile 3	3424 (8.8)	2671 (12.2)	11	9125 (9.3)	7125 (11.0)	5.6	12 549 (9.2)	9796 (11.3)	7
Age Decile 4	3399 (8.7)	2706 (12.3)	11.7	9250 (9.5)	6985 (10.8)	4.4	12 649 (9.3)	9691 (11.2)	6.4
Age Decile 5	3420 (8.8)	2673 (12.2)	11.1	9206 (9.4)	7029 (10.9)	4.8	12 626 (9.2)	9702 (11.2)	6.5
Age Decile 6	3448 (8.8)	2653 (12.1)	10.6	9319 (9.5)	6948 (10.7)	4	12 767 (9.3)	9601 (11.1)	5.8
Age Decile 7	3609 (9.3)	2482 (11.3)	6.7	9371 (9.6)	6860 (10.6)	3.4	12 980 (9.5)	9342 (10.8)	4.3
Age Decile 8	4477 (11.5)	1622 (7.4)	14.1	9524 (9.7)	6725 (10.4)	2.2	14 001 (10.2)	8347 (9.6)	2
Age Decile 9	4839 (12.4)	1260 (5.7)	23.4	10 277 (10.5)	5968 (9.2)	4.3	15 116 (11.1)	7228 (8.3)	9.2
Age Decile 10	5394 (13.8)	701 (3.2)	38.9	12 844 (13.1)	3401 (5.3)	27.5	18 238 (13.3)	4102 (4.7)	30.4
Cohort entry, April 2013–September 2013	9005 (23.1)	1488 (6.8)	47	22 263 (22.8)	4382 (6.8)	46.3	31 268 (22.9)	5870 (6.8)	46.5
Cohort entry, October 2013–March 2014	8284 (21.2)	2594 (11.8)	25.6	20 746 (21.2)	7782 (12.0)	24.9	29 030 (21.2)	10 376 (12.0)	25.1
Cohort entry, April 2014–September 2014	8049 (20.6)	4801 (21.8)	2.9	20 977 (21.5)	16 699 (25.8)	10.3	29 026 (21.2)	21 500 (24.8)	8.5
Cohort entry, October 2014–March 2015	7006 (18.0)	6522 (29.7)	27.8	18 509 (18.9)	20 519 (31.7)	29.7	25 515 (18.7)	27 041 (31.2)	29.3
Cohort entry, April 2015–September 2015	6649 (17.1)	6571 (29.9)	30.7	15 253 (15.6)	15 307 (23.7)	20.4	21 902 (16.0)	21 878 (25.2)	23
Diabetes, no complications	31 988 (82.0)	17 588 (80.0)	5.1	83 895 (85.8)	52 982 (81.9)	10.7	115 883 (84.7)	70 570 (81.4)	8.9
Diabetes, ocular complications	1662 (4.3)	1085 (4.9)	3.2	3319 (3.4)	3029 (4.7)	6.5	4981 (3.6)	4114 (4.7)	5.5
Diabetes, neurologic complications	3386 (8.7)	2263 (10.3)	5.5	5777 (5.9)	5458 (8.4)	9.8	9163 (6.7)	7721 (8.9)	8.2
Diabetes, other complications	2995 (7.7)	1701 (7.7)	0.2	6287 (6.4)	4833 (7.5)	4.1	9282 (6.8)	6534 (7.5)	2.9
Hypoglycemia	55 (0.1)	24 (0.1)	0.9	93 (0.1)	100 (0.2)	1.7	148 (0.1)	124 (0.1)	1
Hypercholesterolemia	7079 (18.2)	3638 (16.6)	4.2	13 521 (13.8)	9088 (14.0)	0.6	20 600 (15.1)	12 726 (14.7)	1.1
Hyperglyceridemia	1122 (2.9)	775 (3.5)	3.7	2048 (2.1)	1499 (2.3)	1.5	3170 (2.3)	2274 (2.6)	2
Other hyperlipidemia	6055 (15.5)	4102 (18.7)	8.3	11 290 (11.6)	9554 (14.8)	9.5	17 345 (12.7)	13 656 (15.8)	8.8
Other lipid abnormality	20 144 (51.7)	11 303 (51.4)	0.5	40 412 (41.3)	28 164 (43.5)	4.4	60 556 (44.3)	39 467 (45.5)	2.5
Hypertension	28 531 (73.2)	15 707 (71.5)	3.8	58 330 (59.7)	38 390 (59.3)	0.7	86 861 (63.5)	54 097 (62.4)	2.3
Hypertension, malignant	741 (1.9)	286 (1.3)	4.8	1271 (1.3)	628 (1.0)	3.1	2012 (1.5)	914 (1.1)	3.7
Myocardial infarction	311 (0.8)	112 (0.5)	3.6	639 (0.7)	247 (0.4)	3.8	950 (0.7)	359 (0.4)	3.8
Peripheral vascular disease	1219 (3.1)	439 (2.0)	7.1	1816 (1.9)	891 (1.4)	3.8	3035 (2.2)	1330 (1.5)	5
Other ischemic heart disease	4754 (12.2)	1950 (8.9)	10.8	8692 (8.9)	4876 (7.5)	4.9	13 446 (9.8)	6826 (7.9)	6.9
Coronary artery bypass grafting/percutaneous coronary intervention	212 (0.5)	70 (0.3)	3.4	534 (0.5)	156 (0.2)	4.9	746 (0.5)	226 (0.3)	4.5
Ischemic stroke	1170 (3.0)	373 (1.7)	8.6	2256 (2.3)	965 (1.5)	6	3426 (2.5)	1338 (1.5)	6.8
Transient ischemic attack	306 (0.8)	103 (0.5)	4	612 (0.6)	265 (0.4)	3	918 (0.7)	368 (0.4)	3.3
Atrial fibrillation	1402 (3.6)	484 (2.2)	8.3	2643 (2.7)	1105 (1.7)	6.8	4045 (3.0)	1589 (1.8)	7.4
Arrhythmia	1372 (3.5)	514 (2.3)	7	2636 (2.7)	1232 (1.9)	5.3	4008 (2.9)	1746 (2.0)	5.9
Congestive heart failure	1230 (3.2)	388 (1.8)	9	1892 (1.9)	809 (1.3)	5.5	3122 (2.3)	1197 (1.4)	6.7
Other cardiovascular disease	100 (0.3)	30 (0.1)	2.7	179 (0.2)	90 (0.1)	1.1	279 (0.2)	120 (0.1)	1.6
Peripheral circulatory disorder	335 (0.9)	134 (0.6)	2.9	613 (0.6)	283 (0.4)	2.6	948 (0.7)	417 (0.5)	2.8
Other chronic heart disease	4539 (11.6)	1851 (8.4)	10.7	8227 (8.4)	4592 (7.1)	4.9	12 766 (9.3)	6443 (7.4)	6.9
Obesity, not morbid	4660 (12.0)	3559 (16.2)	12.2	8385 (8.6)	7023 (10.9)	7.7	13 045 (9.5)	10 582 (12.2)	8.6
Obesity, morbid	1803 (4.6)	1644 (7.5)	12	3437 (3.5)	3336 (5.2)	8.1	5240 (3.8)	4980 (5.7)	9
Smoking	2740 (7.0)	1257 (5.7)	5.4	3623 (3.7)	1905 (2.9)	4.2	6363 (4.7)	3162 (3.6)	5
Alcohol use	103 (0.3)	52 (0.2)	0.6	174 (0.2)	88 (0.1)	1.1	277 (0.2)	140 (0.2)	1
Weight loss	446 (1.1)	129 (0.6)	6	706 (0.7)	266 (0.4)	4.1	1152 (0.8)	395 (0.5)	4.8
Anticoagulant use	1449 (3.7)	582 (2.6)	6.1	3199 (3.3)	1562 (2.4)	5.2	4648 (3.4)	2144 (2.5)	5.5
Antiarrhythmic drug use	315 (0.8)	108 (0.5)	3.9	640 (0.7)	312 (0.5)	2.3	955 (0.7)	420 (0.5)	2.8
Digoxin use	506 (1.3)	159 (0.7)	5.7	1018 (1.0)	375 (0.6)	5.2	1524 (1.1)	534 (0.6)	5.4
Angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use	25 717 (66.0)	14 430 (65.7)	0.6	64 314 (65.8)	44 214 (68.3)	5.4	90 031 (65.8)	58 644 (67.7)	3.9
β-Blocker use	10 812 (27.7)	5091 (23.2)	10.5	25 225 (25.8)	15 866 (24.5)	2.9	36 037 (26.4)	20 957 (24.2)	5
Dihydropyridine calcium-channel blocker use	7145 (18.3)	3391 (15.4)	7.7	17 040 (17.4)	10 770 (16.6)	2.1	24 185 (17.7)	14 161 (16.3)	3.6
Nondihydropyridine calcium-channel blocker use	1176 (3.0)	561 (2.6)	2.8	2865 (2.9)	1803 (2.8)	0.9	4041 (3.0)	2364 (2.7)	1.4
Loop diuretic use	2777 (7.1)	1283 (5.8)	5.2	5687 (5.8)	3761 (5.8)	0	8464 (6.2)	5044 (5.8)	1.6
Other diuretic use	11 412 (29.3)	6251 (28.4)	1.8	29 379 (30.1)	19 918 (30.8)	1.6	40 791 (29.8)	26 169 (30.2)	0.8
Antianginal drug use	686 (1.8)	256 (1.2)	5	1396 (1.4)	826 (1.3)	1.3	2082 (1.5)	1082 (1.2)	2.3
Other antihypertensive agent use	1449 (3.7)	632 (2.9)	4.7	3012 (3.1)	1830 (2.8)	1.5	4461 (3.3)	2462 (2.8)	2.5
Insulin use	4851 (12.4)	7031 (32.0)	48.4	10 688 (10.9)	21 192 (32.8)	54.8	15 539 (11.4)	28 223 (32.6)	53
Metformin use	31 018 (79.5)	16 468 (74.9)	11	80 781 (82.6)	48 818 (75.5)	17.7	111 799 (81.8)	65 286 (75.3)	15.7
DPP-4 inhibitor use	14 771 (37.9)	7918 (36.0)	3.8	33 650 (34.4)	22 455 (34.7)	0.6	48 421 (35.4)	30 373 (35.0)	0.8
Sulfonylurea use	283 (0.7)	182 (0.8)	1.2	890 (0.9)	749 (1.2)	2.4	1173 (0.9)	931 (1.1)	2.2
Meglitinide use	149 (0.4)	90 (0.4)	0.4	247 (0.3)	232 (0.4)	1.9	396 (0.3)	322 (0.4)	1.4
α-Glucosidase use	2907 (7.5)	2121 (9.7)	7.9	6989 (7.2)	6002 (9.3)	7.8	9896 (7.2)	8123 (9.4)	7.7
Thiazolidinedione use	1156 (3.0)	4898 (22.3)	60.8	3248 (3.3)	15 812 (24.4)	64.1	4404 (3.2)	20 710 (23.9)	63.4
Constipation	702 (1.8)	265 (1.2)	4.9	1017 (1.0)	688 (1.1)	0.2	1719 (1.3)	953 (1.1)	1.5
Broad-spectrum antibiotic use	8307 (21.3)	4994 (22.7)	3.4	21 953 (22.5)	15 573 (24.1)	3.8	30 260 (22.1)	20 567 (23.7)	3.8
Any antibiotic use	7931 (20.3)	4822 (21.9)	3.9	20 867 (21.3)	15 195 (23.5)	5.1	28 798 (21.1)	20 017 (23.1)	4.9
Glucocorticoid use	3886 (10.0)	2128 (9.7)	0.9	10 154 (10.4)	6591 (10.2)	0.7	14 040 (10.3)	8719 (10.1)	0.7
Use of DMARDs, nonbiologic	318 (0.8)	162 (0.7)	0.9	875 (0.9)	559 (0.9)	0.3	1193 (0.9)	721 (0.8)	0.4
Use of DMARDs, biologic	185 (0.5)	131 (0.6)	1.7	605 (0.6)	435 (0.7)	0.7	790 (0.6)	566 (0.7)	1

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Appendix Table 3–Continued

Covariate	Optum			MarketScan			Combined		
	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %
Intestinal infections	146 (0.4)	88 (0.4)	0.4	392 (0.4)	250 (0.4)	0.2	538 (0.4)	338 (0.4)	0.1
Mycotic infections	2738 (7.0)	1278 (5.8)	4.9	5811 (5.9)	3547 (5.5)	2	8549 (6.3)	4825 (5.6)	2.9
Viral infections	1141 (2.9)	604 (2.7)	1.1	2692 (2.8)	1686 (2.6)	0.9	3833 (2.8)	2290 (2.6)	1
Other bacterial infections	475 (1.2)	252 (1.1)	0.7	987 (1.0)	675 (1.0)	0.3	1462 (1.1)	927 (1.1)	0
Other nonbacterial infections	183 (0.5)	92 (0.4)	0.8	479 (0.5)	293 (0.5)	0.5	662 (0.5)	385 (0.4)	0.6
Asthma	2029 (5.2)	1053 (4.8)	1.9	3854 (3.9)	2437 (3.8)	0.9	5883 (4.3)	3490 (4.0)	1.4
Chronic obstructive pulmonary disease	2500 (6.4)	953 (4.3)	9.2	4112 (4.2)	2250 (3.5)	3.8	6612 (4.8)	3203 (3.7)	5.6
Adrenal disorder	100 (0.3)	88 (0.4)	2.5	207 (0.2)	185 (0.3)	1.5	307 (0.2)	273 (0.3)	1.7
Low frailty	12 537 (32.2)	7784 (35.4)	6.9	32 403 (33.1)	21 769 (33.7)	1.1	44 940 (32.9)	29 553 (34.1)	2.6
Medium frailty	12 540 (32.2)	7780 (35.4)	6.9	31 850 (32.6)	22 266 (34.4)	3.9	44 390 (32.5)	30 046 (34.7)	4.7
High frailty	13 916 (35.7)	6412 (29.2)	13.9	33 495 (34.3)	20 654 (31.9)	5	47 411 (34.7)	27 066 (31.2)	7.3
Number of drugs, low	13 158 (33.7)	6336 (28.8)	10.6	35 163 (36.0)	16 787 (26.0)	21.8	48 321 (35.3)	23 123 (26.7)	18.8
Number of drugs, medium	14 469 (37.1)	8327 (37.9)	1.6	37 232 (38.1)	24 667 (38.1)	0.1	51 701 (37.8)	32 994 (38.1)	0.5
Number of drugs, high	11 366 (29.1)	7313 (33.3)	8.9	25 353 (25.9)	23 235 (35.9)	21.7	36 719 (26.9)	30 548 (35.2)	18.2
0 ED visits	35 421 (90.8)	20 406 (92.9)	7.4	85 329 (87.3)	57 603 (89.0)	5.4	120 750 (88.3)	78 009 (90.0)	5.5
1 ED visit	2006 (5.1)	767 (3.5)	8.1	8889 (9.1)	5288 (8.2)	3.3	10 895 (8.0)	6055 (7.0)	3.7
>1 ED visit	1566 (4.0)	803 (3.7)	1.9	3530 (3.6)	1798 (2.8)	4.7	5096 (3.7)	2601 (3.0)	4
0 hospitalizations	37 520 (96.2)	21 425 (97.5)	7.3	94 214 (96.4)	63 207 (97.7)	7.8	131 734 (96.3)	84 632 (97.7)	7.7
1 hospitalization	1348 (3.5)	515 (2.3)	6.6	3309 (3.4)	1382 (2.1)	7.6	4657 (3.4)	1897 (2.2)	7.4
>1 hospitalization	125 (0.3)	36 (0.2)	3.2	225 (0.2)	100 (0.2)	1.7	350 (0.3)	136 (0.2)	2.2
<3 outpatient visits	14 168 (36.3)	7750 (35.3)	2.2	36 286 (37.1)	21 785 (33.7)	7.2	50 454 (36.9)	29 535 (34.1)	5.9
3–4 outpatient visits	12 810 (32.9)	7453 (33.9)	2.3	32 399 (33.1)	21 786 (33.7)	1.1	45 209 (33.1)	29 239 (33.7)	1.4
>4 outpatient visits	12 015 (30.8)	6773 (30.8)	0	29 063 (29.7)	21 118 (32.6)	6.3	41 078 (30.0)	27 891 (32.2)	4.6
Mammogram	611 (1.6)	347 (1.6)	0.1	1637 (1.7)	1132 (1.7)	0.6	2248 (1.6)	1479 (1.7)	0.5
Colonoscopy	591 (1.5)	299 (1.4)	1.3	1437 (1.5)	1016 (1.6)	0.8	2028 (1.5)	1315 (1.5)	0.3
Flu vaccine	7964 (20.4)	4280 (19.5)	2.4	17 220 (17.6)	11 724 (18.1)	1.3	25 184 (18.4)	16 004 (18.5)	0.1

DMARD = disease-modifying antirheumatic drug; DPP-4 = dipeptidyl peptidase-4; ED = emergency department; GLP-1 = glucagon-like peptide-1 receptor; SD = standardized difference; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Table 4. Distribution of Baseline Covariates After Propensity Score Matching: Cohort 1 (SGLT-2 vs. DPP-4 Inhibitors)

Covariate	Optum			MarketScan			Combined		
	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %
Male	9118 (56.5)	9059 (56.1)	0.7	24 527 (53.6)	24 443 (53.5)	0.4	33 645 (54.4)	33 502 (54.1)	0.5
Age Decile 1	1887 (11.7)	1861 (11.5)	0.5	4934 (10.8)	4859 (10.6)	0.5	6821 (11.0)	6720 (10.9)	0.5
Age Decile 2	1848 (11.4)	1876 (11.6)	0.5	4905 (10.7)	4909 (10.7)	0	6753 (10.9)	6785 (11.0)	0.2
Age Decile 3	1848 (11.4)	1850 (11.5)	0	4908 (10.7)	4862 (10.6)	0.3	6756 (10.9)	6712 (10.8)	0.2
Age Decile 4	1890 (11.7)	1881 (11.6)	0.2	4833 (10.6)	4737 (10.4)	0.7	6723 (10.9)	6618 (10.7)	0.5
Age Decile 5	1898 (11.8)	1853 (11.5)	0.9	4795 (10.5)	4838 (10.6)	0.3	6693 (10.8)	6691 (10.8)	0
Age Decile 6	1877 (11.6)	1847 (11.4)	0.6	4783 (10.5)	4815 (10.5)	0.2	6660 (10.8)	6662 (10.8)	0
Age Decile 7	1789 (11.1)	1807 (11.2)	0.4	4768 (10.4)	4751 (10.4)	0.1	6557 (10.6)	6558 (10.6)	0
Age Decile 8	1347 (8.3)	1379 (8.5)	0.7	4631 (10.1)	4668 (10.2)	0.3	5978 (9.7)	6047 (9.8)	0.4
Age Decile 9	1133 (7.0)	1122 (6.9)	0.3	4356 (9.5)	4360 (9.5)	0	5489 (8.9)	5482 (8.9)	0
Age Decile 10	630 (3.9)	671 (4.2)	1.3	2816 (6.2)	2930 (6.4)	1	3446 (5.6)	3601 (5.8)	1.1
Cohort entry, April 2013–September 2013	1120 (6.9)	1274 (7.9)	3.6	3330 (7.3)	3697 (8.1)	3	4450 (7.2)	4971 (8.0)	3.2
Cohort entry, October 2013–March 2014	2037 (12.6)	2080 (12.9)	0.8	5789 (12.7)	6108 (13.4)	2.1	7826 (12.6)	8188 (13.2)	1.7
Cohort entry, April 2014–September 2014	3636 (22.5)	3540 (21.9)	1.4	11 552 (25.3)	11 670 (25.5)	0.6	15 188 (24.5)	15 210 (24.6)	0.1
Cohort entry, October 2014–March 2015	4622 (28.6)	4542 (28.1)	1.1	13 954 (30.5)	13 464 (29.4)	2.3	18 576 (30.0)	18 006 (29.1)	2
Cohort entry, April 2015–September 2015	4732 (29.3)	4711 (29.2)	0.3	11 104 (24.3)	10 790 (23.6)	1.6	15 836 (25.6)	15 501 (25.1)	1.2
Diabetes, no complications	13 199 (81.7)	13 221 (81.9)	0.4	38 664 (84.6)	38 606 (84.4)	0.4	51 863 (83.8)	51 827 (83.8)	0.2
Diabetes, ocular complications	709 (4.4)	694 (4.3)	0.5	1744 (3.8)	1775 (3.9)	0.4	2453 (4.0)	2469 (4.0)	0.1
Diabetes, neurologic complications	1480 (9.2)	1470 (9.1)	0.2	3154 (6.9)	3097 (6.8)	0.5	4634 (7.5)	4567 (7.4)	0.4
Diabetes, other complications	1198 (7.4)	1191 (7.4)	0.2	3037 (6.6)	3101 (6.8)	0.6	4235 (6.8)	4292 (6.9)	0.4
Hypoglycemia	17 (0.1)	19 (0.1)	0.4	55 (0.1)	53 (0.1)	0.1	72 (0.1)	72 (0.1)	0
Hypercholesterolemia	2615 (16.2)	2668 (16.5)	0.9	6227 (13.6)	6323 (13.8)	0.6	8842 (14.3)	8991 (14.5)	0.7
Hyperglyceridemia	557 (3.4)	546 (3.4)	0.4	1053 (2.3)	1037 (2.3)	0.2	1610 (2.6)	1583 (2.6)	0.3
Other hyperlipidemia	2718 (16.8)	2709 (16.8)	0.1	6104 (13.3)	6074 (13.3)	0.2	8822 (14.3)	8783 (14.2)	0.2
Other lipid abnormality	8177 (50.6)	8200 (50.8)	0.3	19 242 (42.1)	19 284 (42.2)	0.2	27 419 (44.3)	27 484 (44.4)	0.2
Hypertension	11 368 (70.4)	11 438 (70.8)	1	26 703 (58.4)	26 884 (58.8)	0.8	38 071 (61.5)	38 322 (61.9)	0.8
Hypertension, malignant	228 (1.4)	219 (1.4)	0.5	465 (1.0)	492 (1.1)	0.6	693 (1.1)	711 (1.1)	0.3
Myocardial infarction	107 (0.7)	90 (0.6)	1.4	188 (0.4)	189 (0.4)	0	295 (0.5)	279 (0.5)	0.4
Peripheral vascular disease	315 (2.0)	338 (2.1)	1	655 (1.4)	643 (1.4)	0.2	970 (1.6)	981 (1.6)	0.1
Other ischemic heart disease	1480 (9.2)	1453 (9.0)	0.6	3390 (7.4)	3377 (7.4)	0.1	4870 (7.9)	4830 (7.8)	0.2
Coronary artery bypass grafting/percutaneous coronary intervention	58 (0.4)	57 (0.4)	0.1	135 (0.3)	132 (0.3)	0.1	193 (0.3)	189 (0.3)	0.1
Ischemic stroke	318 (2.0)	304 (1.9)	0.6	740 (1.6)	739 (1.6)	0	1058 (1.7)	1043 (1.7)	0.2
Transient ischemic attack	90 (0.6)	84 (0.5)	0.5	200 (0.4)	204 (0.4)	0.1	290 (0.5)	288 (0.5)	0
Atrial fibrillation	370 (2.3)	371 (2.3)	0	805 (1.8)	851 (1.9)	0.8	1175 (1.9)	1222 (2.0)	0.6
Arrhythmia	419 (2.6)	406 (2.5)	0.5	880 (1.9)	901 (2.0)	0.3	1299 (2.1)	1307 (2.1)	0.1
Congestive heart failure	318 (2.0)	309 (1.9)	0.4	611 (1.3)	609 (1.3)	0	929 (1.5)	918 (1.5)	0.1
Other cardiovascular disease	20 (0.1)	23 (0.1)	0.5	75 (0.2)	63 (0.1)	0.7	95 (0.2)	86 (0.1)	0.4
Peripheral circulatory disorder	105 (0.7)	102 (0.6)	0.2	203 (0.4)	209 (0.5)	0.2	308 (0.5)	311 (0.5)	0.1
Other chronic heart disease	1404 (8.7)	1381 (8.6)	0.5	3171 (6.9)	3185 (7.0)	0.1	4575 (7.4)	4566 (7.4)	0.1
Obesity, not morbid	2340 (14.5)	2376 (14.7)	0.6	4506 (9.9)	4556 (10.0)	0.4	6846 (11.1)	6932 (11.2)	0.4
Obesity, morbid	988 (6.1)	1005 (6.2)	0.4	1991 (4.4)	2054 (4.5)	0.7	2979 (4.8)	3059 (4.9)	0.6
Smoking	1023 (6.3)	992 (6.1)	0.8	1470 (3.2)	1449 (3.2)	0.3	2493 (4.0)	2441 (3.9)	0.4
Alcohol use	45 (0.3)	41 (0.3)	0.5	72 (0.2)	67 (0.1)	0.3	117 (0.2)	108 (0.2)	0.3
Weight loss	105 (0.7)	114 (0.7)	0.7	216 (0.5)	217 (0.5)	0	321 (0.5)	331 (0.5)	0.2
Anticoagulant use	429 (2.7)	427 (2.6)	0.1	1093 (2.4)	1135 (2.5)	0.6	1522 (2.5)	1562 (2.5)	0.4
Antiarrhythmic drug use	87 (0.5)	90 (0.6)	0.3	221 (0.5)	238 (0.5)	0.5	308 (0.5)	328 (0.5)	0.5
Digoxin use	127 (0.8)	117 (0.7)	0.7	286 (0.6)	289 (0.6)	0.1	413 (0.7)	406 (0.7)	0.1
Angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use	10 347 (64.1)	10 411 (64.5)	0.8	30 376 (66.4)	30 358 (66.4)	0.1	40 723 (65.8)	40 769 (65.9)	0.2
β-Blocker use	3784 (23.4)	3778 (23.4)	0.1	10 876 (23.8)	11 022 (24.1)	0.7	14 660 (23.7)	14 800 (23.9)	0.5
Dihydropyridine calcium-channel blocker use	2556 (15.8)	2558 (15.8)	0	7543 (16.5)	7599 (16.6)	0.3	10 099 (16.3)	10 157 (16.4)	0.3
Nondihydropyridine calcium-channel blocker use	386 (2.4)	413 (2.6)	1.1	1268 (2.8)	1261 (2.8)	0.1	1654 (2.7)	1674 (2.7)	0.2
Loop diuretic use	902 (5.6)	929 (5.8)	0.7	2434 (5.3)	2457 (5.4)	0.2	3336 (5.4)	3386 (5.5)	0.4
Other diuretic use	4486 (27.8)	4541 (28.1)	0.8	13 729 (30.0)	13 958 (30.5)	1.1	18 215 (29.4)	18 499 (29.9)	1
Antianginal drug use	199 (1.2)	204 (1.3)	0.3	581 (1.3)	566 (1.2)	0.3	780 (1.3)	770 (1.2)	0.1
Other antihypertensive agent use	475 (2.9)	480 (3.0)	0.2	1278 (2.8)	1298 (2.8)	0.3	1753 (2.8)	1778 (2.9)	0.2
Insulin use	3310 (20.5)	3376 (20.9)	1	8528 (18.6)	8691 (19.0)	0.9	11 838 (19.1)	12 067 (19.5)	0.9

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Appendix Table 4–Continued

Covariate	Optum			MarketScan			Combined		
	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %
Metformin use	12 544 (77.7)	12 484 (77.3)	0.9	35 936 (78.6)	35 835 (78.4)	0.5	48 480 (78.4)	48 319 (78.1)	0.6
DPP-4 inhibitor use	5929 (36.7)	5889 (36.5)	0.5	16 279 (35.6)	16 163 (35.3)	0.5	22 208 (35.9)	22 052 (35.6)	0.5
Sulfonylurea use	106 (0.7)	113 (0.7)	0.5	475 (1.0)	460 (1.0)	0.3	581 (0.9)	573 (0.9)	0.1
Meglitinide use	60 (0.4)	62 (0.4)	0.2	145 (0.3)	146 (0.3)	0	205 (0.3)	208 (0.3)	0.1
α-Glucosidase use	1375 (8.5)	1400 (8.7)	0.6	3806 (8.3)	3775 (8.3)	0.2	5181 (8.4)	5175 (8.4)	0
Thiazolidinedione use	1097 (6.8)	1231 (7.6)	3.2	3173 (6.9)	3684 (8.1)	4.2	4270 (6.9)	4915 (7.9)	4
Constipation	202 (1.3)	210 (1.3)	0.4	470 (1.0)	478 (1.0)	0.2	672 (1.1)	688 (1.1)	0.2
Broad-spectrum antibiotic use	3618 (22.4)	3592 (22.2)	0.4	10 775 (23.6)	10 895 (23.8)	0.6	14 393 (23.3)	14 487 (23.4)	0.4
Any antibiotic use	3537 (21.9)	3487 (21.6)	0.8	10 535 (23.0)	10 578 (23.1)	0.2	14 072 (22.7)	14 065 (22.7)	0
Glucocorticoid use	1592 (9.9)	1567 (9.7)	0.5	4671 (10.2)	4786 (10.5)	0.8	6263 (10.1)	6353 (10.3)	0.5
Use of DMARDs, nonbiologic	125 (0.8)	118 (0.7)	0.5	384 (0.8)	401 (0.9)	0.4	509 (0.8)	519 (0.8)	0.2
Use of DMARDs, biologic	99 (0.6)	93 (0.6)	0.5	290 (0.6)	288 (0.6)	0.1	389 (0.6)	381 (0.6)	0.2
Intestinal infections	59 (0.4)	66 (0.4)	0.7	178 (0.4)	195 (0.4)	0.6	237 (0.4)	261 (0.4)	0.6
Mycotic infections	952 (5.9)	941 (5.8)	0.3	2425 (5.3)	2461 (5.4)	0.4	3377 (5.5)	3402 (5.5)	0.2
Viral infections	456 (2.8)	456 (2.8)	0	1189 (2.6)	1204 (2.6)	0.2	1645 (2.7)	1660 (2.7)	0.2
Other bacterial infections	178 (1.1)	190 (1.2)	0.7	497 (1.1)	484 (1.1)	0.3	675 (1.1)	674 (1.1)	0
Other nonbacterial infections	62 (0.4)	67 (0.4)	0.5	226 (0.5)	214 (0.5)	0.4	288 (0.5)	281 (0.5)	0.2
Asthma	792 (4.9)	783 (4.8)	0.3	1677 (3.7)	1730 (3.8)	0.6	2469 (4.0)	2513 (4.1)	0.4
Chronic obstructive pulmonary disease	779 (4.8)	753 (4.7)	0.8	1639 (3.6)	1675 (3.7)	0.4	2418 (3.9)	2428 (3.9)	0.1
Adrenal disorder	53 (0.3)	52 (0.3)	0.1	125 (0.3)	106 (0.2)	0.8	178 (0.3)	158 (0.3)	0.6
Low frailty	5842 (36.2)	5801 (35.9)	0.5	15 822 (34.6)	15 760 (34.5)	0.3	21 664 (35.0)	21 561 (34.8)	0.3
Medium frailty	5548 (34.4)	5561 (34.4)	0.2	15 635 (34.2)	15 528 (34.0)	0.5	21 183 (34.2)	21 089 (34.1)	0.3
High frailty	4757 (29.5)	4785 (29.6)	0.4	14 272 (31.2)	14 441 (31.6)	0.8	19 029 (30.8)	19 226 (31.1)	0.7
Number of drugs, low	5497 (34.0)	5466 (33.9)	0.4	14 610 (31.9)	14 585 (31.9)	0.1	20 107 (32.5)	20 051 (32.4)	0.2
Number of drugs, medium	6024 (37.3)	6049 (37.5)	0.3	17 661 (38.6)	17 559 (38.4)	0.5	23 685 (38.3)	23 608 (38.2)	0.3
Number of drugs, high	4626 (28.6)	4632 (28.7)	0.1	13 458 (29.4)	13 585 (29.7)	0.6	18 084 (29.2)	18 217 (29.4)	0.5
0 ED visits	14 931 (92.5)	14 943 (92.5)	0.3	40 510 (88.6)	40 456 (88.5)	0.4	55 441 (89.6)	55 399 (89.5)	0.2
1 ED visit	605 (3.7)	614 (3.8)	0.3	3868 (8.5)	3900 (8.5)	0.3	4473 (7.2)	4514 (7.3)	0.3
>1 ED visit	611 (3.8)	590 (3.7)	0.7	1351 (3.0)	1373 (3.0)	0.3	1962 (3.2)	1963 (3.2)	0
0 hospitalizations	15 711 (97.3)	15 721 (97.4)	0.4	44 578 (97.5)	44 573 (97.5)	0.1	60 289 (97.4)	60 294 (97.4)	0.1
1 hospitalization	406 (2.5)	398 (2.5)	0.3	1079 (2.4)	1082 (2.4)	0	1485 (2.4)	1480 (2.4)	0.1
>1 hospitalization	30 (0.2)	28 (0.2)	0.3	72 (0.2)	74 (0.2)	0.1	102 (0.2)	102 (0.2)	0
<3 outpatient visits	5965 (36.9)	5976 (37.0)	0.1	16 594 (36.3)	16 488 (36.1)	0.5	22 559 (36.5)	22 464 (36.3)	0.3
3–4 outpatient visits	5404 (33.5)	5381 (33.3)	0.3	15 288 (33.4)	15 288 (33.4)	0	20 692 (33.4)	20 669 (33.4)	0.1
>4 outpatient visits	4778 (29.6)	4790 (29.7)	0.2	13 847 (30.3)	13 953 (30.5)	0.5	18 625 (30.1)	18 743 (30.3)	0.4
Mammogram	252 (1.6)	244 (1.5)	0.4	798 (1.7)	791 (1.7)	0.1	1050 (1.7)	1035 (1.7)	0.2
Colonoscopy	213 (1.3)	230 (1.4)	0.9	690 (1.5)	706 (1.5)	0.3	903 (1.5)	936 (1.5)	0.4
Flu vaccine	3097 (19.2)	3108 (19.2)	0.2	8172 (17.9)	8171 (17.9)	0	11 269 (18.2)	11 279 (18.2)	0

DMARD = disease-modifying antirheumatic drug; DPP-4 = dipeptidyl peptidase-4; ED = emergency department; GLP-1 = glucagon-like peptide-1 receptor; SD = standardized difference; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Table 5. Distribution of Baseline Covariates Before Propensity Score Matching: Cohort 2 (SGLT-2 Inhibitors vs. GLP-1 Agonists)

Covariate	Optum			MarketScan			Combined		
	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %
Male	8764 (47.6)	15 490 (58.4)	21.7	23 346 (47.2)	44 919 (55.6)	16.9	32 110 (47.3)	60 409 (56.3)	18.1
Age Decile 1	2101 (11.4)	2391 (9.0)	7.9	5876 (11.9)	7144 (8.8)	10	7977 (11.8)	9535 (8.9)	9.4
Age Decile 2	1947 (10.6)	2542 (9.6)	3.3	5375 (10.9)	7653 (9.5)	4.6	7322 (10.8)	10 195 (9.5)	4.3
Age Decile 3	1809 (9.8)	2686 (10.1)	1	5048 (10.2)	7976 (9.9)	1.1	6857 (10.1)	10 662 (9.9)	0.5
Age Decile 4	1772 (9.6)	2721 (10.3)	2.1	4831 (9.8)	8189 (10.1)	1.2	6603 (9.7)	10 910 (10.2)	1.5
Age Decile 5	1721 (9.4)	2771 (10.4)	3.7	4850 (9.8)	8175 (10.1)	1.1	6571 (9.7)	10 946 (10.2)	1.7
Age Decile 6	1738 (9.4)	2752 (10.4)	3.1	4659 (9.4)	8368 (10.4)	3.2	6397 (9.4)	11 120 (10.4)	3.2
Age Decile 7	1719 (9.3)	2775 (10.5)	3.8	4705 (9.5)	8322 (10.3)	2.7	6424 (9.5)	11 097 (10.3)	2.9
Age Decile 8	1663 (9.0)	2828 (10.7)	5.5	4655 (9.4)	8366 (10.4)	3.2	6318 (9.3)	11 194 (10.4)	3.8
Age Decile 9	1961 (10.7)	2532 (9.5)	3.7	4463 (9.0)	8556 (10.6)	5.3	6424 (9.5)	11 088 (10.3)	2.9
Age Decile 10	1968 (10.7)	2524 (9.5)	3.9	5010 (10.1)	8018 (9.9)	0.7	6978 (10.3)	10 542 (9.8)	1.5
Cohort entry, October 2013–March 2014	3899 (21.2)	1689 (6.4)	44	10 687 (21.6)	5172 (6.4)	44.9	14 586 (21.5)	6861 (6.4)	44.6
Cohort entry, April 2014–September 2014	3859 (21.0)	3094 (11.7)	25.4	10 602 (21.4)	9685 (12.0)	25.5	14 461 (21.3)	12 779 (11.9)	25.4
Cohort entry, October 2014–March 2015	3405 (18.5)	5809 (21.9)	8.5	9990 (20.2)	20 805 (25.8)	13.3	13 395 (19.7)	26 614 (24.8)	12.2
Cohort entry, April 2015–September 2015	3155 (17.1)	8018 (30.2)	31.1	8734 (17.7)	25 168 (31.2)	31.8	11 889 (17.5)	33 186 (30.9)	31.7
Cohort entry, October 2013–March 2014	4081 (22.2)	7912 (29.8)	17.5	9459 (19.1)	19 937 (24.7)	13.5	13 540 (19.9)	27 849 (26.0)	14.3
Diabetes, no complications	14 567 (79.2)	21 540 (81.2)	5.1	40 480 (81.8)	67 051 (83.0)	3.1	55 047 (81.1)	88 591 (82.6)	3.9
Diabetes, ocular complications	887 (4.8)	1224 (4.6)	1	2067 (4.2)	3468 (4.3)	0.6	2954 (4.4)	4692 (4.4)	0.1
Diabetes, neurologic complications	2065 (11.2)	2495 (9.4)	6	4262 (8.6)	6123 (7.6)	3.8	6327 (9.3)	8618 (8.0)	4.6
Diabetes, other complications	1498 (8.1)	1984 (7.5)	2.5	3842 (7.8)	5897 (7.3)	1.8	5340 (7.9)	7881 (7.3)	2
Hypoglycemia	43 (0.2)	26 (0.1)	3.3	96 (0.2)	89 (0.1)	2.2	139 (0.2)	115 (0.1)	2.5
Hypercholesterolemia	3115 (16.9)	4604 (17.4)	1.1	6651 (13.4)	11 696 (14.5)	3	9766 (14.4)	16 300 (15.2)	2.3
Hyperglyceridemia	566 (3.1)	908 (3.4)	2	1110 (2.2)	1799 (2.2)	0.1	1676 (2.5)	2707 (2.5)	0.3
Other hyperlipidemia	3237 (17.6)	4817 (18.2)	1.5	6713 (13.6)	11 700 (14.5)	2.6	9950 (14.7)	16 517 (15.4)	2.1
Other lipid abnormality	9757 (53.0)	13 660 (51.5)	3.1	21 044 (42.5)	35 324 (43.7)	2.4	30 801 (45.4)	48 984 (45.7)	0.6
Hypertension	13 320 (72.4)	19 062 (71.9)	1.2	28 988 (58.6)	48 143 (59.6)	2.1	42 308 (62.3)	67 205 (62.6)	0.7
Hypertension, malignant	293 (1.6)	339 (1.3)	2.6	507 (1.0)	825 (1.0)	0	800 (1.2)	1164 (1.1)	0.9
Myocardial infarction	106 (0.6)	148 (0.6)	0.2	222 (0.4)	306 (0.4)	1.1	328 (0.5)	454 (0.4)	0.9
Peripheral vascular disease	479 (2.6)	576 (2.2)	2.8	782 (1.6)	1228 (1.5)	0.5	1261 (1.9)	1804 (1.7)	1.3
Other ischemic heart disease	1892 (10.3)	2436 (9.2)	3.7	3927 (7.9)	6215 (7.7)	0.9	5819 (8.6)	8651 (8.1)	1.8
Coronary artery bypass grafting/percutaneous coronary intervention	62 (0.3)	89 (0.3)	0	143 (0.3)	190 (0.2)	1.1	205 (0.3)	279 (0.3)	0.8
Ischemic stroke	400 (2.2)	485 (1.8)	2.5	799 (1.6)	1265 (1.6)	0.4	1199 (1.8)	1750 (1.6)	1
Transient ischemic attack	117 (0.6)	121 (0.5)	2.4	211 (0.4)	328 (0.4)	0.3	328 (0.5)	449 (0.4)	1
Atrial fibrillation	489 (2.7)	579 (2.2)	3.1	1031 (2.1)	1451 (1.8)	2.1	1520 (2.2)	2030 (1.9)	2.4
Arrhythmia	507 (2.8)	625 (2.4)	2.5	1087 (2.2)	1486 (1.8)	2.5	1594 (2.3)	2111 (2.0)	2.6
Congestive heart failure	482 (2.6)	464 (1.7)	6	742 (1.5)	1002 (1.2)	2.2	1224 (1.8)	1466 (1.4)	3.5
Other cardiovascular disease	34 (0.2)	35 (0.1)	1.3	61 (0.1)	116 (0.1)	0.6	95 (0.1)	151 (0.1)	0
Peripheral circulatory disorder	157 (0.9)	152 (0.6)	3.3	309 (0.6)	334 (0.4)	2.9	466 (0.7)	486 (0.5)	3.1
Other chronic heart disease	1801 (9.8)	2318 (8.7)	3.6	3676 (7.4)	5879 (7.3)	0.6	5477 (8.1)	8197 (7.6)	1.6
Obesity, not morbid	3503 (19.0)	3840 (14.5)	12.2	6614 (13.4)	7791 (9.6)	11.7	10 117 (14.9)	11 631 (10.8)	12.2
Obesity, morbid	1835 (10.0)	1579 (6.0)	14.9	3476 (7.0)	3398 (4.2)	12.3	5311 (7.8)	4977 (4.6)	13.2
Smoking	1155 (6.3)	1523 (5.7)	2.3	1528 (3.1)	2352 (2.9)	1	2683 (4.0)	3875 (3.6)	1.8
Alcohol use	32 (0.2)	63 (0.2)	1.4	60 (0.1)	110 (0.1)	0.4	92 (0.1)	173 (0.2)	0.7
Weight loss	101 (0.5)	178 (0.7)	1.6	181 (0.4)	344 (0.4)	1	282 (0.4)	522 (0.5)	1.1
Anticoagulant use	573 (3.1)	671 (2.5)	3.5	1434 (2.9)	1999 (2.5)	2.6	2007 (3.0)	2670 (2.5)	2.9
Antiarrhythmic drug use	93 (0.5)	127 (0.5)	0.4	293 (0.6)	407 (0.5)	1.2	386 (0.6)	534 (0.5)	1
Digoxin use	152 (0.8)	187 (0.7)	1.4	368 (0.7)	542 (0.7)	0.9	520 (0.8)	729 (0.7)	1
Angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use	12 145 (66.0)	17 601 (66.4)	0.7	33 668 (68.1)	55 470 (68.7)	1.3	45 813 (67.5)	73 071 (68.1)	1.3
β-Blocker use	4801 (26.1)	6250 (23.6)	5.9	12 569 (25.4)	19 723 (24.4)	2.3	17 370 (25.6)	25 973 (24.2)	3.2
Dihydropyridine calcium-channel blocker use	3017 (16.4)	4239 (16.0)	1.1	8017 (16.2)	13 617 (16.9)	1.8	11 034 (16.3)	17 856 (16.6)	1.1
Nondihydropyridine calcium-channel blocker use	506 (2.8)	682 (2.6)	1.1	1476 (3.0)	2225 (2.8)	1.4	1982 (2.9)	2907 (2.7)	1.3
Loop diuretic use	1451 (7.9)	1430 (5.4)	10	3519 (7.1)	4252 (5.3)	7.7	4970 (7.3)	5682 (5.3)	8.3
Other diuretic use	5671 (30.8)	7370 (27.8)	6.7	16 125 (32.6)	24 414 (30.2)	5.1	21 796 (32.1)	31 784 (29.6)	5.4
Antianginal drug use	312 (1.7)	349 (1.3)	3.1	678 (1.4)	980 (1.2)	1.4	990 (1.5)	1329 (1.2)	1.9
Other antihypertensive agent use	625 (3.4)	751 (2.8)	3.3	1559 (3.2)	2220 (2.7)	2.4	2184 (3.2)	2971 (2.8)	2.6

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Appendix Table 5–Continued

Covariate	Optum			MarketScan			Combined		
	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %	DPP-4, *n* (%)	SGLT-2, *n* (%)	SD, %
Insulin use	6676 (36.3)	6299 (23.8)	27.6	17 563 (35.5)	18 882 (23.4)	26.8	24 239 (35.7)	25 181 (23.5)	27
Metformin use	13 345 (72.5)	20 866 (78.7)	14.3	37 664 (76.1)	64 041 (79.3)	7.6	51 009 (75.1)	84 907 (79.1)	9.5
DPP-4 inhibitor use	4914 (26.7)	9392 (35.4)	18.9	14 294 (28.9)	31 808 (39.4)	22.3	19 208 (28.3)	41 200 (38.4)	21.6
Sulfonylurea use	6749 (36.7)	10 482 (39.5)	5.9	18 054 (36.5)	30 575 (37.9)	2.8	24 803 (36.5)	41 057 (38.3)	3.6
Meglitinide use	191 (1.0)	272 (1.0)	0.1	597 (1.2)	1139 (1.4)	1.8	788 (1.2)	1411 (1.3)	1.4
α-Glucosidase use	64 (0.3)	112 (0.4)	1.2	185 (0.4)	374 (0.5)	1.4	249 (0.4)	486 (0.5)	1.3
Thiazolidinedione use	1624 (8.8)	2591 (9.8)	3.2	4610 (9.3)	7535 (9.3)	0	6234 (9.2)	10 126 (9.4)	0.9
Constipation	272 (1.5)	327 (1.2)	2.1	458 (0.9)	793 (1.0)	0.6	730 (1.1)	1120 (1.0)	0.3
Broad-spectrum antibiotic use	4381 (23.8)	5896 (22.2)	3.8	12 135 (24.5)	18 991 (23.5)	2.4	16 516 (24.3)	24 887 (23.2)	2.7
Any antibiotic use	4270 (23.2)	5659 (21.3)	4.5	11 826 (23.9)	18 460 (22.9)	2.5	16 096 (23.7)	24 119 (22.5)	2.9
Glucocorticoid use	1929 (10.5)	2419 (9.1)	4.6	5222 (10.6)	7876 (9.8)	2.7	7151 (10.5)	10 295 (9.6)	3.1
Use of DMARDs, nonbiologic	197 (1.1)	193 (0.7)	3.6	400 (0.8)	664 (0.8)	0.2	597 (0.9)	857 (0.8)	0.9
Use of DMARDs, biologic	129 (0.7)	161 (0.6)	1.2	347 (0.7)	493 (0.6)	1.1	476 (0.7)	654 (0.6)	1.1
Intestinal infections	74 (0.4)	106 (0.4)	0	175 (0.4)	290 (0.4)	0.1	249 (0.4)	396 (0.4)	0
Mycotic infections	1277 (6.9)	1573 (5.9)	4.1	2954 (6.0)	4361 (5.4)	2.5	4231 (6.2)	5934 (5.5)	3
Viral infections	519 (2.8)	748 (2.8)	0	1342 (2.7)	2112 (2.6)	0.6	1861 (2.7)	2860 (2.7)	0.5
Other bacterial infections	258 (1.4)	295 (1.1)	2.6	502 (1.0)	795 (1.0)	0.3	760 (1.1)	1090 (1.0)	1
Other nonbacterial infections	96 (0.5)	88 (0.3)	2.9	247 (0.5)	389 (0.5)	0.3	343 (0.5)	477 (0.4)	0.9
Asthma	1113 (6.0)	1227 (4.6)	6.3	2195 (4.4)	2841 (3.5)	4.7	3308 (4.9)	4068 (3.8)	5.3
Chronic obstructive pulmonary disease	1106 (6.0)	1189 (4.5)	6.9	1887 (3.8)	2767 (3.4)	2.1	2993 (4.4)	3956 (3.7)	3.7
Adrenal disorder	94 (0.5)	90 (0.3)	2.6	184 (0.4)	189 (0.2)	2.5	278 (0.4)	279 (0.3)	2.6
Low frailty	5620 (30.5)	9354 (35.3)	10.1	15 933 (32.2)	27 491 (34.0)	3.9	21 553 (31.8)	36 845 (34.3)	5.5
Medium frailty	5906 (32.1)	9067 (34.2)	4.4	16 069 (32.5)	27 333 (33.8)	2.9	21 975 (32.4)	36 400 (33.9)	3.3
High frailty	6873 (37.4)	8101 (30.5)	14.4	17 470 (35.3)	25 943 (32.1)	6.8	24 343 (35.9)	34 044 (31.7)	8.7
Number of drugs, low	4028 (21.9)	7964 (30.0)	18.6	10 509 (21.2)	22 509 (27.9)	15.4	14 537 (21.4)	30 473 (28.4)	16.2
Number of drugs, medium	6764 (36.8)	10 427 (39.3)	5.3	19 293 (39.0)	32 070 (39.7)	1.5	26 057 (38.4)	42 497 (39.6)	2.5
Number of drugs, high	7607 (41.3)	8131 (30.7)	22.4	19 670 (39.8)	26 188 (32.4)	15.3	27 277 (40.2)	34 319 (32.0)	17.1
0 ED visits	16 688 (90.7)	24 647 (92.9)	8.1	43 476 (87.9)	72 223 (89.4)	4.9	60 164 (88.6)	96 870 (90.3)	5.4
1 ED visit	897 (4.9)	946 (3.6)	6.5	4365 (8.8)	6310 (7.8)	3.7	5262 (7.8)	7256 (6.8)	3.8
>1 ED visit	814 (4.4)	929 (3.5)	4.7	1631 (3.3)	2234 (2.8)	3.1	2445 (3.6)	3163 (2.9)	3.7
0 hospitalizations	17 889 (97.2)	25 884 (97.6)	2.3	48 194 (97.4)	79 001 (97.8)	2.6	66 083 (97.3)	104 885 (97.8)	2.7
1 hospitalization	477 (2.6)	594 (2.2)	2.3	1190 (2.4)	1650 (2.0)	2.5	1667 (2.5)	2244 (2.1)	2.4
>1 hospitalization	33 (0.2)	44 (0.2)	0.3	88 (0.2)	116 (0.1)	0.9	121 (0.2)	160 (0.1)	0.7
<3 outpatient visits	5388 (29.3)	9642 (36.4)	15.1	14 367 (29.0)	28 705 (35.5)	13.9	19 755 (29.1)	38 347 (35.7)	14.2
3–4 outpatient visits	6239 (33.9)	9024 (34.0)	0.2	16 985 (34.3)	27 243 (33.7)	1.3	23 224 (34.2)	36 267 (33.8)	0.9
>4 outpatient visits	6772 (36.8)	7856 (29.6)	15.3	18 120 (36.6)	24 819 (30.7)	12.5	24 892 (36.7)	32 675 (30.5)	13.2
Mammogram	347 (1.9)	390 (1.5)	3.2	993 (2.0)	1348 (1.7)	2.5	1340 (2.0)	1738 (1.6)	2.7
Colonoscopy	267 (1.5)	321 (1.2)	2.1	723 (1.5)	1228 (1.5)	0.5	990 (1.5)	1549 (1.4)	0.1
Flu vaccine	3836 (20.8)	5321 (20.1)	1.9	8989 (18.2)	14 533 (18.0)	0.5	12 825 (18.9)	19 854 (18.5)	1

DMARD = disease-modifying antirheumatic drug; DPP-4 = dipeptidyl peptidase-4; ED = emergency department; GLP-1 = glucagon-like peptide-1 receptor; SD = standardized difference; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Table 6. Distribution of Baseline Covariates After Propensity Score Matching: Cohort 2 (SGLT-2 Inhibitors vs. GLP-1 Agonists)

Covariate	Optum			MarketScan			Combined		
	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %
Male	7423 (50.7)	7438 (50.8)	0.2	20 292 (49.1)	20 248 (49.0)	0.3	27 715 (49.5)	27 686 (49.4)	0.1
Age Decile 1	1545 (10.6)	1558 (10.6)	0.3	4554 (11.0)	4533 (11.0)	0.2	6099 (10.9)	6091 (10.9)	0
Age Decile 2	1530 (10.4)	1519 (10.4)	0.3	4330 (10.5)	4300 (10.4)	0.3	5860 (10.5)	5819 (10.4)	0.2
Age Decile 3	1436 (9.8)	1468 (10.0)	0.7	4218 (10.2)	4262 (10.3)	0.3	5654 (10.1)	5730 (10.2)	0.4
Age Decile 4	1443 (9.9)	1449 (9.9)	0.1	4065 (9.8)	4081 (9.9)	0.1	5508 (9.8)	5530 (9.9)	0.1
Age Decile 5	1419 (9.7)	1453 (9.9)	0.8	4137 (10.0)	4079 (9.9)	0.5	5556 (9.9)	5532 (9.9)	0.1
Age Decile 6	1440 (9.8)	1424 (9.7)	0.4	4004 (9.7)	3964 (9.6)	0.3	5444 (9.7)	5388 (9.6)	0.3
Age Decile 7	1423 (9.7)	1396 (9.5)	0.6	4047 (9.8)	4024 (9.7)	0.2	5470 (9.8)	5420 (9.7)	0.3
Age Decile 8	1403 (9.6)	1425 (9.7)	0.5	3977 (9.6)	4030 (9.7)	0.4	5380 (9.6)	5455 (9.7)	0.5
Age Decile 9	1508 (10.3)	1478 (10.1)	0.7	3879 (9.4)	3948 (9.5)	0.6	5387 (9.6)	5426 (9.7)	0.2
Age Decile 10	1495 (10.2)	1478 (10.1)	0.4	4125 (10.0)	4131 (10.0)	0	5620 (10.0)	5609 (10.0)	0.1
Cohort entry, October 2013–March 2014	1731 (11.8)	1670 (11.4)	1.3	5229 (12.6)	5122 (12.4)	0.8	6960 (12.4)	6792 (12.1)	0.9
Cohort entry, April 2014–September 2014	2723 (18.6)	2717 (18.5)	0.1	8253 (20.0)	8303 (20.1)	0.3	10 976 (19.6)	11 020 (19.7)	0.2
Cohort entry, October 2014–March 2015	3178 (21.7)	3245 (22.2)	1.1	9819 (23.8)	9870 (23.9)	0.3	12 997 (23.2)	13 115 (23.4)	0.5
Cohort entry, April 2015–September 2015	3097 (21.2)	3023 (20.6)	1.3	8705 (21.1)	8603 (20.8)	0.6	11 802 (21.1)	11 626 (20.8)	0.8
Cohort entry, October 2013–March 2014	3913 (26.7)	3993 (27.3)	1.2	9330 (22.6)	9454 (22.9)	0.7	13 243 (23.7)	13 447 (24.0)	0.9
Diabetes, no complications	11 659 (79.6)	11 680 (79.7)	0.3	33 849 (81.9)	33 765 (81.7)	0.6	45 508 (81.3)	45 445 (81.2)	0.3
Diabetes, ocular complications	705 (4.8)	703 (4.8)	0.1	1761 (4.3)	1816 (4.4)	0.6	2466 (4.4)	2519 (4.5)	0.5
Diabetes, neurologic complications	1584 (10.8)	1567 (10.7)	0.4	3509 (8.5)	3559 (8.6)	0.4	5093 (9.1)	5126 (9.2)	0.2
Diabetes, other complications	1179 (8.1)	1173 (8.0)	0.2	3213 (7.8)	3208 (7.8)	0.1	4392 (7.8)	4381 (7.8)	0.1
Hypoglycemia	25 (0.2)	22 (0.2)	0.5	72 (0.2)	72 (0.2)	0	97 (0.2)	94 (0.2)	0.1
Hypercholesterolemia	2458 (16.8)	2451 (16.7)	0.1	5615 (13.6)	5588 (13.5)	0.2	8073 (14.4)	8039 (14.4)	0.2
Hyperglyceridemia	479 (3.3)	469 (3.2)	0.4	931 (2.3)	946 (2.3)	0.2	1410 (2.5)	1415 (2.5)	0.1
Other hyperlipidemia	2607 (17.8)	2557 (17.5)	0.9	5739 (13.9)	5619 (13.6)	0.9	8346 (14.9)	8176 (14.6)	0.9
Other lipid abnormality	7739 (52.9)	7747 (52.9)	0.1	17 731 (42.9)	17 788 (43.0)	0.2	25 470 (45.5)	25 535 (45.6)	0.2
Hypertension	10 568 (72.2)	10 512 (71.8)	0.9	24 326 (58.8)	24 292 (58.7)	0.2	34 894 (62.3)	34 804 (62.2)	0.3
Hypertension, malignant	216 (1.5)	211 (1.4)	0.3	417 (1.0)	423 (1.0)	0.1	633 (1.1)	634 (1.1)	0
Myocardial infarction	84 (0.6)	79 (0.5)	0.5	171 (0.4)	190 (0.5)	0.7	255 (0.5)	269 (0.5)	0.4
Peripheral vascular disease	361 (2.5)	367 (2.5)	0.3	659 (1.6)	672 (1.6)	0.2	1020 (1.8)	1039 (1.9)	0.3
Other ischemic heart disease	1456 (9.9)	1450 (9.9)	0.2	3214 (7.8)	3304 (8.0)	0.8	4670 (8.3)	4754 (8.5)	0.5
Coronary artery bypass grafting/percutaneous coronary intervention	50 (0.3)	49 (0.3)	0.1	113 (0.3)	121 (0.3)	0.4	163 (0.3)	170 (0.3)	0.2
Ischemic stroke	303 (2.1)	303 (2.1)	0	659 (1.6)	700 (1.7)	0.8	962 (1.7)	1003 (1.8)	0.6
Transient ischemic attack	85 (0.6)	95 (0.6)	0.9	170 (0.4)	183 (0.4)	0.5	255 (0.5)	278 (0.5)	0.6
Atrial fibrillation	345 (2.4)	369 (2.5)	1.1	804 (1.9)	824 (2.0)	0.3	1149 (2.1)	1193 (2.1)	0.5
Arrhythmia	395 (2.7)	392 (2.7)	0.1	861 (2.1)	852 (2.1)	0.2	1256 (2.2)	1244 (2.2)	0.1
Congestive heart failure	314 (2.1)	329 (2.2)	0.7	592 (1.4)	573 (1.4)	0.4	906 (1.6)	902 (1.6)	0.1
Other cardiovascular disease	25 (0.2)	24 (0.2)	0.2	50 (0.1)	52 (0.1)	0.1	75 (0.1)	76 (0.1)	0
Peripheral circulatory disorder	111 (0.8)	103 (0.7)	0.6	226 (0.5)	233 (0.6)	0.2	337 (0.6)	336 (0.6)	0
Other chronic heart disease	1385 (9.5)	1377 (9.4)	0.2	3019 (7.3)	3108 (7.5)	0.8	4404 (7.9)	4485 (8.0)	0.5
Obesity, not morbid	2553 (17.4)	2600 (17.7)	0.8	5099 (12.3)	5101 (12.3)	0	7652 (13.7)	7701 (13.8)	0.3
Obesity, morbid	1241 (8.5)	1219 (8.3)	0.6	2574 (6.2)	2553 (6.2)	0.2	3815 (6.8)	3772 (6.7)	0.3
Smoking	877 (6.0)	880 (6.0)	0.1	1263 (3.1)	1270 (3.1)	0.1	2140 (3.8)	2150 (3.8)	0.1
Alcohol use	28 (0.2)	32 (0.2)	0.6	50 (0.1)	45 (0.1)	0.4	78 (0.1)	77 (0.1)	0
Weight loss	82 (0.6)	81 (0.6)	0.1	154 (0.4)	151 (0.4)	0.1	236 (0.4)	232 (0.4)	0.1
Anticoagulant use	424 (2.9)	424 (2.9)	0	1121 (2.7)	1138 (2.8)	0.2	1545 (2.8)	1562 (2.8)	0.2
Antiarrhythmic drug use	72 (0.5)	74 (0.5)	0.2	230 (0.6)	228 (0.6)	0.1	302 (0.5)	302 (0.5)	0
Digoxin use	104 (0.7)	108 (0.7)	0.3	302 (0.7)	275 (0.7)	0.8	406 (0.7)	383 (0.7)	0.5
Angiotensin-converting enzyme inhibitor/angiotensin-receptor blocker use	9700 (66.2)	9653 (65.9)	0.7	28 182 (68.2)	28 406 (68.7)	1.1	37 882 (67.7)	38 059 (68.0)	0.7
β-Blocker use	3722 (25.4)	3663 (25.0)	1	10 466 (25.3)	10 468 (25.3)	0	14 188 (25.3)	14 131 (25.2)	0.2
Dihydropyridine calcium-channel blocker use	2364 (16.1)	2329 (15.9)	0.7	6840 (16.5)	6858 (16.6)	0.1	9204 (16.4)	9187 (16.4)	0.1
Nondihydropyridine calcium-channel blocker use	387 (2.6)	396 (2.7)	0.4	1194 (2.9)	1193 (2.9)	0	1581 (2.8)	1589 (2.8)	0.1
Loop diuretic use	1007 (6.9)	1034 (7.1)	0.7	2743 (6.6)	2728 (6.6)	0.2	3750 (6.7)	3762 (6.7)	0.1
Other diuretic use	4340 (29.6)	4309 (29.4)	0.5	13 284 (32.1)	13 399 (32.4)	0.6	17 624 (31.5)	17 708 (31.6)	0.3
Antianginal drug use	221 (1.5)	206 (1.4)	0.9	554 (1.3)	548 (1.3)	0.1	775 (1.4)	754 (1.3)	0.3
Other antihypertensive agent use	469 (3.2)	477 (3.3)	0.3	1250 (3.0)	1256 (3.0)	0.1	1719 (3.1)	1733 (3.1)	0.1

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Appendix Table 6–Continued

Covariate	Optum			MarketScan			Combined		
	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %	GLP-1, *n* (%)	SGLT-2, *n* (%)	SD, %
Insulin use	4743 (32.4)	4805 (32.8)	0.9	13 374 (32.4)	13 432 (32.5)	0.3	18 117 (32.4)	18 237 (32.6)	0.5
Metformin use	10 834 (74.0)	10 837 (74.0)	0	31 752 (76.8)	31 762 (76.8)	0	42 586 (76.1)	42 599 (76.1)	0.1
DPP-4 inhibitor use	4245 (29.0)	4178 (28.5)	1	12 868 (31.1)	12 868 (31.1)	0	17 113 (30.6)	17 046 (30.4)	0.3
Sulfonylurea use	5493 (37.5)	5495 (37.5)	0	15 227 (36.8)	15 355 (37.1)	0.6	20 720 (37.0)	20 850 (37.2)	0.5
Meglitinide use	151 (1.0)	144 (1.0)	0.5	521 (1.3)	501 (1.2)	0.4	672 (1.2)	645 (1.2)	0.4
α-Glucosidase use	53 (0.4)	55 (0.4)	0.2	165 (0.4)	169 (0.4)	0.2	218 (0.4)	224 (0.4)	0.2
Thiazolidinedione use	1342 (9.2)	1338 (9.1)	0.1	3876 (9.4)	3827 (9.3)	0.4	5218 (9.3)	5165 (9.2)	0.3
Constipation	200 (1.4)	207 (1.4)	0.4	394 (1.0)	401 (1.0)	0.2	594 (1.1)	608 (1.1)	0.2
Broad-spectrum antibiotic use	3472 (23.7)	3526 (24.1)	0.8	10 017 (24.2)	10 122 (24.5)	0.6	13 489 (24.1)	13 648 (24.4)	0.7
Any antibiotic use	3343 (22.8)	3310 (22.6)	0.6	9775 (23.6)	9731 (23.5)	0.3	13 118 (23.4)	13 041 (23.3)	0.3
Glucocorticoid use	1507 (10.3)	1504 (10.3)	0.1	4326 (10.5)	4292 (10.4)	0.3	5833 (10.4)	5796 (10.4)	0.2
Use of DMARDs, nonbiologic	145 (1.0)	143 (1.0)	0.1	336 (0.8)	330 (0.8)	0.2	481 (0.9)	473 (0.8)	0.2
Use of DMARDs, biologic	104 (0.7)	95 (0.6)	0.8	287 (0.7)	291 (0.7)	0.1	391 (0.7)	386 (0.7)	0.1
Intestinal infections	54 (0.4)	59 (0.4)	0.5	144 (0.3)	149 (0.4)	0.2	198 (0.4)	208 (0.4)	0.3
Mycotic infections	992 (6.8)	968 (6.6)	0.7	2447 (5.9)	2485 (6.0)	0.4	3439 (6.1)	3453 (6.2)	0.1
Viral infections	387 (2.6)	407 (2.8)	0.8	1119 (2.7)	1117 (2.7)	0	1506 (2.7)	1524 (2.7)	0.2
Other bacterial infections	188 (1.3)	188 (1.3)	0	414 (1.0)	424 (1.0)	0.2	602 (1.1)	612 (1.1)	0.2
Other nonbacterial infections	63 (0.4)	57 (0.4)	0.6	200 (0.5)	209 (0.5)	0.3	263 (0.5)	266 (0.5)	0.1
Asthma	811 (5.5)	826 (5.6)	0.4	1746 (4.2)	1734 (4.2)	0.2	2557 (4.6)	2560 (4.6)	0
Chronic obstructive pulmonary disease	795 (5.4)	802 (5.5)	0.2	1553 (3.8)	1567 (3.8)	0.2	2348 (4.2)	2369 (4.2)	0.2
Adrenal disorder	66 (0.5)	68 (0.5)	0.2	128 (0.3)	137 (0.3)	0.4	194 (0.3)	205 (0.4)	0.3
Low frailty	4673 (31.9)	4683 (32.0)	0.1	13 494 (32.6)	13 496 (32.6)	0	18 167 (32.4)	18 179 (32.5)	0
Medium frailty	4813 (32.9)	4779 (32.6)	0.5	13 510 (32.7)	13 609 (32.9)	0.5	18 323 (32.7)	18 388 (32.8)	0.2
High frailty	5156 (35.2)	5186 (35.4)	0.4	14 332 (34.7)	14 247 (34.5)	0.5	19 488 (34.8)	19 433 (34.7)	0.2
Number of drugs, low	3489 (23.8)	3492 (23.8)	0	9326 (22.6)	9202 (22.3)	0.7	12 815 (22.9)	12 694 (22.7)	0.5
Number of drugs, medium	5548 (37.9)	5503 (37.6)	0.7	16 241 (39.3)	16 327 (39.5)	0.4	21 789 (38.9)	21 830 (39.0)	0.2
Number of drugs, high	5605 (38.3)	5653 (38.6)	0.6	15 769 (38.1)	15 823 (38.3)	0.2	21 374 (38.2)	21 476 (38.4)	0.4
0 ED visits	13 413 (91.6)	13 409 (91.5)	0.2	36 438 (88.2)	36 457 (88.2)	0	49 851 (89.0)	49 866 (89.1)	0.1
1 ED visit	634 (4.3)	623 (4.3)	0.4	3597 (8.7)	3594 (8.7)	0	4231 (7.6)	4217 (7.5)	0.1
>1 ED visit	595 (4.1)	616 (4.2)	0.7	1301 (3.1)	1301 (3.1)	0	1896 (3.4)	1917 (3.4)	0.2
0 hospitalizations	14 260 (97.4)	14 249 (97.3)	0.7	40 307 (97.5)	40 307 (97.5)	0.2	54 567 (97.5)	54 556 (97.4)	0.1
1 hospitalization	355 (2.4)	371 (2.5)	0.7	957 (2.3)	976 (2.4)	0.3	1312 (2.3)	1347 (2.4)	0.4
>1 hospitalization	27 (0.2)	28 (0.2)	0.2	72 (0.2)	69 (0.2)	0.2	99 (0.2)	97 (0.2)	0.1
<3 outpatient visits	4579 (31.3)	4589 (31.3)	0.1	12 621 (30.5)	12 548 (30.3)	0.4	17 200 (30.7)	17 137 (30.6)	0.2
3–4 outpatient visits	5007 (34.2)	4970 (33.9)	0.6	14 166 (34.3)	14 193 (34.3)	0.1	19 173 (34.2)	19 163 (34.2)	0
>4 outpatient visits	5056 (34.5)	5089 (34.7)	0.4	14 549 (35.2)	14 611 (35.3)	0.3	19 605 (35.0)	19 700 (35.2)	0.4
Mammogram	256 (1.7)	263 (1.8)	0.4	814 (2.0)	821 (2.0)	0.1	1070 (1.9)	1084 (1.9)	0.2
Colonoscopy	202 (1.4)	206 (1.4)	0.2	609 (1.5)	616 (1.5)	0.1	811 (1.4)	822 (1.5)	0.2
Flu vaccine	3010 (20.6)	3007 (20.5)	0.1	7570 (18.3)	7600 (18.4)	0.2	10 580 (18.9)	10 607 (18.9)	0.1

DMARD = disease-modifying antirheumatic drug; DPP-4 = dipeptidyl peptidase-4; ED = emergency department; GLP-1 = glucagon-like peptide-1 receptor; SD = standardized difference; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Table 7. Selected Pooled Baseline Characteristics Before Propensity Score Matching*

Characteristic	SGLT-2 vs. DPP-4 Inhibitors (Cohort 1)			SGLT-2 Inhibitors vs. GLP-1 Agonists (Cohort 2)		
	SGLT-2 (*n* = 86 665)	DPP-4 (*n* = 136 741)	Standardized Difference, %	SGLT-2 (*n* = 107 278)	GLP-1 (*n* = 67 882)	Standardized Difference, %
Male sex, *n* (%)	46 661 (53.8)	74 356 (54.4)	1.1	60 409 (56.3)	32 110 (47.3)	18.1
Mean age (SD), *y*	54.4 (9.5)	57.3 (11.6)	38.0	55.0 (9.7)	54.2 (10.3)	11.3
Diabetic severity						
Ocular complications, *n (%)*	4114 (4.7)	4981 (3.6)	5.5	4692 (4.4)	2954 (4.4)	0.1
Neurologic complications, *n (%)*	7721 (8.9)	9163 (6.7)	8.2	8618 (8.0)	6327 (9.3)	4.6
Other or unspecified complications, *n (%)*	6534 (7.5)	9282 (6.8)	2.9	7881 (7.3)	5340 (7.9)	2.0
Mean hemoglobin A_{1c} level (SD), %†	8.8 (1.8)	8.8 (1.9)	0.1	8.8 (1.8)	8.6 (1.9)	0.2
Antidiabetic therapy, *n (%)*						
Metformin	65 286 (75.3)	111 799 (81.8)	15.7	84 907 (79.1)	51 009 (75.1)	9.5
DPP-4 inhibitors	–	–	–	41 200 (38.4)	19 208 (28.3)	21.6
GLP-1 agonists	20 710 (23.9)	4404 (3.2)	63.4	–	–	–
Insulin	28 223 (32.6)	15 539 (11.4)	53.0	25 181 (23.5)	24 239 (35.7)	27.0
Sulfonylureas	30 373 (35.0)	48 421 (35.4)	0.8	41 057 (38.3)	24 803 (36.5)	3.6
Risk factors for UTI, *n (%)*						
Use of broad-spectrum antibiotics	20 567 (23.7)	30 260 (22.1)	3.8	24 887 (23.2)	16 516 (24.3)	2.7
Use of oral steroids	8719 (10.1)	14 040 (10.3)	0.7	10 295 (9.6)	7151 (10.5)	3.1
Use of nonbiologic DMARDs	8719 (10.1)	14 040 (10.3)	0.7	857 (0.8)	597 (0.9)	0.9
Use of biologic DMARDS	721 (0.8)	1193 (0.9)	0.4	654 (0.6)	476 (0.7)	1.1
Mycotic infections	4825 (5.6)	8549 (6.3)	2.9	5934 (5.5)	4231 (6.2)	3.0
	Value			Value		
Propensity score diagnostics						
AUC						
Optum	0.80			0.71		
MarketScan	0.78			0.70		
Average standardized difference, %	6.9			5.1		

AUC = area under the curve; DMARD = disease-modifying antirheumatic drug; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.
* Selected pooled variables are shown; Appendix Tables 3 and 4 show database-specific and pooled baseline characteristics included in the propensity score before matching.
† Available for 10% of the pooled sample and not included in the propensity score model.

Appendix Table 8. Mean Follow-up and Standardized Difference in the Propensity Score–Matched Cohort

Analysis	SGLT-2 vs. DPP-4 Inhibitors (Cohort 1)			SGLT-2 Inhibitors vs. GLP-1 Agonists (Cohort 2)		
	Mean Follow-up in SGLT-2 Group, *d*	Mean Follow-up in DPP-4 Group, *d*	Standardized Difference, %	Mean Follow-up in SGLT-2 Group, *d*	Mean Follow-up in GLP-1 Group, *d*	Standardized Difference, %
As-treated						
Optum	195	188	2.9	208	187	8.3
MarketScan	208	191	6.6	225	193	12.6
Pooled	204	190	5.8	221	191	11.1
Intention-to-treat						
Optum	270	261	3.2	295	292	0.9
MarketScan	257	260	1.1	278	283	1.6
Pooled	274	262	4.2	301	295	1.9

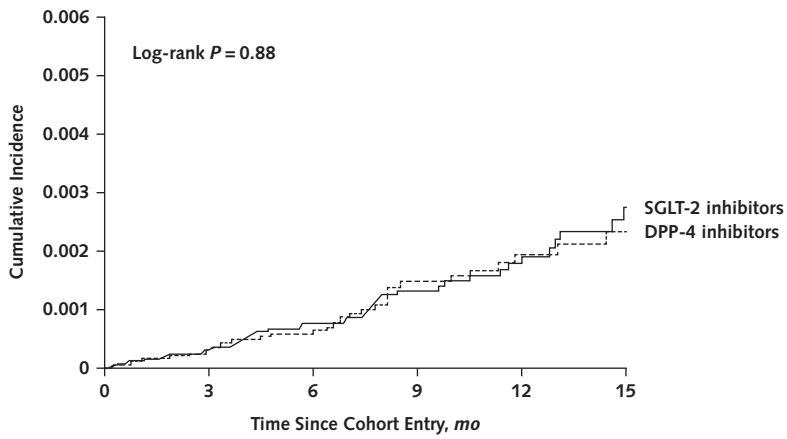
DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Table 9. Reasons for Censoring in the Propensity Score–Matched Cohorts 1 and 2, Stratified by Database*

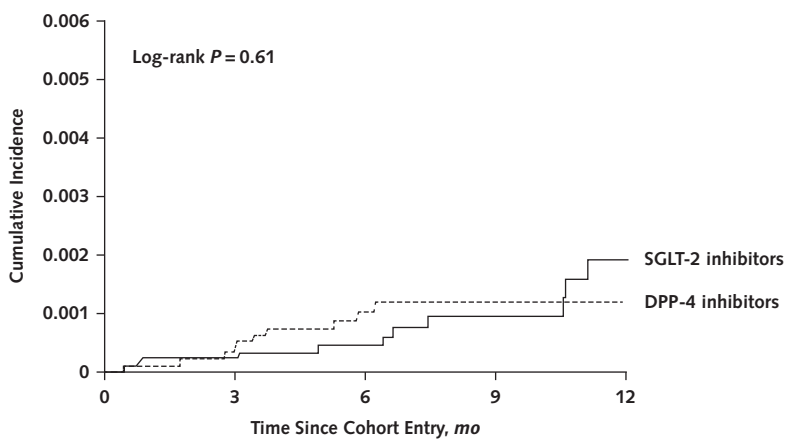
Reason for Censoring	Optum		MarketScan	
	SGLT-2	DPP-4	SGLT-2	DPP-4
Cohort 1: SGLT-2 vs. DPP-4 inhibitors				
Outcome	12 (0.1)	14 (0.1)	49 (0.1)	43 (0.1)
Exposure discontinuation	4104 (25.4)	4344 (26.9)	11 491 (25.1)	12 243 (26.8)
Exposure switching	1044 (6.5)	1145 (7.1)	3277 (7.2)	3602 (7.9)
End of data	7455 (46.2)	7345 (45.5)	20 190 (44.2)	18 281 (40.0)
End of eligibility	3532 (21.9)	3299 (20.4)	10 722 (23.4)	11 560 (25.3)
	SGLT-2	**GLP-1**	**SGLT-2**	**GLP-1**
Cohort 2: SGLT-2 inhibitors vs. GLP-1 agonists				
Outcome	15 (0.1)	19 (0.1)	54 (0.1)	72 (0.2)
Exposure discontinuation	3981 (27.2)	4768 (32.6)	11 043 (26.8)	13 648 (33.0)
Exposure switching	955 (6.5)	1247 (8.5)	2985 (7.2)	4010 (9.7)
End of data	6159 (42.1)	5436 (37.1)	16 762 (40.5)	13 569 (32.8)
End of eligibility	3535 (24.1)	3175 (21.7)	10 554 (25.5)	10 045 (24.3)

DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2.
* Data are numbers (percentages).

Appendix Figure 4. Propensity score–matched Kaplan–Meier curves for cumulative incidence of severe urinary tract infection events in MarketScan (*top*) and Optum (*bottom*) for cohort 1 (SGLT-2 vs. DPP-4 inhibitors).



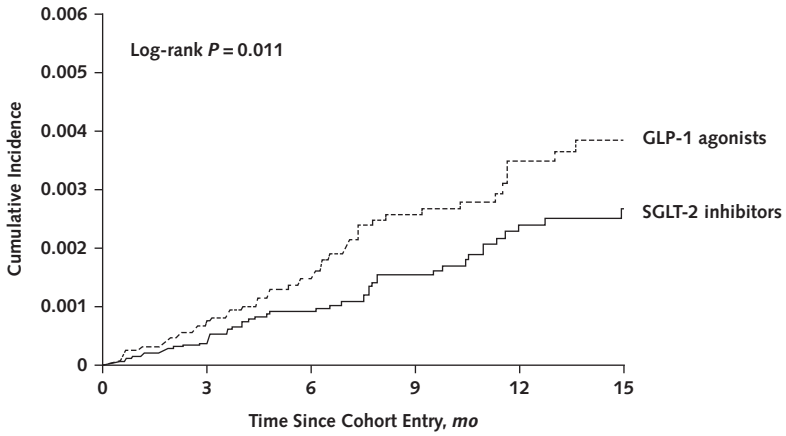
At risk, *n*						
Receiving DPP-4 inhibitor	45 729	33 980	24 689	16 926	11 283	7232
Receiving SGLT-2 inhibitor	45 729	35 039	25 766	18 663	12 684	7946



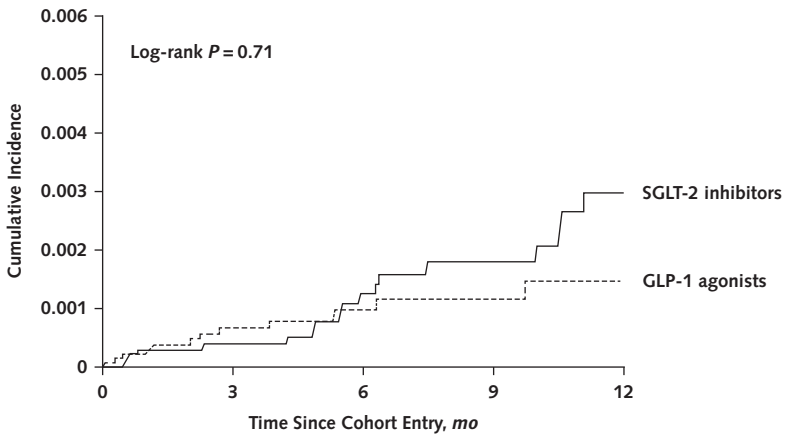
At risk, *n*					
Receiving DPP-4 inhibitor	16 147	10 288	6294	4025	2392
Receiving SGLT-2 inhibitor	16 147	10 765	6747	4137	2596

DPP-4 = dipeptidyl peptidase-4; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Figure 5. Propensity score–matched Kaplan–Meier curves for cumulative incidence of severe urinary tract infection events in MarketScan (*top*) and Optum (*bottom*) for cohort 2 (SGLT-2 inhibitors vs. GLP-1 agonists).



At risk, *n*						
Receiving GLP-1 agonist	41 344	31 035	22 787	16 891	12 389	8635
Receiving SGLT-2 inhibitor	41 344	32 351	23 878	18 553	13 934	9653



At risk, *n*					
Receiving GLP-1 agonist	14 645	8997	5432	3414	2259
Receiving SGLT-2 inhibitor	14 645	9925	6221	4089	2811

GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Table 10. Secondary Outcomes After Propensity Score Matching

Outcome	HR (95% CI) for SGLT-2 vs. DPP-4 Inhibitors	HR (95% CI) for SGLT-2 Inhibitors vs. GLP-1 Agonists
Optum		
Primary outcome	0.82 (0.38–1.77)	1.14 (0.58–2.24)
Individual components of the primary outcome		
Urosepsis	1.14 (0.35–3.74)	0.80 (0.32–1.96)
Pyelonephritis	0.83 (0.30–2.29)	0.98 (0.40–2.40)
Primary UTI hospitalization, primary diagnosis	0.79 (0.24–2.60)	0.90 (0.34–2.41)
Secondary outcomes		
UTI hospitalization, any position	0.52 (0.32–0.86)	0.99 (0.60–1.64)
Outpatient UTI	0.82 (0.70–0.95)	0.93 (0.80–1.08)
MarketScan		
Primary outcome	1.03 (0.68–1.55)	0.64 (0.45–0.91)
Individual components of the primary outcome		
Urosepsis	1.10 (0.64–1.90)	0.49 (0.30–0.78)
Pyelonephritis	0.71 (0.40–1.25)	0.57 (0.35–0.94)
Primary UTI hospitalization, primary diagnosis	0.82 (0.43–1.55)	0.84 (0.47–1.53)
Secondary outcomes		
UTI hospitalization, any position	0.74 (0.56–0.98)	0.74 (0.57–0.96)
Outpatient UTI	1.03 (0.93–1.14)	0.90 (0.82–0.99)

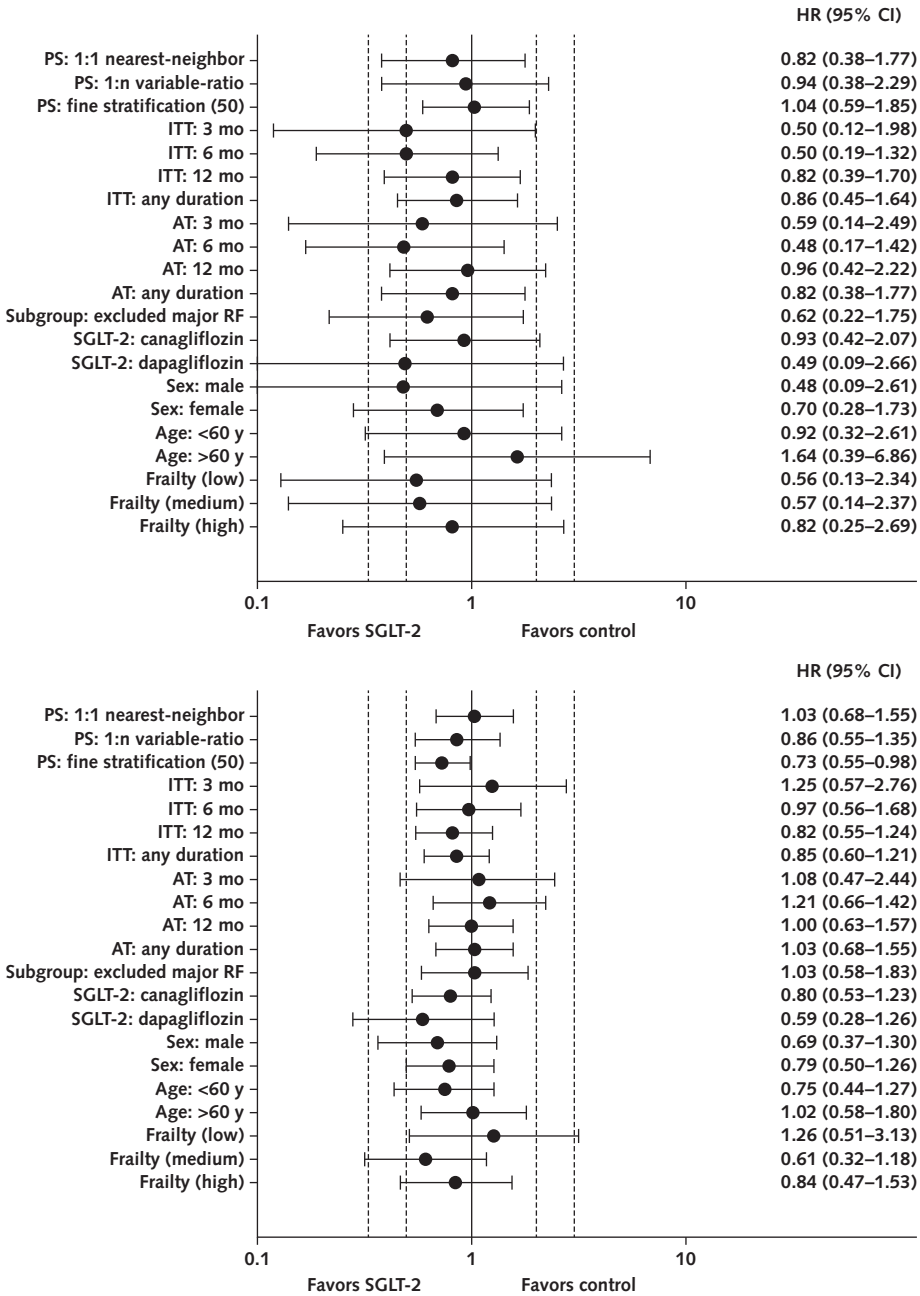
DPP-4 = dipeptidyl peptidase-4; HR = hazard ratio; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.

Appendix Table 11. Incidence Rate of Secondary Outcomes in Propensity Score–Matched Pooled Cohort, per 1000 Person-Years

Outcome	Incidence Rate			
	Cohort 1		Cohort 2	
	SGLT-2 Inhibitors	DPP-4 Inhibitors	SGLT-2 Inhibitors	GLP-1 Agonists
Individual components of the primary outcome				
Sepsis with UTI	1.01	0.90	1.06	1.94
Pyelonephritis	0.81	1.08	1.09	1.67
Primary UTI hospitalization	0.66	0.81	0.89	1.02
Other secondary outcomes				
UTI hospitalization	3.33	4.85	4.06	5.16
Outpatient UTI	34.50	36.05	36.65	41.04

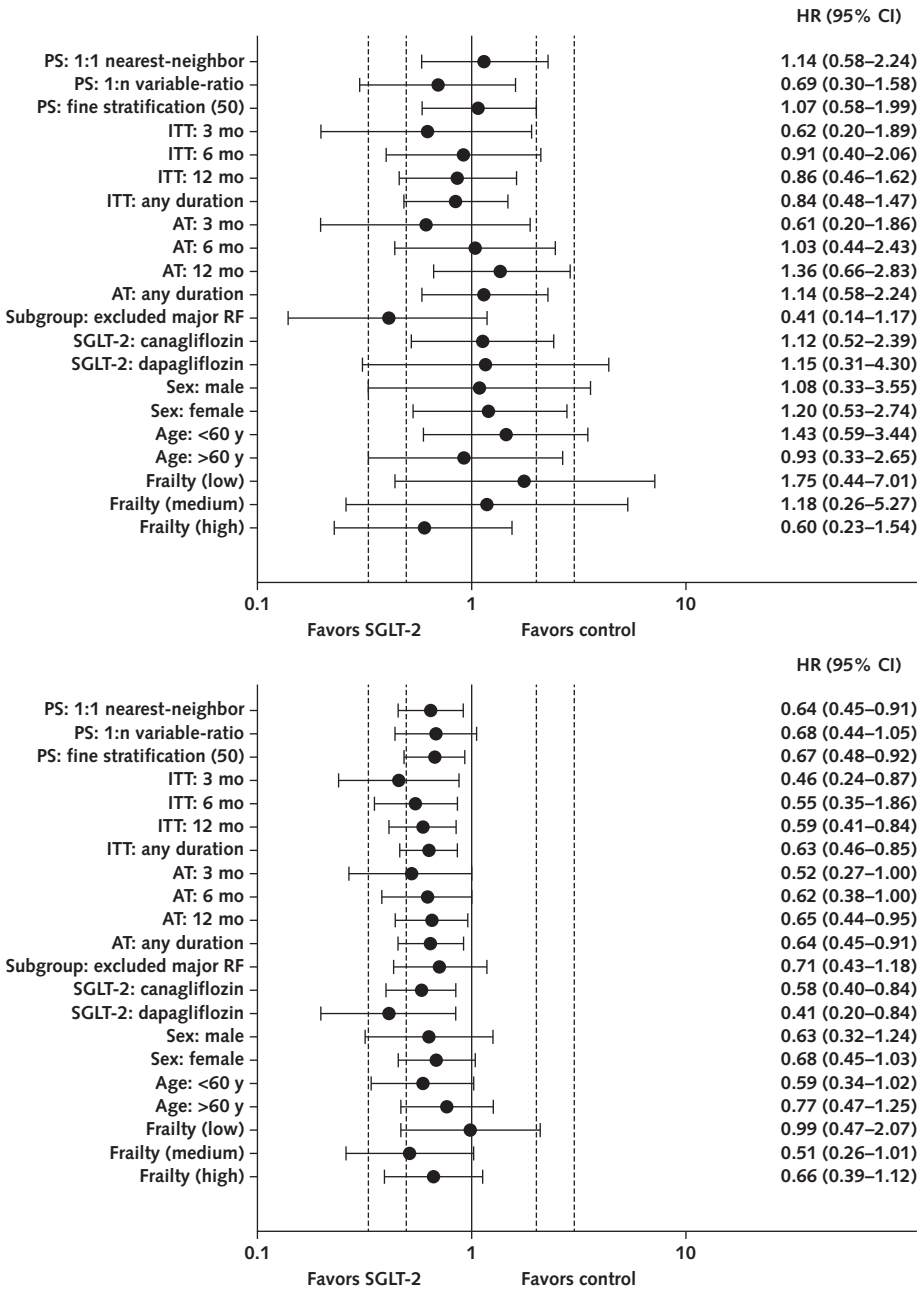
DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1 receptor; SGLT-2 = sodium–glucose cotransporter-2; UTI = urinary tract infection.

Appendix Figure 6. Sensitivity and subgroup analyses for cohort 1 (SGLT-2 vs. DPP-4 inhibitors) for MarketScan (*top*) and Optum (*bottom*).



For the subgroup analysis, the PS was reestimated within each subgroup and patients were rematched on the new reestimated score. Estimates were pooled across the 2 databases using fixed-effects meta-analysis. 1:1 nearest-neighbor matching was the primary analysis in terms of PS specification. The low-risk subgroup was defined as patients without evidence of any use of antibiotics or disease-modifying antirheumatic drugs or history of any infections. See text for details on the subgroups and sensitivity analyses. AT = as-treated; DPP-4 = dipeptidyl peptidase-4; HR = hazard ratio; ITT = intention-to-treat; PS = propensity score; RF = risk factor; SGLT-2 = sodium–glucose cotransporter-2.

Appendix Figure 7. Sensitivity and subgroup analyses for cohort 2 (SGLT-2 inhibitors vs. GLP-1 agonists) for MarketScan (*top*) and Optum (*bottom*).



For the subgroup analysis, the PS was reestimated within each subgroup and patients were rematched on the new reestimated score. Estimates were pooled across the 2 databases using fixed-effects meta-analysis. 1:1 nearest-neighbor matching was the primary analysis in terms of PS specification. The low-risk subgroup was defined as patients without evidence of any use of antibiotics or disease-modifying antirheumatic drugs or history of any infections. See text for details on the subgroups and sensitivity analyses. AT = as-treated; GLP-1 = glucagon-like peptide-1 receptor; HR = hazard ratio; ITT = intention-to-treat; PS = propensity score; RF = risk factor; SGLT-2 = sodium–glucose cotransporter-2.