

Protocol Section

Dipeptidyl Peptidase-4 Inhibitors and Inflammatory Bowel Disease Risk: Impact of Study Design Differences on Comparative Safety Results

A. Lay Summary (Max. 200 words)

A recent cohort study [1] using the British Clinical Practice Research Datalink (CPRD) database found that new use of dipeptidyl peptidase-4 inhibitors (DPP4i) was associated with an increased risk of inflammatory bowel disease (IBD) compared to other oral antidiabetic therapies (hazard ratio, HR 1.75, 95% CI: 1.22 to 2.49 during a median follow-up of 3.6 years). We implemented an active comparator, new user (ACNU) cohort design (Appendix 1) using US MarketScan and Medicare data and found that DPP4i did not increase IBD risk compared to therapeutic alternatives: pooled adjusted HRs (aHRs) for IBD were 0.87 (95% CI: 0.47-1.59) comparing to sulfonylureas (SU) and 0.76 (95% CI: 0.48 – 1.19) comparing to thiazolidinediones (TZD). We suspect that differences between results are primarily driven by different study designs. For example, our ACNU cohort included only patients who were treatment-naïve to both drugs at baseline, whereas Abrahami et al modeled DPP4i exposure as a time-varying variable (Appendix 2) (i.e., allowing the same patient to contribute both DPP4i unexposed and exposed person-time). To explore the impact and robustness of risk estimates to study design differences, this study will apply the ACNU design to CPRD data to assess the association between DPP4i use and IBD risk.

B. Technical Summary (Max. 200 words)

The objective of this study is to implement the active comparator, new user (ACNU) cohort design in CPRD data to assess the association between DPP4i use and IBD risk. The new-user design helps to avoid many time-related biases introduced when including prevalent drug users in cohort studies (Appendix 1), and an active comparator helps to balance the baseline risk of IBD between comparison groups, and control for diabetes severity [2]. We will use propensity scores (PS) to remove remaining imbalances in measured potential confounders between ACNU cohorts and reweight the comparator drug initiators by the propensity score odds ($PS/(1-PS)$) to estimate the average treatment effect in the treated. Patients will be followed from 180 days (the “induction” period) post the second prescription after initiation of DPP4i or active comparator (TZD or SU) until treatment status change in the form of either index drug class discontinuation, or switching to or addition of a drug from the comparator drug class (Appendix 3). We will consider IBD events up to 180 days (the “carry-over” period) after treatment changes to account for diagnostic delay. We will estimate and compare the cumulative incidence of outcomes for

each study cohort using weighted Kaplan-Meier methods, and estimate crude and adjusted HRs using weighted Cox proportional hazards models.

C. Objectives, Specific Aims, and Rationale

The objective of this study is to implement the ACNU design in CPRD data to assess the association between DPP4i use and IBD risk. The goal will be met through the following two specific aims, using data from the UK CPRD.:

Aim 1: To evaluate the association between the initiation of DPP4i versus the initiation of clinically relevant second-line glucose lowering therapies (TZD and SU) and the short-term risk of IBD, based on an active comparator, new user study design.

To date, only one cohort study has been published [1] assessing the association between DPP4i use and IBD risk, and methodological implications between implementing the ACNU design versus modelling exposure as time-varying variable have not been explored. We have used the US MarketScan and Medicare data to examine the association between DPP4i initiation and IBD risk and the preliminary analysis suggests no increase in IBD risk with new use of DPP4i. In this proposed study, we will assess the risk of IBD by implementing the ACNU design using CPRD data and compare the impact of different study designs on estimates of IBD risk. The findings of our studies will enhance understanding of the IBD risk associated with DPP4i use and add to the understanding of the role of study design differences on assessments of adverse event risk in drug safety studies.

D. Background

DPP4i, a second-line glucose lowering drug (GLD), has been shown to reduce haemoglobin A1c (HbA1c) by 0.5-1.0%, by means of decreasing the degradation of the glucagon-like peptide (GLP)-1 and prolonging the insulinotropic effect [3,4]. Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a family of immunologically mediated disorders that cause chronic inflammation of the gastrointestinal tract [5]. A recent cohort study by Abrahimi et al. [1] performed in the British CPRD demonstrated that the use of DPP4i was associated with an increased risk of IBD (hazard ratio (HR) 1.75, 95% CI 1.22 to 2.49) during a median follow-up of 3.6 years [1]. In this study, use of DPP4i was modelled as a time-varying exposure allowing patient to switch from non-DPP4i to DPP4i (i.e., allowing the same patient to contribute both unexposed and exposed person-time).

Current biological evidence on the association between DPP4i and IBD is conflicting. On one hand, studies in mice have shown that DPP4i have a proliferative effect on the colonic epithelium and a minimal effect in the amelioration of colitis to decrease both disease activity

and disease severity, indicating potential clinical application of this novel drug class for IBD [6,7]. On the other hand, studies have indicated that lower concentrations of DPP-4 have been detected in tissue and plasma from patients with IBD than healthy controls, suggesting that lower DPP-4 concentrations may be inversely associated with increased IBD activity [8-10].

There has been little epidemiological research assessing the risk of IBD among patients with Type 2 diabetes mellitus (T2D) treated with DPP4i, using large, real-world patient populations. To address this gap, we implemented an active comparator, new user (ACNU) cohort design using US MarketScan and Medicare data, respectively, and found that DPP4i had a mildly *protective* effect (rather than increasing IBD risk) compared to therapeutic alternatives: the pooled aHRs for IBD were 0.87 (95% CI: 0.47-1.59) by comparing DPP4i to sulfonylureas (SU) and 0.76 (95% CI: 0.48 – 1.19) by comparing DPP4i to thiazolidinediones (TZD).

We suspect that the inconsistent results are primarily due to differences in study design choices. For example, in our ACNU cohort, only patients who were treatment-naïve at baseline to both drugs were included [2], and both DPP4i and active comparators (therapeutic alternatives, SU or TZD) were analyzed identically, in as-treated fashion (censoring patients when treatment discontinued or changed) (Appendix 3) and initial treatment analysis (mimicking the intent-to-treat analysis in randomized trials ignoring treatment changes) (Appendix 4). On the other hand, the study by Abrahimi et al. [1] modelled the use of DPP4i as a time-varying exposure, allowing patient to switch from non-DPP4i to DPP4i (i.e. allowing the same patient to contribute both unexposed and exposed person-time). As a result, follow-up time for DPP4i patients was actually analyzed differently than patients on comparator drugs. As shown in Appendix 2, the study by Abrahimi et al. [1] only analyzed DPP4i and active comparators in the same way (analogous to an intention to treat approach) when patients initiated DPP4i (scenario 2) or initiated other oral GLDs and did not initiate DPP4i during follow-up (scenario 3). However, if patients started other oral GLDs and switched to DPP4i (scenario 1), these patients are actually analyzed by as-treated analysis, i.e. censoring for treatment change, but these same censored patients are reconsidered as DPP4i initiators during follow-up (i.e., after the 180-day lag time), thus allowing the same patient to contribute both unexposed (before censoring) and exposed person-time (after censoring). Therefore, if a large proportion of patients switched from other oral GLDs to DPP4i during follow-up, the results are likely to be different between our ACNU design (both initial treatment and as treated analyses) [2] and their study design where DPP4i use was modeled as a time-varying exposure [1].

In this study, we will use the data from CPRD to implement the ACNU design with the same outcome definition and covariates to assess whether DPP4i is associated with an increased IBD risk. We will then compare the risk estimates obtained using the ACNU design with those obtained by modelling DPP4i as time-varying variable.

E. Study Type

Clinical and Methodological

F. Study Design

This study proposes to use data from the CPRD to implement the ACNU cohort design to assess the association between new use of DPP4i and IBD risk, and compare the estimates with published results where DPP4i use was modeled as time-varying variable. The new-user design helps to avoid many time-related biases introduced when including prevalent drug users in cohort studies (Appendix 1) [2]. The magnitude of the risks and benefits of drugs often vary over time after the start of treatment, which introduces bias in prevalent user designs. Another difficulty in the analysis of prevalent user designs stems from the fact that disease risk factors can be affected by the treatment itself. In a new user design, this difficulty is addressed because potential confounders can be measured at baseline, prior to treatment initiation. Finally, using an active comparator will help to balance the baseline risk of IBD between comparison groups, and provides indirect control for diabetes severity. Besides the key study design difference described in the background section, the comparator group in the time-varying study design by Abrahami et al. included both prevalent users and patients using metformin (non-second line oral GLDs), which may introduce time-related biases and confounding by indication. Therefore, ACNU design can provide additional control for such biases and may provide a more rigorous examine on the association between the IBD risk and DPP4i use.

Aim 1 focuses on assessing IBD risk among DPP4i users by implementing the ACNU design within the CPRD population to explore the differences between the two study designs and the subsequent effect of those differences on hazard ratio estimates.

G. Sample Size

In this large retrospective cohort study based on CPRD data, we will include all beneficiaries meeting our inclusion criteria. We therefore did not perform a sample size calculation to determine the minimum-required study population. We calculate the power of this study as a function of hazard ratio [11] with a two-sided alpha of 0.05, given the conditions listed in Appendix 3.

Calculated power for different hazard ratios.

Hazard ratio	Power	
	DPP4i vs SU	DPP4i vs TZD
1.0	0.050	0.050
1.2	0.114	0.097
1.4	0.288	0.231
1.6	0.519	0.427
1.8	0.727	0.631
2.0	0.859	0.795

H. Data Linkage

Not applicable

I. Study Population

The base population for the analysis will consist of all beneficiaries in the UK Clinical Practice Research Datalink (CPRD), aged 18+, with ≥ 1 prescription dispensing claim for a DPP4i or an active comparator drug between January 01, 2007 and December 21, 2016.

We will apply the same exclusion criteria as the study by Abrahami et al [1] and exclude the following patients:

1. To ensure new use of either DPP4i or an active comparator drug, we will exclude all individuals who do not have at least 12 months of medical history in the CPRD before their initial prescription, during which no use of any of the study drugs (SU, TZD) is detected.
2. Patients with the following conditions in the baseline year will be excluded, to remove patients from the study cohort who may have pre-existing IBD:
 - 1) previous diagnosis of IBD (CD, UC);
 - 2) history of diverticulitis, ischaemic colitis, pseudomembranous colitis, unspecified colitis;
 - 3) prior exposure to 5-aminosalicylic acid (5-ASA)
 - 4) Female patients with a history of polycystic ovary syndrome or gestational diabetes during baseline period, since these are other indications for metformin use.

In our secondary analysis, we will apply the following modified exclusion criteria excluding patients with the following conditions in the 12-month baseline period will be excluded, to remove patients from the study cohort who may have pre-existing IBD:

- 1) previous diagnosis of IBD (CD, UC);
- 2) history of diverticulitis, ischemic colitis, pseudomembranous colitis, unspecific colitis;
- 3) prior exposure to IBD treatments [12,13], including 5-aminosalicylic acid (5-ASA), anti-tumor necrosis factor (anti-TNF), enteral budesonide (we did not exclude patients who used other corticosteroids due to their wide indications for use), and immunosuppressive or immunoregulatory agents (azathioprine, mercaptopurine, methotrexate, and intravenous cyclosporine);
- 4) previous colectomy, ileostomy, ostomy supplies;
- 5) prior colonoscopy or sigmoidoscopy before age 50. This exclusion was implemented to exclude patients who were more likely to be receiving early colonoscopy for possible IBD related diseases, since the 2016 US Preventive Services Task Force guidelines recommend colonoscopy for colorectal cancer only for individuals aged 50-75 [14,15];
- 6) (*DPP4i vs. TZD comparison only*) patients with a diagnosis of congestive heart failure (CHF) in the 12 months prior to the first eligible prescription, as initiation of TZDs is contraindicated in patients with CHF [16].

J. Selection of comparison groups or controls

The comparison groups (cohorts) will be defined by at least **two** same-drug class prescription dispensing claims of DPP4i or active comparator drug, SU or TZD, respectively, between January 1, 2007 and December 31, 2016. All drug classes are identified using British National Formulary product (BNF) code, medcodes, and prodcodes. The date of the second prescription will serve as the index date for the analysis.

K. Exposures, Outcomes, and Covariates

K.1. Exposures and Outcomes

Exposure is defined by at least **two** same-drug class prescription dispensing claims for a DPP4i or an active comparator drug, i.e. the second prescription will serve as the index date for the analysis. For as treated (AT) analysis, follow-up will start 180 days (induction period) after the cohort entry date (the second eligible prescription) until treatment status change in the form of either index drug class discontinuation, or switching to or addition of a drug from the comparator drug class (details provided below in **L. Follow-up** section). For initial treatment (IT) analysis, ignoring censoring for treatment discontinuation and changes during follow-up (details provided below in **M. Statistical Analysis** section).

Comparisons	Index Drug (generic name/BNF code)	Comparator Drug (generic name/BNF code)
I	DPP-4i Sitagliptin (0601023X0, 0601023AD) Saxagliptin (0601023AC, 0601023AH , 0601023AV) Linagliptin (0601023AE, 0601023AF) Alogliptin (0601023AJ, 0601023AJ)	Sulfonylureas Glyburide (0601021H0) Glipizide (0601021P0) Glimepiride (0601021A0)
II	DPP-4i Sitagliptin (0601023X0, 0601023AD) Saxagliptin (0601023AC, 0601023AH , 0601023AV) Linagliptin (0601023AE, 0601023AF) Alogliptin (0601023AJ, 0601023AJ)	Thiazolidinediones Pioglitazone (0601023B0, 0601023W0) Rosiglitazone (0601023S0, 0601023V0)

We use the same outcome algorithm in the study by Abrahami et al [1] (Appendix 4), defined using Read codes. In this algorithm, IBD events qualify as a study outcome only if they were accompanied by at least one supporting event in the 6 months preceding or following the IBD code (Appendix 5). These supporting events consist of prescriptions for aminosalicylates, referrals for endoscopy, referrals to gastroenterology, or IBD-related symptoms (abdominal pain, diarrhea or bloody stools). In the event that the date of a supporting code was before the date of the IBD diagnostic code, the outcome date is defined as the date of the supporting code. Thus, we estimate hazard ratios of IBD with clinically-supporting events, comparing the use of DPP4i with use of SU or TZD, using a Cox proportional hazards model (adjusted for confounders listed in the manuscript). Secondary outcomes include Crohn's disease (CD) and ulcerative colitis (UC), respectively.

We use the same outcome definition and covariates (shown below) as the study by Abrahami [1] as we aim to compare results from different study designs.

K.2. Covariates

Baseline covariates are measured in the 12 months prior to index date. We have the following types of covariates:

- 1) Demographics: age, gender, body mass index, calendar year, alcohol related disorders, smoking status
- 2) Diabetes comorbidities: retinopathy, nephropathy, neuropathy;
- 3) Diabetes severity: duration of treated diabetes, Haemoglobin A1c;
- 4) Pre-existing autoimmune comorbidities: psoriasis, systemic vasculitis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus;

- 5) Cardiovascular comorbidities: myocardial infarction, stroke, peripheral arteriopathy;
- 6) Diabetic medication use: metformin, SU, TZD, Insulin, Glucagon-like peptide-1 receptor agonist, alpha glucosidase inhibitor, meglitinide;
- 7) Other medication use: aspirin, non-steroidal anti-inflammatory drugs, hormonal replacement therapy, oral contraceptives;

L. Follow-up

Patients will be followed after the second prescription (cohort entry date) until treatment status change in the form of either index drug class discontinuation, or switching to or addition of a drug from the comparator drug class (Appendix 6). Treatment discontinuation will be defined as no refill within a period equal to the prescribed days' supply of the last filled prescription plus a 90-day grace period; patients not refilling a prescription of the same drug class will be censored at the end of the 90-day grace period. Treatment switch or augmentation will be defined by a prescription claim for a comparator drug within a period equal to the prescribed days' supply of the last filled prescription plus a 90-day grace period; censoring will occur on the date of the comparator drug fill.

Because we assume that the clinical diagnosis of IBD is not made immediately after symptom onset (1,17), we will start follow-up for the outcome 180 days after the second prescription (latency period) and exclude patients with the outcome within 180 days after their second prescription. Similarly, follow-up for IBD events will continue 180 days (the "carry-over" period) after treatment changes or discontinuation.

In the primary as-treated analysis (Appendix 6), follow-up will start 180 days (induction period) after the cohort entry date (the second eligible prescription) and end at the earliest of the following events: 1) 180 days after treatment discontinuation (the days' supply of the last filled prescription plus a 90-day grace period), 180 days after treatment switching or augmenting (adding DPP4i to the comparator drug class or vice versa); 2) the end of an individual's registration with general practice; 3) death; 4) administrative study end (June 30, 2017), or 5) observation of an incident IBD event, per the definition above. We will use the first incident IBD event date during follow-up to define the outcome date.

M. Statistical Analysis

The active comparator, new user study design tends to synchronize patients with respect to diabetes severity and duration. We will assess this balance by looking at the crude distribution of CPRD data based covariates across treatment cohorts. We will then use propensity scores to remove remaining imbalances in measured potential confounders between study cohorts. Our

primary aim is to identify active comparator drug initiators that will allow us to estimate what would have happened to the actual DPP4i initiators if they had, contrary to the fact, not initiated DPP4i. To achieve this goal, we will estimate the average treatment effect in the treated (ATT) by reweighting the comparator drug initiators by the propensity score odds ($PS/(1-PS)$), i.e. standardized mortality/morbidity ratio (SMR) weights [18]. We will estimate and compare the cumulative incidence of both primary and secondary outcomes for each study cohort using weighted Kaplan-Meier methods. Crude and adjusted hazard ratios (HRs) for both primary and secondary outcomes will be estimated using weighted Cox proportional hazards models, controlling for age, sex, as well as any potential confounders that remain unbalanced after propensity score implementation.

We will stratify analysis by age at cohort entry (<60 and ≥ 60 years) and sex. To assess whether the risk varies with duration of use, we will estimate separate HRs for the first 12 months, and after 12 months of follow-up. Additionally, we will evaluate whether the risk of IBD varies across patients with and without pre-existing autoimmune disease and gastroenterological disease at cohort entry, since patients with pre-existing conditions tend to have more frequent encounters with the healthcare system and may have higher chance for IBD detection and diagnosis. Finally, we will estimate IBD risk for each individual DPP4i agent (Sitagliptin, Saxagliptin, linagliptin, alogliptin).

To examine the robustness of our primary results to changes in study population and condition definitions, we plan to perform the following sensitivity analyses based on our primary analysis (as treated, follow-up starts from second prescription, 180-day latency period) unless stated otherwise:

- 1) We will repeat the analyses changing latency and carry-over periods from 180 days to 0 days, 90 days, and 365 days. We will similarly assess our secondary outcomes, CD and UC, respectively, using different latency and carry-over periods (0 day, 90 days and 365 days).
- 2) We will perform an analysis based on initial treatment (IT) (Appendix 7), ignoring censoring for treatment discontinuation and changes during follow-up. This approach mimics the intention-to-treat analysis in a randomized trial. In this IT analysis, follow-up starts 180 days after the second prescription (latency period) after excluding patients with the outcome within 180 days after their second prescription, and follow-up is terminated at the earliest of the following events: 3 years after drug initiation; death, the end of registration with the general practice, end of study (June 30, 2017), or an incident IBD event.
- 3) We will require only one study drug prescription in the exposure definition, and use the first prescription as the cohort entry date, i.e., follow-up starts on 180 days (latency period) after the first prescription and ends on 180 days (carry-over effect) after treatment change.
- 4) For Aim 1, to assess whether DPP4i is associated with IBD risk, we will use a more rigorous outcome definition in sensitivity analysis. The outcome of interest is incident IBD defined by the

first IBD diagnosis (read code in Appendix 5) during follow-up which is preceded by a colonoscopy/sigmoidoscopy and biopsy within 30 days before diagnosis, and followed by a prescription claim for IBD medication treatment within 30 days after diagnosis (Appendix 8). We also assess incident CD and UC, respectively.

And we will apply the modified outcome with primary exclusion criteria and the modified exclusion criteria in 4), respectively.

- 5) We will modify our outcome in 4) to remove the biopsy requirement, as some colonoscopy codes already include biopsy (i.e., outcome defined as: the date of first IBD diagnosis with a colonoscopy/sigmoidoscopy within 30 days prior and an IBD treatment within 30 days after). The date of IBD diagnosis will be considered as the event date. Additionally, we will also perform a sensitivity analysis using the date of IBD treatment instead of the date of IBD diagnosis as event date, to quantify the potential for time related bias in our primary outcome definition.
- 6) We will additionally censor patients when they receive medications that could potentially induce IBD progression [19] (Appendix 10).
- 7) We will conduct analysis using multivariable-adjusted Cox regression in place of SMR-weighted Cox regression.

N. Plans for Addressing Confounding Data

The active comparator, new user study design tends to synchronize patients with respect to diabetes severity, duration and baseline IBD risk. We will repeat the primary analysis using multiple imputation for variables with incomplete data (i.e. missing values for haemoglobin A1c, BMI and smoking). To impute missing data, we will use an ordinal regression model with explanatory variables and cumulative hazard, use of DPP4i at cohort entry and all confounders listed in the manuscript. Using Rubin's rules [20], we will combine the results of 10 imputations to estimate the value of missing variables.

O. Limitations of the study design, data sources and analytical methods

This study has some limitations. First, some exposure misclassification is possible as prescriptions in the CPRD are written by general practitioners and not specialists. Nevertheless, type 2 diabetes is managed almost entirely through primary care in the UK, thus such misclassification is likely to be minimal [1]. Second, outcome misclassification is also possible although IBD has been shown to be well recorded in the CPRD. Therefore, we use a more rigorous outcome algorithm in sensitivity. Third, residual confounding from unknown or unmeasured variables is possible. Abrahami et al. [1] were subject to the same limitations in their study, and we don't expect these limitations to differentially affect our study designs. However, this does not affect our aim to compare different study designs' effect on hazard ratio.

P. Patient or User Groups Involvement:

Not intended.

Q. Plans for Disseminating and Communicating Study Results

We plan to communicate the results at conferences and in publications. There are no restrictions on the extent or timing of publications.

R. Reference

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APPENDIX 1. New User Algorithm

Definitions/Conventions

Washout Period (WP) = minimum length of time that a patient must be drug-free prior to becoming eligible for the new user cohort

Grace Period (GP) = maximum length of time that a user can go after the last prescription date plus the days supply without a drug before being considered discontinued from drug use

Days Supply (DS) = assumed (or imputed) number of days supply to use as Days Supply when true value is unknown (usually 30 days)

W_i = Days since start of washout period prior to 1st RX fill of i th period of use for patient

G_j = Days from last day covered by the j th RX fill to the $(j+1)$ th RX fill date

Cohort Eligibility

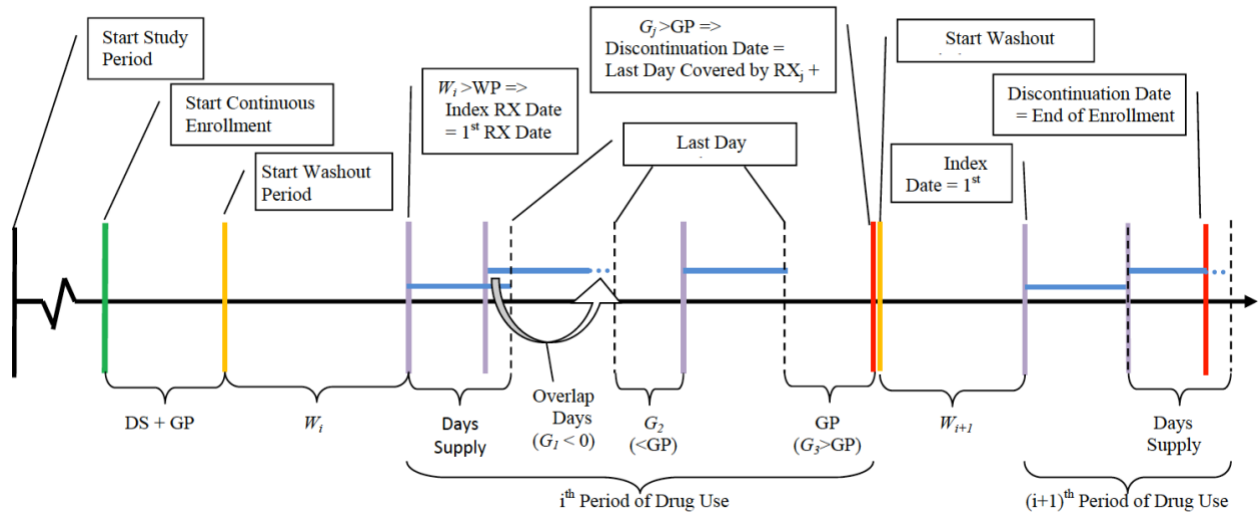
If $W_1 > WP$ then patient's period of drug use is eligible for the new user cohort.

If $W_i > WP$ and $i > 1$ then patient's i th period of drug use is eligible for new user cohort IFF the analysis allows for previous users to become new users.

Drug Discontinuation/Censor Date

If $G_j > GP$ then the patient is considered discontinued from drug use on the last day covered by the j th RX fill + GP

If (End of Enrollment) – GP < (Last Day Covered by an RX Fill) then the patient is censored at End of Enrollment



Algorithm

1. Set (Last Day Covered) = (Start of Continuous Enrollment) + (Days Supply) + (Grace Period).
2. Set (Index Date) = (1st RX Fill Date following Start of Continuous Enrollment).
3. Let $W = (\text{Index Date}) - (\text{Last Day Covered})$. If $W > (\text{Washout Period})$ then flag the period of drug use as eligible for the new user cohort.
4. Let $G = (\text{RX Fill Date}) - (\text{Previous Last Day Covered})$. Sequentially cycle through the subsequent prescription claims for the patient, applying the appropriate step below, until (Discontinuation Date) is set:
 - a. If $G > (\text{Grace Period})$ then set (Discontinuation Date) = $\max(\text{Previous Last Day Covered}, \text{RX Fill Date}) + (\text{Days Supply}) + (\text{Grace Period})$.
 - b. If $G \leq (\text{Grace Period})$ then set (Last Day Covered) = $\max(\text{Previous Last Day Covered}, \text{RX Fill Date}) + (\text{Days Supply})$. If $(\text{Last Day Covered}) + (\text{Grace Period}) > (\text{End of Continuous Enrollment})$ and the patient has no additional RX claims with (RX Fill Date) $\leq (\text{End of Continuous Enrollment})$, then set (Discontinuation Date) = (End of Continuous Enrollment). Otherwise, repeat Step 3 for the next prescription.
5. If the record was flagged for inclusion in the new user cohort in Step 3, output the record containing Index Date and Discontinuation Date3.
6. Set (Index Date) = (1st RX Fill Date following Discontinuation Date).
 - a. If the patient is continuously enrolled from (Discontinuation Date) to (Index Date), set (Last Day Covered) = (Discontinuation Date).
 - b. If the patient has a gap in enrollment between (Discontinuation Date) and (Index Date), then set (Last Day Covered) = (Start of Next Period of Continuous Enrollment) + (Days Supply) + (Grace Period) and set (Index Date) = (1st RX Fill Date following Start of Next Period Continuous Enrollment).
7. Repeat Steps 3-7 for the patient's remaining RX fills.

APPENDIX 2. Modelling treatment (DPP4i) as time-varying variable

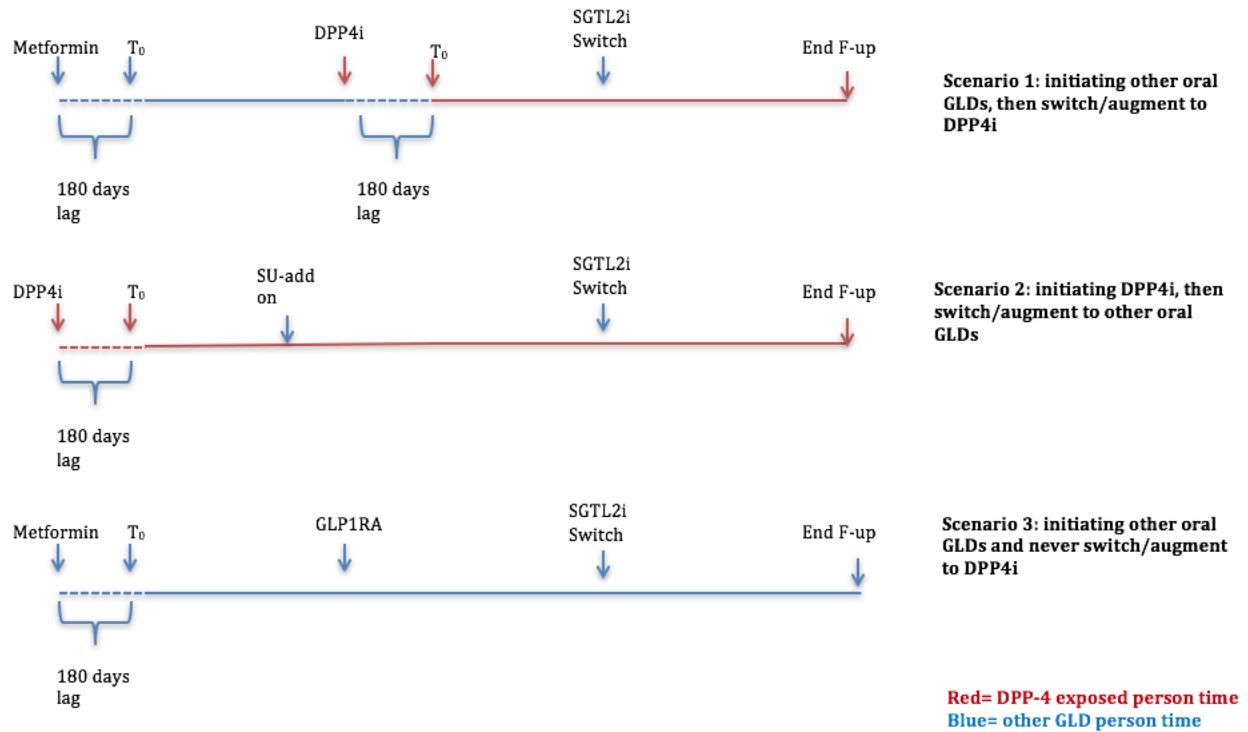


Figure legend. Abbreviations: T₀, the time follow up starts; DPP4i, Dipeptidyl peptidase-4 inhibitors; SGLT2i, Sodium-glucose cotransporter 2 inhibitors; End F-up, end of follow-up; SU, sulfonylureas; GLP1RA, Glucagon-like peptide-1 receptor agonists; OOGLD, other oral glucose lowering drugs.

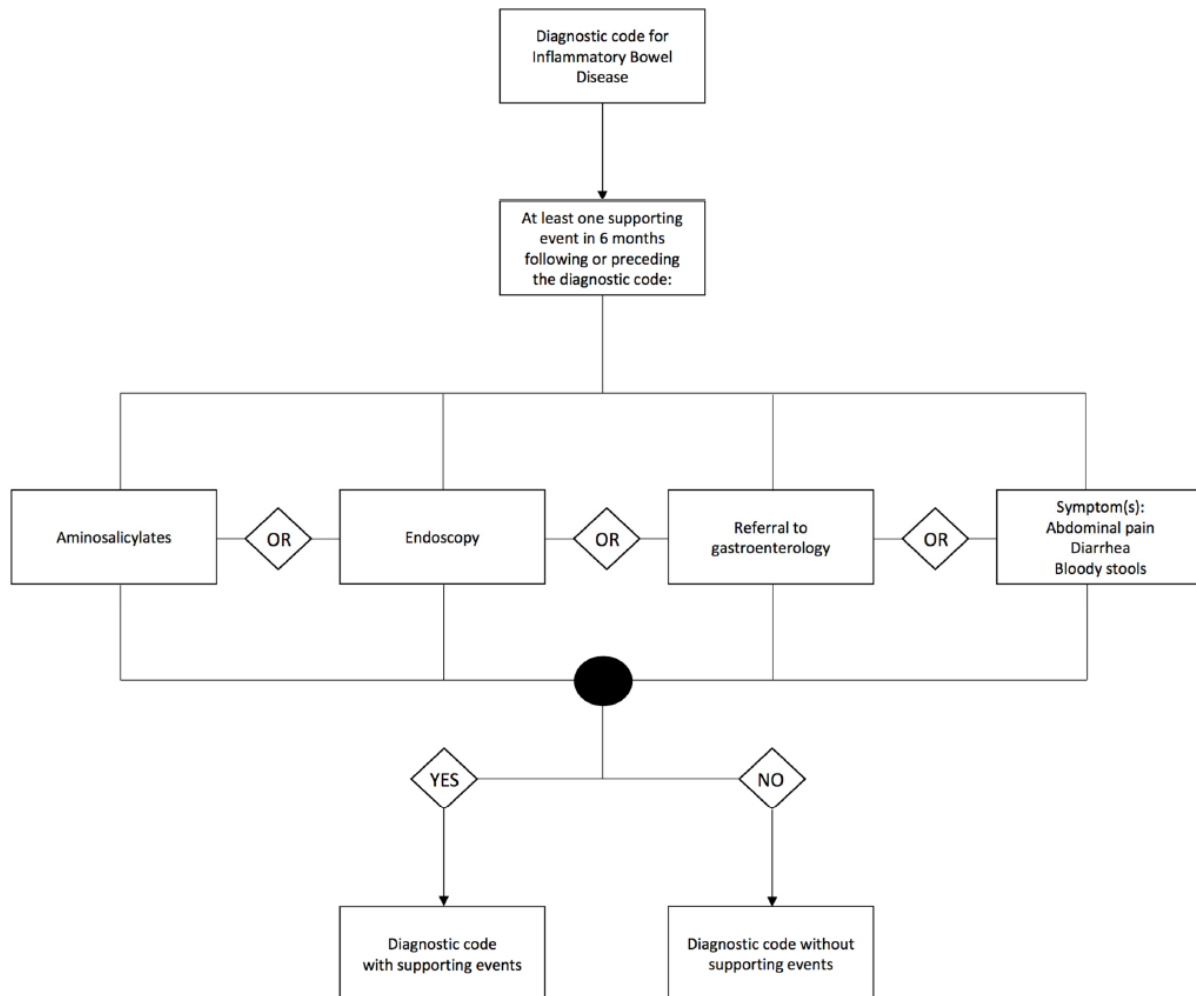
APPENDIX 3. Parameter values for power calculation.

Parameter	Value	
Cohorts	DPP4i vs SU	DPP4i vs TZD
Alpha	0.05	0.05
Group allocation proportion*	0.4 vs 0.6	0.6 vs 0.4
Total N	167210 (72310 + 94900)	119230 (72310 + 46920)
% loss to follow-up	0	0
Follow-up (years)	2	2
2-year cumulative incidence rate for control**	34.5 cases/100,000 person-year	34.5 cases/100,000 person-year
Range for hazard ratio	1.0-2.0	1.0-2.0
Comparison Method	Log-Rank Test	Log-Rank Test

*Assuming the sample size of DPP4i, SU, and TZD in our ACNU design will be 10 times as large as the reported “newly treated” sample size in the study by Abrahami et al (1), which is 72310, 94900, and 46920, respectively (in ACNU design, we require patients to be treatment-naïve for both intervention and control drug rather than being “newly treated”).

**Assuming the incidence rate of SU and TZD group is equal to the incidence rate of other oral antidiabetic drugs (except DPP4i) in the study by Abrahami et al (1)

APPENDIX 4. Algorithm Used to Identify Supported Inflammatory Bowel Disease



APPENDIX 5. Algorithm Used to Identify Supported Inflammatory Bowel Disease

Read Code	Read Term
J40..00	Regional enteritis - Crohn's disease
J40..11	Crohn's disease
J401z00	Crohn's disease of the large bowel NOS
J401z11	Crohn's colitis
J40z.11	Crohn's disease NOS
Jyu4000	[X]Other Crohn's disease
J41..12	Ulcerative colitis and/or proctitis
J410.00	Ulcerative proctocolitis
J410000	Ulcerative ileocolitis
J410100	Ulcerative colitis
J410z00	Ulcerative proctocolitis NOS
J411.00	Ulcerative (chronic) enterocolitis
J412.00	Ulcerative (chronic) ileocolitis
J413.00	Ulcerative pancolitis
Jyu4100	[X]Other ulcerative colitis
J436.00	Microscopic colitis
J436000	Collagenous colitis
J436100	Lymphocytic colitis
J4z6.00	Indeterminate colitis
J4...12	Inflammatory bowel disease

NOS=not otherwise specified.

APPENDIX 6. Overview of study design and new user cohort for as treated analysis.

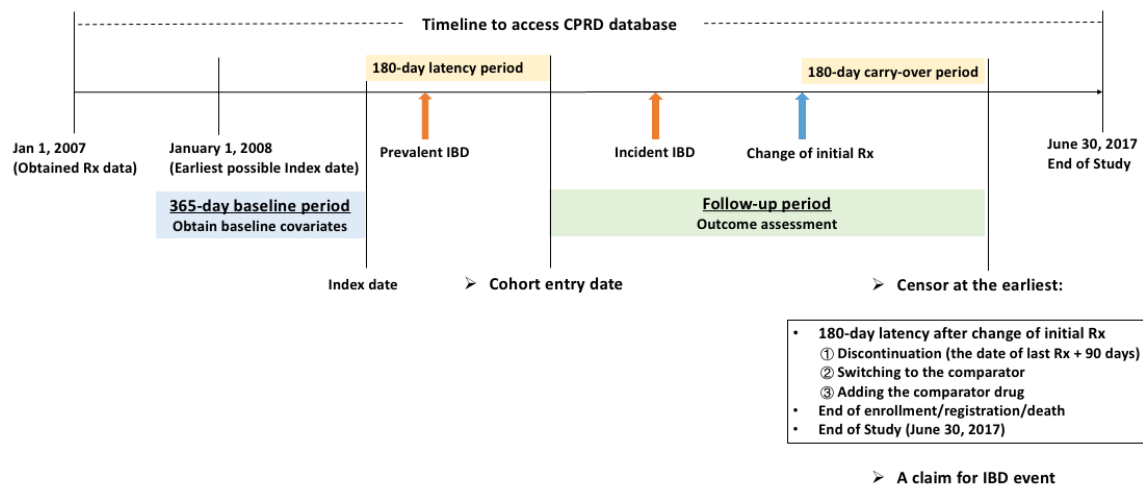


Figure legend. Overview of study design and new user cohort for as treated analysis. Rx, prescription. Treatment discontinuation is defined as no refill within a period equal to the prescribed duration of the last filled prescription (Stopping) plus a grace period of 90 days for DPP4i and their comparators, respectively. Switching is defined as discontinuing the current treatment and started filling the comparator drug. Augmenting is defined as a subsequent addition of a comparator drug. New users are defined as the first dispensing of a prescription in a given drug class after a washout period of 12 months for this drug class.

APPENDIX 7. Overview of study design and new user cohort for initial treatment analysis.

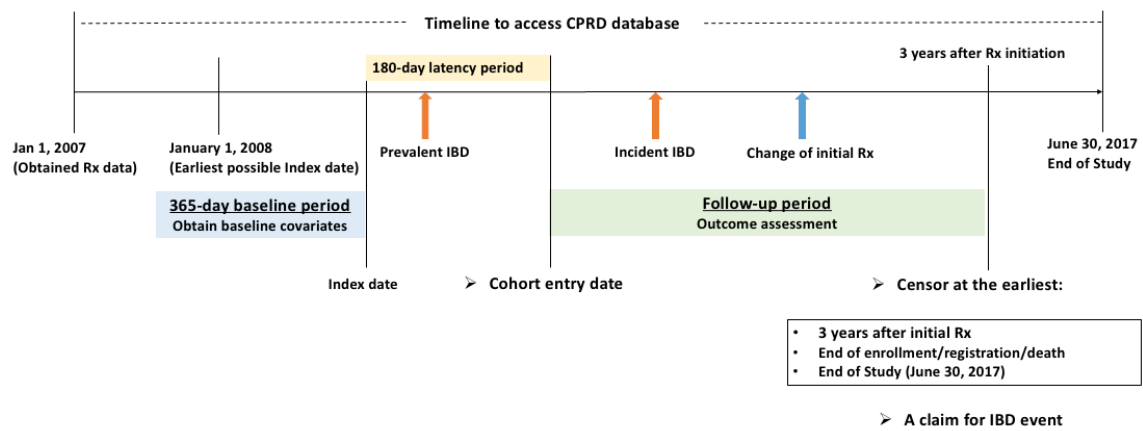


Figure legend. Overview of study design and new user cohort for initial treatment analysis. Rx, prescription. New users were defined as the first dispensing of a prescription in a given drug class after a washout period of 12 months for this drug class.

APPENDIX 8. Algorithm Used to Identify incident Inflammatory Bowel Disease in sensitivity analysis.

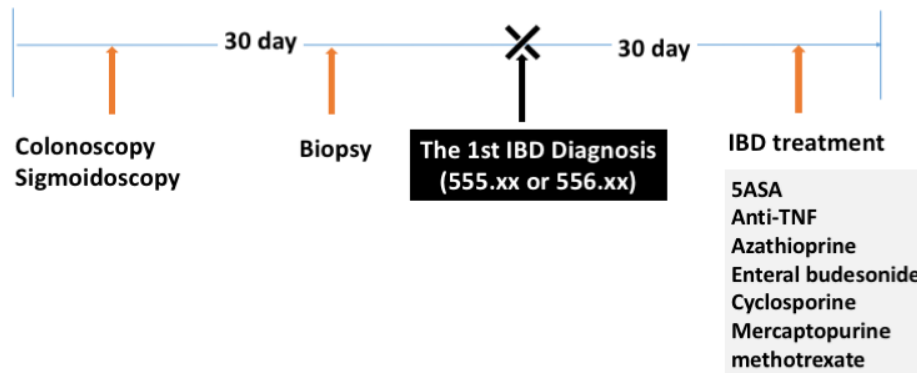


Figure legend. Modified outcome algorithm.

APPENDIX 9. Medications considered as inflammatory bowel disease therapy*.

Class	Medications
5-Aminosalicylic Acid (5-ASA)	Sulfasalazine,
	Mesalazine
	Olsalazine
	Balsalazide
Anti-Tumor Necrosis Factor (anti-TNF)	Infliximab
	Adalimumab
	Certolizumab pegol
	Natalizumab
	Vedolizumab
	Golimumab
	Ustekinumab
Corticosteroid†	Enteral budesonide
Immunosuppressive and immunoregulatory agents	Azathioprine
	Mercaptopurine
	Methotrexate
	Intravenous cyclosporine

*Due to the wide indications, antibiotics are not considered as therapy to treat inflammatory bowel disease.

†Due to the wide indications, only enteral budesonide is considered as the corticosteroid therapy to treat inflammatory bowel disease.

Reference

1. Podolsky DK. Inflammatory Bowel Disease. *N Engl J Med* 2002 Aug 8;347(6):417-29
2. Feuerstein JD, Nguyen GC, Kupfer SS et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology* 2017 Sep;153(3):827-834.

APPENDIX 10. Drugs that may induce inflammatory bowel disease¹.

Drug
Oral contraceptives
Hormonal replacement therapy
Aspirin
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
Isotretinoin
Mycophenolate mofetil
Etanercept
Ipilimumab
Rituximab

Reference

Dubeau M-F, Lacucci M, Beck PL, et al. Drug-induced inflammatory bowel disease and IBD-like conditions. *Inflamm Bowel Dis* 2013 Feb;19(2):445-56.