Risk of Inflammatory Bowel Disease in New Users of Dipeptidyl Peptidase-4 Inhibitors, Sodium Glucose Cotransporter-2 Inhibitors, or Sulfonylureas in the U.S. Food and Drug Administration's Sentinel System

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Conflict of Interest and Acknowledgement Statements

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Background

Previous studies were inconclusive regarding the potential risk of inflammatory bowel disease (IBD: Crohn's disease [CD], ulcerative colitis [UC], and indeterminate colitis) after dipeptidyl peptidase-4 inhibitor (DPP-4i) exposure.

Objective

Compare the risk of incident IBD between new users of DPP-4i and sodium glucose co-transporter-2 inhibitors (SGLT-2i) and between new users of DPP-4i and sulfonylureas (SU).

Methods

Data Source: Claims data from six Data Partners of the U.S. FDA Sentinel System

Study Period: 1/1/2008 - 08/31/2024

Study Population: New users of DPP-4i, SGLT-2i, or SU aged ≥18 years with type 2 diabetes (T2D), who had ≥365 days of continuous insurance coverage and met all the following criteria in the 365 days before the first dispensing of a study drug:

- Use of oral antidiabetic drugs
- Absence of evidence of type 1 diabetes (T1D), IBD, IBD treatment, diverticulitis, colitis, endoscopy, intestine or colon surgery, and use of glucagon-like peptide-1 (GLP1) agonists
- No use of study drugs

Study Drug Exposure: Identified via National Drug Codes in outpatient dispensing data, allowing 30-day episode gap and extension

Incident IBD Algorithm:[a] Having an ICD-9 or ICD-10 diagnosis code, preceded by endoscopy and biopsy procedures *and* followed by IBD treatment

Blackout Period: IBD events in the first 180 days following the first dispensing of study drug were excluded to rule out latent cases.

At-risk Follow-up: Began after the end of blackout period and ended at the first occurrence of an IBD event, exposure to comparator drug or GLP1 agonist, discontinuation of study drug, insurance disenrollment, death, or study end.

Statistical Analyses: Average treatment effect on the treated (ATT) weights were calculated for SGLT-2i and for SU to balance observed baseline covariates between DPP-4i/SGLT-2i cohorts and between DPP-4i/SU cohorts.

In weighted cohorts, we reported adjusted hazard ratios (HR) and 95% confidence intervals (CI) for IBD, for CD and UC subgroups, by sex, and for age (18-59, ≥60 years) subgroups.

Sensitivity Analyses: Used 0-day and 365-day blackout period; 14-day Episode Gap and Extension

[a] IBD algorithm in Wang T et al, *Diabetes Care* 2019;42:2065-74

Table 1. Adjusted Rate of Incident IBD (Cases/100,000 person-years)

Study Cohort	DPP-4i	SGLT-2i	DPP-4i	SU
Overall	22	19	32	30
Female	20	17	32	32
Male	25	20	31	29
Age 18-59 years	24	27	34	31
Age ≥60 years	21	14	31	29

Results

Weighted DPP-4i (n=595,991) and SGLT-2i (n=582,658) cohorts:

- Balanced baseline variables; mean age 66 years, 29% aged 18-59 years, 50% female, and 20% with evidence of smoking
- Identified 161 and 101 IBD cases in the DPP-4i and SGLT-2i cohorts during a mean at-risk follow-up of 1.23 and 0.94 person-years (PY), respectively

Weighted DPP-4i (n=401,143) and SU (n=397,938) cohorts:

- Balanced baseline variables; mean age 65 years, 33% aged 18-59 years, 51% female, and 20% with evidence of smoking
- Identified 163 and 164 IBD cases in the DPP-4i and SU cohorts during a mean follow-up of 1.29 and 1.37 PY, respectively

Figure 1. Forest Plot of Adjusted HR (95%) Comparing DPP-4i with SGLT-2i Cohorts

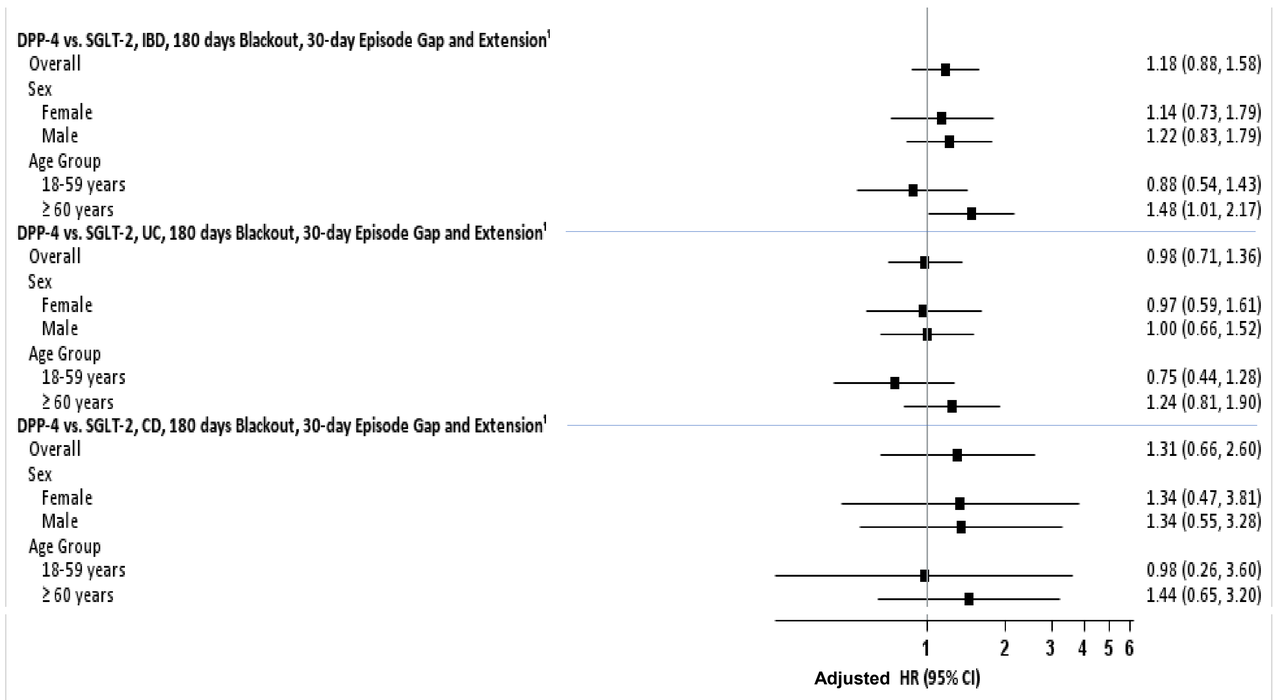
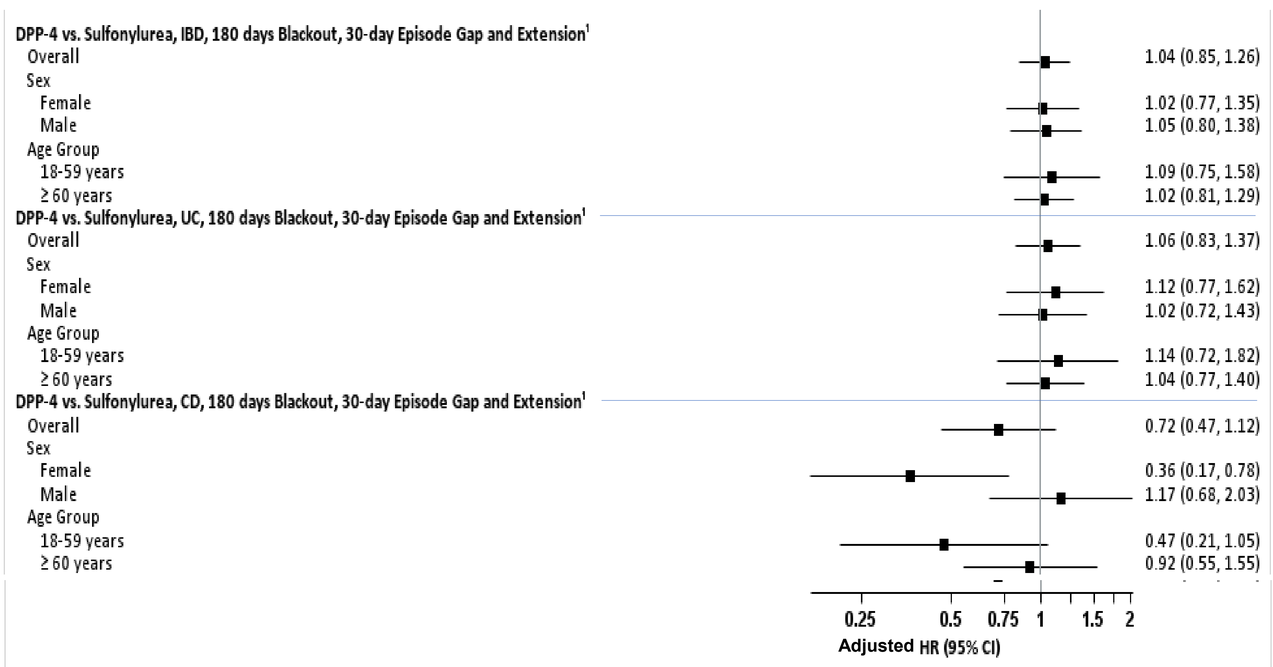


Figure 2. Forest Plot of Adjusted HR (95%) Comparing DPP-4i with SU Cohorts



[b]Abrahami D et al, 2018 *BMJ*;360:K872; Wang T et al, *Diabetes Care* 2019;42:2065-74

Conclusions

- Incidence of IBD in new users of DPP-4i and comparator drug ranged from 19 to 32 cases/100,000 PY in our study and 12 to 38 cases/100,000 PY in the literature.[b]
- Overall risk of IBD, UC, and CD did not differ substantially in the DPP-4i/SGLT-2i or DPP-4i/SU cohorts. Subgroup analyses yielded consistent findings.
- Among new users aged ≥60 years, the risk of IBD appeared numerically greater in the DPP-4i than SGLT-2i cohorts (Fig 1). However, our study was not powered to detect a meaningful effect in the subgroup. This subgroup result does not provide conclusive evidence of a lower risk of IBD related to SGLT-2i use. Further investigation is needed.
- **Limitations**: At-risk PY and baseline covariates assessment excluded the 180-day blackout period, leading to potential bias. However, sensitivity analyses with 0-day and 360-day blackout periods reported consistent findings. Longer term risk assessment is limited by the average DPP-4i exposure of <2 years.