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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors might increase the risk of intestinal obstruction, but real-world evidence for this severe adverse event is lacking. Thus, the objective of this study was to determine whether GLP-1 RAs and DPP-4 inhibitors are associated with an increased risk of intestinal obstruction compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors. We used the United Kingdom Clinical Practice Research Datalink and linked databases to assemble two new-user, active comparator cohorts (2013-2019). The first included 25,617 and 67,261 GLP-1 RA and SGLT-2 inhibitor users, respectively. The second included 131,927 and 40,615 DPP-4 inhibitor and SGLT-2 inhibitor users, respectively. Propensity score fine stratification weighted Cox proportional hazards models were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of intestinal obstruction requiring hospitalization. GLP-1 RAs were associated with an increased risk of intestinal obstruction compared with SGLT-2 inhibitors (1.9 vs. 1.1 per 1000 person-years, respectively; HR: 1.69, 95% CI: 1.04-2.74). The highest HR was observed after 1.6 years of use (HR: 3.48, 95% CI: 1.79-6.79). DPP-4 inhibitors were also associated with an increased risk (2.7 vs. 1.0 per 1000 person-years; HR: 2.59, 95% CI: 1.52-4.42), with the highest HR observed after 1.8 years of use (HR: 9.53, 95% CI: 4.47-20.30). The number needed to harm after one year of use was 1223 and 603 for GLP-1 RAs and DPP-4 inhibitors, respectively. In this large real-world study, GLP-1 RAs and DPP-4 inhibitors were associated with an increased risk of intestinal obstruction.

INTRODUCTION

Incretin-based drugs, which include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, are commonly used as second-to-third line drugs in the management of type 2 diabetes. These drugs have been shown to either reduce (GLP-1 RAs) or have neutral (DPP-4 inhibitors) effects on cardiovascular outcomes.[1–8] They induce their clinical effects by increasing the action of incretin hormones (notably GLP-1), leading to insulin secretion and reduced hyperglycemia.[9] However, increased GLP-1 action also reduces gastrointestinal motility,[10] which can lead to constipation. Over the years, case reports and certain regulatory agencies, such as the Japanese and European Medicines Agencies (EMA), have documented more severe intestinal effects with GLP-1 RAs and DPP-4 inhibitors, such as paralytic ileus and intestinal obstruction.[11–14] Intestinal obstruction is a severe condition requiring hospital admission, and its complications include ischemia, necrosis, or perforation of the intestine.[15,16]

To our knowledge, intestinal obstruction was never described in randomized controlled trials investigating incretin-based drugs. The only observational study on the topic reported no increased risk of paralytic ileus with alogliptin but compared with other incretin-based drugs.[17] In contrast, a recent pharmacovigilance analysis using the World Health Organization (WHO) pharmacovigilance database observed an increased reporting odds of intestinal obstruction with incretin-based drugs compared with other antidiabetic drugs, with a stronger signal for DPP-4 inhibitors.[18] However, analyses of disproportionate reporting in adverse drug reaction databases are not intended to estimate or quantify risk.

Given the potential severity of intestinal obstruction and uncertainties related to its association with incretin-based drugs, we conducted a population-based cohort study to determine whether the use of GLP-1 RAs and DPP-4 inhibitors, separately, is associated with an increased risk

of intestinal obstruction when compared with use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

RESEARCH DESIGN AND METHODS

Data Sources

We conducted a population-based cohort study by linking the United Kingdom (UK) Clinical Practice Research Datalink (CPRD), using the GOLD and Aurum databases (with patients appearing in both databases deduplicated), with the Hospital Episode Statistics (HES) repository and the Office for National Statistics database (ONS). The CPRD is a large primary care database of more than 50 million patients enrolled in over 2,000 general practices shown to be representative of the UK population.[19] Diagnoses recorded in the CPRD have been validated, generating high sensitivities and positive predictive values for various diagnoses.[19–21]

The HES repository contains records of inpatient information in National Health Services hospitals,[22] and the ONS is a database of electronic death certificates.[23] Linkage to these databases is restricted to English practices that have consented to the linkage scheme, representing about 85% of all English practices in the CPRD.[24] These linkable patients have been shown to be representative of the overall CPRD population,[25] and linkage between the CPRD and these other data sources has been well validated.[19,26] The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (Protocol 20_185R) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Population

We used a new-user, active comparator study design where initiators of incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors) were compared with initiators of SGLT-2 inhibitors between January 1, 2013 (the year the first SGLT-2 inhibitor entered the UK market) and December 31, 2019. We chose SGLT2 inhibitors as the comparator group because they are used

at the same disease stage as GLP-1 RAs and DPP-4 inhibitors[27] and have not been associated with intestinal obstruction. Thus, we created two new-user cohorts, with the first consisting of new users of GLP-1 RAs (dulaglutide, exenatide, liraglutide [except the weight loss formulation], lixisenatide, semaglutide) and SGLT-2 inhibitors, and the second consisting of new users of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) and SGLT-2 inhibitors. For both cohorts, cohort entry was defined as the date of the first prescription of the incretin-based drug class of interest or an SGLT-2 inhibitor during the study period.

To be included in the cohorts, all patients were required to be at least 18 years of age and have at least one year of medical history in the CPRD before cohort entry. We excluded patients concomitantly prescribed the incretin-based drug of interest and an SGLT-2 inhibitor at cohort entry. We also excluded those previously prescribed the incretin-based drug class of interest (i.e., before January 1, 2013) and those previously diagnosed with end-stage renal disease or undergoing dialysis (as these are contraindications to receiving SGLT-2 inhibitors) ever before cohort entry.

Follow-Up Period

We used an on-treatment exposure definition, where patients were followed from cohort entry while continuously exposed to the drug classes of interest until the occurrence of intestinal obstruction (defined as a hospitalization with a primary or secondary diagnosis of intestinal obstruction [ICD-10 codes listed in **Supplemental Table 1**]), treatment discontinuation or crossover to one of the study drug classes, death from any cause, end of registration with the general practice, or end of the study period (March 31, 2020). Patients were considered

continuously exposed if one prescription overlapped the date of the next prescription, using a 60-day grace period, in the event of non-overlapping prescriptions.

Potential Confounders

We considered 57 potential confounders, all measured at or before cohort entry. These included the year of cohort entry, age, sex, body mass index, alcohol-related disorders, and smoking status. We also considered variables related to diabetes severity, including hemoglobin A1C (last measure before cohort entry), duration of diabetes (defined by the date of the first of either a hemoglobin A1C ≥6.5%, a diagnosis of type 2 diabetes, or prescription for any antidiabetic drug), antidiabetic drugs used in the year before cohort entry (metformin, sulfonylureas, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, DPP-4 inhibitors in the GLP-1 RA vs. SGLT-2 inhibitor cohort, GLP-1 RAs in the DPP-4 inhibitor vs. SGLT-2 inhibitor cohort, and insulin), presence of microvascular (nephropathy, neuropathy, retinopathy; assessed ever before cohort entry), and macrovascular complications (peripheral vascular disease, ischemic stroke, myocardial infarction, heart failure; assessed ever before cohort entry). We also considered prescription drugs previously associated with reduced intestinal motility or constipation.[28,29] Additionally, we adjusted for abdominal surgeries ever before cohort entry (a known risk factor for mechanical intestinal obstruction), other surgeries in the 30 days before cohort entry (as postoperative paralytic ileus is a common cause of intestinal obstruction), gastroparesis, abdominal cancers, and other cancers ever before cohort entry. Finally, we adjusted for conditions known to be associated with constipation or bowel obstruction ever before cohort entry, including multiple sclerosis, Parkinson's disease, irritable bowel syndrome, hypothyroidism, panhypopituitarism, systemic sclerosis, myotonic dystrophy, diverticular disease, abdominal wall hernia, inflammatory bowel disease, ischemic colitis, bezoars,

intussusception, adhesions, retroperitoneal fibrosis, appendiceal mucocele, gallstone ileus, endometriosis, tuberculosis, and previous intestinal obstruction.[29,30] Age and duration of diabetes were modeled as continuous variables using restricted cubic spline models with five knots.

Statistical Analysis

We used propensity score fine stratification to control for confounding.[31] For each cohort, we estimated the predicted probability of receiving an incretin-based drug (GLP-1 RA or DPP-4 inhibitor) versus an SGLT-2 inhibitor using multivariable logistic regression models conditional on the potential confounders listed above. Patients in the non-overlapping regions of the propensity score distributions were trimmed, and 50 strata were created based on the propensity score distribution of the incretin-based drug users. Within each stratum, patients who received an incretin-based drug received a weight of 1, while patients who received an SGLT-2 inhibitor were reweighted proportional to the number of exposed individuals in the stratum.[31]

Descriptive statistics were used to summarize the characteristics of the exposure groups before and after propensity score weighting. Covariate balance between the exposure groups was examined using standardized differences, with standardized differences less than 0.10 indicative of good balance. Weighted incidence rates of intestinal obstruction were calculated for each exposure group, with confidence intervals (CIs) based on the Poisson distribution, as well as weighted Kaplan-Meier curves were constructed for each exposure group. Weighted Cox proportional hazards models were fit to estimate hazard ratios (HRs) with 95% CIs using robust variance estimators of intestinal obstruction, comparing incretin-based drug users with SGLT-2 inhibitor users. Finally, we calculated the number needed to harm after one year of use using the Kaplan-Meier approach.[32]

Secondary Analyses

We conducted four sets of secondary analyses. First, we determined if the association varied according to duration of use. This variable was modeled on a continuous scale, using restricted cubic spline models that produced a smooth risk function over time.[33] Second, we determined the association with individual GLP-1 RAs and DPP-4 inhibitors. Third, we repeated the analyses restricting the outcome to diagnoses more closely related to decreased motility (ICD-10 codes: K56.0, K56.7, and K59.2). Finally, we assessed whether there was effect measure modification by age (≥70 vs. <70 years), sex, severity of diabetes (as measured by a composite of nephropathy, retinopathy, and neuropathy), the use of drugs associated with decreased intestinal motility (as listed above), history of abdominal surgery, and use of incretin-based drugs before cohort entry. Effect measure modification was assessed by including interaction terms between these variables and the exposure variable in the outcome model.

Sensitivity Analyses

We performed the following four sensitivity analyses to assess the robustness of our results. First, we varied the grace periods between non-overlapping prescriptions to 30 and 90 days to assess possible exposure misclassification. Second, to assess the validity of the outcome definition, we restricted the hospitalized events to those recorded in the primary position. Third, we excluded patients who underwent surgery in the 30 days before cohort entry and censored on new surgeries during the follow-up period (to exclude events potentially attributable to surgeries). Finally, we assessed the potential impact of informative censoring by reweighing the

cohorts using inverse probability of censoring weighting to account for treatment termination and switching, death from any cause, and administrative censoring.

RESULTS

In the first cohort, there were 25,617 new GLP-1 RA users and 67,261 new SGLT-2 inhibitor users who met the study inclusion criteria (**Supplemental Figure 1**). Before propensity score weighting, the exposure groups were generally similar on most characteristics, with the exception that GLP-1 RA users were more likely to be obese, were more likely to have uncontrolled diabetes, had a higher prevalence of micro- and macrovascular complications of diabetes, and were more likely to have used certain prescriptions drugs (**Table 1**). After propensity score weighting, the groups were well balanced across all covariates (**Table 1**). The GLP-1 RA and SGLT-2 inhibitor users were followed for a median (Q1, Q3) of 0.9 (0.4, 2.1) and 0.5 (0.2, 1.5) years, respectively.

In the second cohort, there were 131,927 new DPP-4 inhibitor users and 40,615 new SGLT-2 inhibitor users who met the study inclusion criteria (**Supplemental Figure 2**). Before propensity score weighting, DPP-4 inhibitor users had a higher prevalence of micro- and macrovascular complications of diabetes (**Table 2**). In contrast, SGLT-2 inhibitor users were more likely to be obese and have uncontrolled diabetes. The groups were well balanced after propensity score weighting (**Table 2**). The DPP-4 inhibitor and SGLT-2 inhibitor users were followed for a median (Q1, Q3) of 1.1 (0.5, 2.5) and 0.8 (0.3, 1.8) years, respectively.

Table 3 presents the results of the primary analyses. The use of GLP-1 RAs was associated with an increased risk of intestinal obstruction when compared with the use of SGLT-2 inhibitors, (weighted incidence rates: 1.9 vs. 1.1 per 1000 person-years, respectively; HR: 1.69, 95% CI: 1.04-2.74). The cumulative incidence curves diverged after eight months of use (**Figure 1**). The risk gradually increased with duration of use; the highest HR was observed after around 1.6 years of use (HR: 3.48, 95% CI: 1.79-6.79), which gradually decreased with longer durations

of use (**Supplemental Figure 3**). The use of DPP-4 inhibitors was also associated with an increased risk of intestinal obstruction when compared with SGLT-2 inhibitors (weighted incidence rates: 2.7 vs. 1.0 per 1000 person-years, respectively; HR: 2.59, 95% CI: 1.52-4.42). The cumulative incidence curves diverged after four months of use (**Figure 2**). The highest HR was observed at around 1.8 years of use (HR: 9.53, 95% CI: 4.47-20.30), with HRs gradually decreasing thereafter (**Supplemental Figure 4**). Overall, the number needed to harm after one year of use was 1223 and 603 for GLP-1 RAs and DPP-4 inhibitors, respectively.

Secondary Analyses

The secondary analyses are presented in **Supplemental Tables 2-10**. All GLP-1 RAs generated elevated HRs for intestinal obstruction with wide CIs, except for semaglutide that did not generate any events (**Supplemental Table 2**). For DDP-4 inhibitors, linagliptin generated the highest HR (HR 3.65, 95% CI: 1.93-6.90) (**Supplemental Table 3**). When restricting the outcome to diagnostic codes most related to intestinal obstruction, there were fewer exposed events in both cohorts. The GLP-1 RAs were no longer associated with intestinal obstruction, while DPP-4 inhibitors were associated with a higher HR (**Supplemental Table 4**). In terms of effect measure modification, the HRs were higher among those ≥70 years than those <70 years for both GLP-1 RA and DPP-4 inhibitor analyses, although the CIs overlapped (**Supplemental Table 5**). Sex and diabetes severity did not significantly modify the associations (**Supplemental Tables 6** and **7**). The risk was particularly increased among GLP-1 RA and DPP-4 inhibitor users that used drugs known to decrease intestinal motility versus those who did not especially for GLP-1 RA for which a trend towards significance was showed for this interaction (**Supplemental Table 8**). Finally, there was no effect modification according to history of

abdominal surgery and by use of other incretin-based drugs before cohort entry (**Supplemental Table 9** and **10**).

Sensitivity Analyses

The results of the sensitivity analyses are summarized in **Figure 3** and presented in detail in **Supplemental Tables 11-14**. Overall, these sensitivity analyses generated findings that were generally similar to those of the primary analyses for both cohorts. Restricting the outcome to hospitalized events recorded in the primary position provided the lower risk estimates as well as larger confidence intervals. Excluding and censoring on any surgery seemed to show higher risk estimates with GLP-1 RA but also with increased confidence interval.

DISCUSSION

The results of this large population-based study indicate that use of GLP-1 RAs and DPP-4 inhibitors is associated with an increased risk of intestinal obstruction when compared with use of SGLT-2 inhibitors. The cumulative incidence curves diverged after four to eight months of treatment, and the highest associations were observed at around 1.6 to 1.8 years of use. Overall, these findings remained consistent in several sensitivity analyses. Slight differences observed in the sensitivity analyses restricting the outcome to hospitalized events recorded in the primary position or excluding and censoring on any surgery likely results from a decreased number of events and a loss of statistical power.

To our knowledge, this is the first observational study to specifically investigate the association between GLP-1 RAs and DPP-4 inhibitors and intestinal obstruction versus a clinically relevant comparator. This contrasts with a previous Japanese study that compared alogliptin with other incretin-based drugs on the risk of paralytic ileus.[17] While the authors reported null associations using other DPP-4 inhibitors (incidence rate ratio [IRR]: 1.15, 95% CI: 0.75-1.75) and GLP-1 RAs (IRR: 0.42, 95% CI: 0.14-1.20) as comparators, these drugs may not have neutral effects. These findings differ from those of a recent disproportionality analysis using the WHO pharmacovigilance database (VigiBase), which generated elevated reporting odds ratios (RORs) for intestinal obstruction with GLP-1 RAs (ROR: 3.05, 95% CI: 2.54-3.66 and DPP-4 inhibitors (ROR 8.66, 95% CI: 7.27-10.32).[18] These findings are consistent with those of our study, including the higher point estimate observed with DPP-4 inhibitors.

Our finding that incretin-based drugs are associated with an increased risk of intestinal obstruction is biologically plausible. Indeed, increased GLP-1 action has been shown to inhibit small intestinal motility in both animal and human studies,[10,34] as well as colonic transit in

rats.[35,36] In human studies, gastrointestinal transit time was reduced by exendine-(9-39), an inverse agonist of GLP-1,[37] and increased by the GLP-1 RA liraglutide.[38] GLP-1 suppresses intestinal contractions via a non-fully understood mechanism potentially involving i) the central nervous system via vagal cholinergic pathways or direct action on central GLP-1 receptors[9,39] and/or ii) the enteric nervous system by inhibiting neurotransmission through presynaptic GLP-1 receptors modulating nitric oxide release.[40,41] Furthermore, the inhibition of gastrointestinal motility by GLP-1 may be exacerbated in patients with diabetes, where gastrointestinal motor function may already be affected by diabetic neuropathy. This rationale for an increased risk of intestinal obstruction involving GLP-1 action on the nervous system is in line with the rapid onset (approximately 3 months of use) observed in our study.

Another interesting finding of our study was that DPP-4 inhibitors were associated with a higher increased risk of intestinal obstruction than GLP-1 RAs. This result contrasts with short term clinical trial data showing that GLP-1 RAs are associated with slower gastric emptying compared to DPP-4 inhibitors.[42] Nevertheless, a differential effect of DPP-4 inhibitors on intestinal motility could imply the action of the DPP-4 enzyme in the metabolism of several other peptides than GLP-1, such as peptide YY (PYY) and glucagon-like peptide-2 (GLP-2).[43] PYY, physiologically released with GLP-1 by entero-endocrine L cells in response to meal ingestion, appears to decrease human intestinal transit.[44,45] GLP-2 is considered an intestinotrophic peptide that inhibits gastrointestinal motility at supra-physiological levels by promoting smooth muscle relaxation and possibly inhibiting intestinal cholinergic activity.[46–48] Therefore, although long term effects of DPP-4 inhibitors on these intestinal peptides are not demonstrated, DPP-4 inhibitors may exert additional inhibitory effects on gastrointestinal motility, thereby increasing the risk of intestinal obstruction. The analysis for interaction with

drugs known to decrease intestinal motility was close to statistical significance for GLP-1 RA. This result suggests that the risk of intestinal obstruction could be reduced by limiting concomitant exposure to drugs known to decrease bowel motility and could be of interest for risk management with GLP1 RA in clinical practice.

This study has several strengths. First, we assembled large cohorts of patients newly treated with either incretin-based drugs or SGLT-2 inhibitors using a population-based database shown to be representative and of high quality.[19] Second, we used a new-user, active comparator design, which reduced the possibility of prevalent user biases.[49] Finally, the use of SGLT-2 inhibitors as an active comparator group likely reduced confounding by indication, as these drugs are used at a similar stage as the incretin-based drugs.[27] Furthermore, these drugs have not been associated with an increased risk of intestinal obstruction.

This study has some limitations. First, misclassification of exposure is possible since the CPRD records written prescriptions, and thus it is unknown whether the drugs were filled and used as intended. However, such misclassification is likely to be non-differential between the exposure groups. Furthermore, the CPRD records prescriptions written by general practitioners and not by specialists, although type 2 diabetes is almost entirely managed by general practitioners in the United Kingdom.[50] Second, outcome misclassification is possible and the outcome definition has not been formerly validated in CPRD or elsewhere, although the use of hospitalized events likely minimized this potential bias. Third, given the observational nature of this study, residual confounding is possible. However, using an active comparator used at a similar stage of the disease and propensity score fine stratification that included 57 potential confounders likely minimized this potential bias.[31] Finally, while the primary analyses were well-powered to assess the association with GLP-1 RAs and DPP-4 inhibitors, some secondary

analyses generated point estimates with wide CIs and thus should be interpreted with caution. This includes the duration analyses that were based on relatively short median durations of follow up, which likely reflect duration patterns observed in the setting of real-world practice.

In summary, the results of this study indicate that, compared with SGLT-2 inhibitors, GLP-1 RAs and DPP-4 inhibitors may be associated with an increased risk of intestinal obstruction. This possible increased risk should be balanced with the established clinical benefits of these drug classes.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Case reports and a pharmacovigilance analysis have linked glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors, commonly-prescribed second-line antidiabetic drugs, with an increased risk of intestinal obstruction. To date, real-world evidence for this possible association is lacking

What question did this study address?

We used real-world data to determine whether GLP-1 RAs and DPP-4 inhibitors are associated with an increased risk of intestinal obstruction, when compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

What does this study add to our knowledge?

The results of this large population-based study indicate that the use of GLP-1 RAs and DPP-4 inhibitors may be associated with an increased risk of intestinal obstruction, compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors. The number needed to harm after one year of use was 1223 and 603 for GLP-1 RAs and DPP-4 inhibitors, respectively.

How might this change clinical pharmacology or translational science?

Physicians should balance the potential risk of intestinal obstruction with the use of incretin-based drugs with their known beneficial clinical effects.

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AUTHOR CONTRIBUTIONS

All authors designed the research. JLF and LA performed the research. HY, LA, JLF analyzed the data. JLF wrote the first draft of the manuscript, and all authors provided critical input.

DETAILS OF ETHICAL APPROVAL

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (Protocol 20_185R) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

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FIGURE LEGENDS

Figure 1: Weighted cumulative incidence curves of intestinal obstruction for glucagon-like peptide 1 receptor agonists versus sodium-glucose cotransporter-2 inhibitors

Figure 2: Weighted cumulative incidence curves of intestinal obstruction for dipeptidyl peptidase 4 inhibitors versus sodium-glucose cotransporter-2 inhibitors

Figure 3: Forest plot summarizing the primary and sensitivity analyses for the risk of intestinal obstruction associated with the use of glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors versus sodium-glucose cotransporter-2 inhibitors

Table 1. Baseline Characteristics of the GLP-1 RA and SGLT-2 Inhibitor Exposure Groups Before and After Propensity Score Weighting

Characteristics	Before Weighting			After Weighting		
	GLP-1 RAs	SGLT-2 Inhibitors	ASD	GLP-1 RAs	SGLT-2 Inhibitors	ASD
Total	25,617	67,261		25,617	67,261	
Age, years, mean (SD)	57.6 (11.8)	58.2 (11.0)	0.05	57.6 (11.8)	57.6 (11.9)	0.01
Male, n (%)	13,090 (51.1)	39,962 (59.4)	0.17	13,090 (51.1)	33,649 (50.0)	0.02
Year of cohort entry, n (%)						
2013	4,311 (16.8)	992 (1.5)	0.55	4,311 (16.8)	9,797 (14.6)	0.06
2014	3,650 (14.2)	4,575 (6.8)	0.24	3,650 (14.2)	10,471 (15.6)	0.04
2015	3,633 (14.2)	8,994 (13.4)	0.02	3,633 (14.2)	10,512 (15.6)	0.04
2016	3,153 (12.3)	10,167 (15.1)	0.08	3,153 (12.3)	8,590 (12.8)	0.01
2017	3,208 (12.5)	11,761 (17.5)	0.14	3,208 (12.5)	8,402 (12.5)	0.00
2018	3,444 (13.4)	13,817 (20.5)	0.19	3,444 (13.4)	8,560 (12.7)	0.02
2019	4,218 (16.5)	16,955 (25.2)	0.22	4,218 (16.5)	10,928 (16.2)	0.01
Alcohol-related disorders, n (%)	2,021 (7.9)	5,521 (8.2)	0.01	2,021 (7.9)	5,250 (7.8)	0.00
Body mass index, n (%)						
<30 kg/m²	2,539 (9.9)	22,656 (33.7)	0.60	2,539 (9.9)	6,437 (9.6)	0.01
≥30 kg/m²	22,682 (88.5)	44,164 (65.7)	0.57	22,682 (88.5)	59,835 (89.0)	0.01
Unknown	396 (1.5)	441 (0.7)	0.09	396 (1.5)	989 (1.5)	0.01
Smoking status, n (%)						
Ever	21,099 (82.4)	53,422 (79.4)	0.07	21,099 (82.4)	55,393 (82.4)	0.00
Never	4,506 (17.6)	13,828 (20.6)	0.08	4,506 (17.6)	11,852 (17.6)	0.00
Unknown	12 (0.0)	11 (0.0)	0.02	12 (0.0)	16 (0.0)	0.01
Hemoglobin A1c, n (%)						
≤7.0% [53 mmol/mol]	1,752 (6.8)	3,000 (4.5)	0.10	1,752 (6.8)	5,012 (7.5)	0.02
7.1%-8.0% [54-64 mmol/mol]	3,830 (15.0)	14,465 (21.5)	0.17	3,830 (15.0)	9,851 (14.6)	0.01
>8.0% [65 mmol/mol]	19,823 (77.4)	49,654 (73.8)	0.08	19,823 (77.4)	51,859 (77.1)	0.01
Unknown	212 (0.8)	142 (0.2)	0.09	212 (0.8)	539 (0.8)	0.00
Duration of diabetes, years, mean (SD)	9.9 (7.6)	9.1 (7.0)	0.11	9.9 (7.6)	10.0 (7.9)	0.02
Previous use of antidiabetic drugs, n (%)						
Metformin	22,749 (88.8)	62,592 (93.1)	0.15	22,749 (88.8)	59,399 (88.3)	0.02
Sulfonylureas	13,489 (52.7)	29,683 (44.1)	0.17	13,489 (52.7)	35,434 (52.7)	0.00
Thiazolidinediones	2,380 (9.3)	4,294 (6.4)	0.11	2,380 (9.3)	6,498 (9.7)	0.01
Meglitinides	140 (0.5)	293 (0.4)	0.02	140 (0.5)	432 (0.6)	0.01
Alpha-glucosidase inhibitors	76 (0.3)	142 (0.2)	0.02	76 (0.3)	178 (0.3)	0.01
DPP-4 inhibitors	11,806 (46.1)	28,636 (42.6)	0.07	11,806 (46.1)	31,948 (47.5)	0.03
Insulin	6,746 (26.3)	7,917 (11.8)	0.38	6,746 (26.3)	18,846 (28.0)	0.04
Nephropathy, n (%)	3,217 (12.6)	2,011 (3.0)	0.36	3,217 (12.6)	8,190 (12.2)	0.01
Neuropathy, n (%)	7,146 (27.9)	14,105 (21.0)	0.16	7,146 (27.9)	19,319 (28.7)	0.02
Retinopathy, n (%)	10,495 (41.0)	25,263 (37.6)	0.07	10,495 (41.0)	27,314 (40.6)	0.01

Stroke, n (%)	1,121 (4.4)	2,381 (3.5)	0.04	1,121 (4.4)	2,954 (4.4)	0.00
Myocardial infarction, n (%)	1,868 (7.3)	4,200 (6.2)	0.04	1,868 (7.3)	5,008 (7.4)	0.01
Peripheral vascular disease, n (%)	2,562 (10.0)	5,072 (7.5)	0.09	2,562 (10.0)	6,746 (10.0)	0.00
Heart failure, n (%)	1,718 (6.7)	2,334 (3.5)	0.15	1,718 (6.7)	4,502 (6.7)	0.00
Antihistamines, n (%)	3,578 (14.0)	7,870 (11.7)	0.07	3,578 (14.0)	9,441 (14.0)	0.00
Antispasmodics, n (%)	1,340 (5.2)	2,833 (4.2)	0.05	1,340 (5.2)	3,631 (5.4)	0.01
Antidepressants, n (%)	9,348 (36.5)	18,178 (27.0)	0.20	9,348 (36.5)	25,484 (37.9)	0.03
Antipsychotics, n (%)	1,703 (6.6)	3,292 (4.9)	0.08	1,703 (6.6)	4,709 (7.0)	0.01
Iron supplements, n (%)	2,345 (9.2)	4,875 (7.2)	0.07	2,345 (9.2)	6,339 (9.4)	0.01
Aluminum, n (%)	117 (0.5)	199 (0.3)	0.03	117 (0.5)	319 (0.5)	0.00
Opioids, n (%)	10,118 (39.5)	19,896 (29.6)	0.21	10,118 (39.5)	27,254 (40.5)	0.02
Diuretics, n (%)	5,600 (21.9)	8,516 (12.7)	0.25	5,600 (21.9)	14,678 (21.8)	0.00
Calcium channel blockers, n (%)	8,232 (32.1)	19,528 (29.0)	0.07	8,232 (32.1)	21,675 (32.2)	0.00
5-HT3 antagonists, n (%)	21 (0.1)	55 (0.1)	0.00	21 (0.1)	90 (0.1)	0.02
Abdominal surgery, n (%)	5,238 (20.4)	11,188 (16.6)	0.10	5,238 (20.4)	14,307 (21.3)	0.02
Other Surgeries, n (%)	610 (2.4)	1,353 (2.0)	0.03	610 (2.4)	1,672 (2.5)	0.01
Gastroparesis, n (%)	251 (1.0)	668 (1.0)	0.00	251 (1.0)	749 (1.1)	0.01
Abdominal cancers, n (%)	408 (1.6)	1,032 (1.5)	0.00	408 (1.6)	1,044 (1.6)	0.00
Other cancers, n (%)	1,859 (7.3)	4,005 (6.0)	0.05	1,859 (7.3)	4,947 (7.4)	0.00
Multiple sclerosis, n (%)	92 (0.4)	167 (0.2)	0.02	92 (0.4)	220 (0.3)	0.01
Parkinson’s disease, n (%)	74 (0.3)	135 (0.2)	0.02	74 (0.3)	207 (0.3)	0.00
Irritable bowel syndrome, n (%)	2,465 (9.6)	5,481 (8.1)	0.05	2,465 (9.6)	6,771 (10.1)	0.01
Hypothyroidism, n (%)	3,502 (13.7)	7,679 (11.4)	0.07	3,502 (13.7)	9,325 (13.9)	0.01
Panhypopituitarism, n (%)	94 (0.4)	143 (0.2)	0.03	94 (0.4)	262 (0.4)	0.00
Systemic sclerosis, n (%)	8 (0.0)	8 (0.0)	0.01	8 (0.0)	23 (0.0)	0.00
Myotonic dystrophy, n (%)	15 (0.1)	36 (0.1)	0.00	15 (0.1)	54 (0.1)	0.01
Diverticular disease, n (%)	2,118 (8.3)	4,735 (7.0)	0.05	2,118 (8.3)	5,673 (8.4)	0.01
Abdominal wall hernia, n (%)	1,657 (6.5)	3,393 (5.0)	0.06	1,657 (6.5)	4,523 (6.7)	0.01
Inflammatory bowel disease, n (%)	381 (1.5)	1,063 (1.6)	0.01	381 (1.5)	1,091 (1.6)	0.01
Ischemic colitis, n (%)	87 (0.3)	177 (0.3)	0.01	87 (0.3)	226 (0.3)	0.00
Bezoars, n (%)	13 (0.1)	22 (0.0)	0.01	13 (0.1)	29 (0.0)	0.00
Intussusception, n (%)	24 (0.1)	58 (0.1)	0.00	24 (0.1)	61 (0.1)	0.00
Adhesions, n (%)	116 (0.5)	264 (0.4)	0.01	116 (0.5)	318 (0.5)	0.00
Retroperitoneal fibrosis, n (%)	21 (0.1)	34 (0.1)	0.01	21 (0.1)	54 (0.1)	0.00
Appendiceal mucocele, n (%)	14 (0.1)	39 (0.1)	0.00	14 (0.1)	43 (0.1)	0.00
Gallstone ileus, n (%)	1,235 (4.8)	2,645 (3.9)	0.04	1,235 (4.8)	3,371 (5.0)	0.01
Endometriosis, n (%)	601 (2.3)	1,316 (2.0)	0.03	601 (2.3)	1,650 (2.5)	0.01
Tuberculosis, n (%)	149 (0.6)	301 (0.4)	0.02	149 (0.6)	372 (0.6)	0.00
Prior intestinal obstruction, n (%)	334 (1.3)	732 (1.1)	0.02	334 (1.3)	910 (1.4)	0.00

Abbreviations: ASD, absolute standardized difference; DPP-4, dipeptidyl peptidase 4; SD, standard deviation; GLP-1, glucagon-like peptide 1 receptor agonist; SGLT-2, sodium-glucose cotransporter-2.

Table 2. Baseline Characteristics of the DPP-4 Inhibitor and SGLT-2 Inhibitor Exposure Groups Before and After Propensity Score Weighting

Characteristics	Before Weighting			After Weighting		
	DPP-4 Inhibitors	SGLT-2 Inhibitors	ASD	DPP-4 Inhibitors	SGLT-2 Inhibitors	ASD
Total	131,927	40,615		131,927	40,615	
Age, years, mean (SD)	64.6 (13.3)	56.6 (11.0)	0.66	64.6 (13.3)	65.0 (13.7)	0.03
Male, n (%)	75,750 (57.4)	23,450 (57.7)	0.01	75,750 (57.4)	23,676 (58.3)	0.02
Year of cohort entry, n (%)						
2013	16,757 (12.7)	633 (1.6)	0.44	16,757 (12.7)	4,358 (10.7)	0.06
2014	17,278 (13.1)	3,061 (7.5)	0.18	17,278 (13.1)	5,317 (13.1)	0.00
2015	19,165 (14.5)	5,523 (13.6)	0.03	19,165 (14.5)	5,979 (14.7)	0.01
2016	20,998 (15.9)	6,050 (14.9)	0.03	20,998 (15.9)	6,496 (16.0)	0.00
2017	20,616 (15.6)	6,878 (16.9)	0.04	20,616 (15.6)	6,439 (15.9)	0.01
2018	19,945 (15.1)	8,073 (19.9)	0.13	19,945 (15.1)	6,409 (15.8)	0.02
2019	17,168 (13.0)	10,397 (25.6)	0.32	17,168 (13.0)	5,617 (13.8)	0.02
Alcohol-related disorders, n (%)	10,320 (7.8)	3,451 (8.5)	0.02	10,320 (7.8)	3,114 (7.7)	0.01
Body mass index, n (%)						
<30 kg/m²	58,954 (44.7)	10,239 (25.2)	0.42	58,954 (44.7)	19,171 (47.2)	0.05
≥30 kg/m²	71,676 (54.3)	29,991 (73.8)	0.42	71,676 (54.3)	20,916 (51.5)	0.06
Unknown	1,297 (1.0)	385 (0.9)	0.00	1,297 (1.0)	528 (1.3)	0.03
Smoking status, n (%)						
Ever	106,799 (81.0)	32,194 (79.3)	0.04	106,799 (81.0)	32,932 (81.1)	0.00
Never	25,085 (19.0)	8,411 (20.7)	0.04	25,085 (19.0)	7,656 (18.9)	0.00
Unknown	43 (0.0)	10 (0.0)	0.00	43 (0.0)	27 (0.1)	0.01
Hemoglobin A1c, n (%)						
≤7.0% [53 mmol/mol]	12,412 (9.4)	2,428 (6.0)	0.13	12,412 (9.4)	3,656 (9.0)	0.01
7.1%-8.0% [54-64 mmol/mol]	37,510 (28.4)	8,966 (22.1)	0.15	37,510 (28.4)	11,400 (28.1)	0.01
>8.0% [65 mmol/mol]	81,278 (61.6)	29,094 (71.6)	0.21	81,278 (61.6)	25,257 (62.2)	0.01
Unknown	727 (0.6)	127 (0.3)	0.04	727 (0.6)	303 (0.7)	0.02
Duration of diabetes, years, mean (SD)	9.2 (7.8)	8.7 (7.4)	0.08	9.2 (7.8)	9.1 (7.2)	0.02
Previous use of antidiabetic drugs, n (%)						
Metformin	116,179 (88.1)	37,873 (93.2)	0.18	116,179 (88.1)	36,208 (89.2)	0.03
Sulfonylureas	57,673 (43.7)	14,654 (36.1)	0.16	57,673 (43.7)	17,782 (43.8)	0.00
Thiazolidinediones	7,813 (5.9)	2,728 (6.7)	0.03	7,813 (5.9)	2,567 (6.3)	0.02
Meglitinides	476 (0.4)	145 (0.4)	0.00	476 (0.4)	102 (0.3)	0.02
Alpha-glucosidase inhibitors	278 (0.2)	60 (0.1)	0.01	278 (0.2)	59 (0.1)	0.02
GLP-1 RAs	1,800 (1.4)	4,641 (11.4)	0.42	1,800 (1.4)	819 (2.0)	0.05
Insulin	10,328 (7.8)	7,770 (19.1)	0.34	10,328 (7.8)	3,314 (8.2)	0.01
Nephropathy, n (%)	23,854 (18.1)	1,101 (2.7)	0.52	23,854 (18.1)	7,530 (18.5)	0.01
Neuropathy, n (%)	31,777 (24.1)	8,175 (20.1)	0.10	31,777 (24.1)	9,926 (24.4)	0.01

Retinopathy, n (%)	49,897 (37.8)	14,405 (35.5)	0.05	49,897 (37.8)	14,787 (36.4)	0.03
Stroke, n (%)	8,638 (6.5)	1,376 (3.4)	0.15	8,638 (6.5)	2,783 (6.9)	0.01
Myocardial infarction, n (%)	11,693 (8.9)	2,516 (6.2)	0.10	11,693 (8.9)	3,462 (8.5)	0.01
Peripheral vascular disease, n (%)	13,401 (10.2)	3,107 (7.6)	0.09	13,401 (10.2)	4,167 (10.3)	0.00
Heart failure, n (%)	11,321 (8.6)	1,541 (3.8)	0.20	11,321 (8.6)	3,534 (8.7)	0.00
Antihistamines, n (%)	15,337 (11.6)	4,691 (11.5)	0.00	15,337 (11.6)	4,580 (11.3)	0.01
Antispasmodics, n (%)	5,713 (4.3)	1,758 (4.3)	0.00	5,713 (4.3)	1,838 (4.5)	0.01
Antidepressants, n (%)	33,456 (25.4)	12,071 (29.7)	0.10	33,456 (25.4)	10,643 (26.2)	0.02
Antipsychotics, n (%)	7,436 (5.6)	2,058 (5.1)	0.03	7,436 (5.6)	2,609 (6.4)	0.03
Iron supplements, n (%)	13,510 (10.2)	2,655 (6.5)	0.13	13,510 (10.2)	3,683 (9.1)	0.04
Aluminum, n (%)	509 (0.4)	119 (0.3)	0.02	509 (0.4)	107 (0.3)	0.02
Opioids, n (%)	42,268 (32.0)	12,609 (31.0)	0.02	42,268 (32.0)	13,500 (33.2)	0.03
Diuretics, n (%)	28,091 (21.3)	5,643 (13.9)	0.20	28,091 (21.3)	8,661 (21.3)	0.00
Calcium channel blockers, n (%)	43,845 (33.2)	11,807 (29.1)	0.09	43,845 (33.2)	13,543 (33.3)	0.00
5HT3 antagonists, n (%)	150 (0.1)	39 (0.1)	0.01	150 (0.1)	49 (0.1)	0.00
Abdominal surgery, n (%)	24,416 (18.5)	7,135 (17.6)	0.02	24,416 (18.5)	7,838 (19.3)	0.02
Other surgeries, n (%)	3,741 (2.8)	877 (2.2)	0.04	3,741 (2.8)	1,080 (2.7)	0.01
Gastroparesis, n (%)	1,514 (1.1)	421 (1.0)	0.01	1,514 (1.1)	549 (1.4)	0.02
Abdominal cancers, n (%)	3,696 (2.8)	568 (1.4)	0.10	3,696 (2.8)	1,047 (2.6)	0.01
Other cancers, n (%)	13,389 (10.1)	2,279 (5.6)	0.17	13,389 (10.1)	4,670 (11.5)	0.04
Multiple sclerosis, n (%)	444 (0.3)	105 (0.3)	0.01	444 (0.3)	137 (0.3)	0.00
Parkinson’s disease, n (%)	775 (0.6)	75 (0.2)	0.06	775 (0.6)	258 (0.6)	0.01
Irritable bowel syndrome, n (%)	9,625 (7.3)	3,536 (8.7)	0.05	9,625 (7.3)	2,871 (7.1)	0.01
Hypothyroidism, n (%)	16,476 (12.5)	4,742 (11.7)	0.02	16,476 (12.5)	4,805 (11.8)	0.02
Panhypopituitarism, n (%)	309 (0.2)	82 (0.2)	0.01	309 (0.2)	79 (0.2)	0.01
Systemic sclerosis, n (%)	38 (0.0)	10 (0.0)	0.00	38 (0.0)	12 (0.0)	0.00
Myotonic dystrophy, n (%)	64 (0.0)	19 (0.0)	0.00	64 (0.0)	28 (0.1)	0.01
Diverticular disease, n (%)	13,190 (10.0)	2,696 (6.6)	0.12	13,190 (10.0)	4,130 (10.2)	0.01
Abdominal wall hernia, n (%)	5,936 (4.5)	2,264 (5.6)	0.05	5,936 (4.5)	1,953 (4.8)	0.01
Inflammatory bowel disease, n (%)	2,185 (1.7)	638 (1.6)	0.01	2,185 (1.7)	585 (1.4)	0.02
Ischemic colitis, n (%)	586 (0.4)	101 (0.2)	0.03	586 (0.4)	116 (0.3)	0.03
Bezoars, n (%)	36 (0.0)	11 (0.0)	0.00	36 (0.0)	10 (0.0)	0.00
Intussusception, n (%)	119 (0.1)	35 (0.1)	0.00	119 (0.1)	41 (0.1)	0.00
Adhesions, n (%)	553 (0.4)	160 (0.4)	0.00	553 (0.4)	189 (0.5)	0.01
Retroperitoneal fibrosis, n (%)	76 (0.1)	20 (0.0)	0.00	76 (0.1)	15 (0.0)	0.01
Appendiceal mucocele, n (%)	76 (0.1)	26 (0.1)	0.00	76 (0.1)	12 (0.0)	0.01
Gallstone ileus, n (%)	5,381 (4.1)	1,723 (4.2)	0.01	5,381 (4.1)	1,729 (4.3)	0.01
Endometriosis, n (%)	2,101 (1.6)	837 (2.1)	0.03	2,101 (1.6)	637 (1.6)	0.00
Tuberculosis, n (%)	685 (0.5)	205 (0.5)	0.00	685 (0.5)	294 (0.7)	0.03
Prior intestinal obstruction, n (%)	2,212 (1.7)	412 (1.0)	0.06	2,212 (1.7)	542 (1.3)	0.03

Abbreviations: ASD, absolute standardized difference; DPP-4, dipeptidyl peptidase 4; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2.

Table 3. Hazard Ratios for Intestinal Obstruction Comparing GLP-1 RAs and DPP-4 Inhibitors with SGLT-2 Inhibitors

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) *†	Crude HR	Weighted HR (95% CI) †
GLP-1 RAs vs. SGLT-2 inhibitors						
SGLT-2 inhibitors	67,261	63	69,860	1.1 (0.9-1.4)	1.00	1.00 [Reference]
GLP-1 RAs	25,617	70	37,520	1.9 (1.5-2.4)	2.03	1.69 (1.04-2.74)
DPP-4 inhibitors vs. SGLT-2 inhibitors						
SGLT-2 inhibitors	40,615	44	50,823	1.0 (0.8-1.3)	1.00	1.00 [Reference]
DPP-4 inhibitors	131,927	608	224,385	2.7 (2.5-2.9)	3.10	2.59 (1.52-4.42)

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase 4; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; SGLT-2, sodium-glucose cotransporter-2.

* Per 1000 person-years.

† The models were weighted using propensity score fine stratification.