30 August 2024

Study report

Title: Association between exposure to esomeprazole/omeprazole and risk of sexual dysfunction in men

Administrative details	
Substance(s)	Esomeprazole, omeprazole
Condition/ADR(s)	Sexual dysfunction
Short title of topic	Esomeprazole/omeprazole use and Sexual dysfunction in men
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Reviewer(s)	Valentijn De Jong

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1. Brief description of the study (for publication in HMA-EMA Catalogue of RWD studies)

A cohort study which investigated a potentially increased risk of sexual dysfunction (SD) among male patients prescribed esomeprazole/omeprazole when compared to: (a) being prescribed alternative treatments from the same drug class (i.e., other proton pump inhibitors, PPIs); (b) being prescribed alternative treatments from another drug class (i.e., histamine type 2 receptor antagonists (H2RAs)); and (c) not being prescribed PPIs or H2RAs despite indications for them (non-initiators).

2. Background

Sexual dysfunction (SD) disorders are defined as disorders of sexual desire and psychophysiological alterations of the sexual response cycle in men and women. (Shamloul & Ghanem, 2013; Valeiro et al., 2022) In men, SD can be classified as erectile dysfunction (ED), decreased libido, or abnormal ejaculation. (Hatzichristou et al., 2016; Romano et al., 2022; Shamloul & Ghanem, 2013) In women, SD includes painful intercourse and altered sexual desire, arousal and orgasm that causes distress. Normal sexual function is coordinated at different levels by multiple regulatory systems including vascular, neurological, and endocrine factors. (Calabro et al., 2019; Romano et al., 2022; Shamloul & Ghanem, 2013) Psychological and social factors may also play a role. (Calabro et al., 2019; Romano et al., 2022; Shamloul & Ghanem, 2013) Chronic disorders may impair sexual health at different levels by altering the physiological mechanisms underlying a normal sexual function or by acting at the psychological level. (Romano et al., 2022; Shamloul & Ghanem, 2013; Shen, 2019; Stringer, 2016) Moreover, medicines used in the treatment of chronic disorders may affect the functioning of the regulatory systems involved in normal sexual function, such as antihypertensive drugs, antidepressants (e.g., SSRIs) and central nervous system agents (e.g., benzodiazepines). (Rothmore, 2020; Shamloul & Ghanem, 2013; Valeiro et al., 2022)

Proton pump inhibitors (PPIs) are indicated for the management of peptic ulcer disease and gastroesophageal reflux disease. PPIs are frequently used (and often overused) medications with adverse effects including vitamin B12 deficiency, Clostridium difficile colitis, and increased risk of chronic kidney disease. (Cao et al., 2018; Laine et al., 2000; Lazarus et al., 2016) SD has been suggested as a side effect of PPIs, although the evidence is sparse, and the pathophysiology mechanism is not clear. Some evidence suggest that PPIs may contribute to impaired nitric oxide generation and endothelial dysfunction. (Nolde et al., 2021; Pinheiro et al., 2016; Yepuri et al., 2016)

During routine signal detection activities, six individual case safety reports of SD with suspected association to esomeprazole use were retrieved from EudraVigilance and an additional 18 cases were identified in the published literature. Of these, 23 comprise male individuals whose symptoms started between few days to five months after treatment initiation. In 15 of these patients, symptoms improvement was reported after treatment discontinuation. In two cases, symptoms reoccurred after restarting the treatment.

To support the evaluation of the signal of SD after esomeprazole use, a study was proposed to provide further evidence as to whether being prescribed esomeprazole is associated with an increased risk of SD when compared to: (a) being prescribed alternative treatments from the same drug class (i.e.., other PPIs); (b) being prescribed alternative treatments from another drug class (i.e., histamine type 2 receptor antagonists (H2RAs)); and (c) not being prescribed PPIs or H2RAs despite indications for them (non-initiators). The rationale for using multiple comparator groups is based on the fact that some of the available alternative treatments - which are preferable because of their similar indication (active comparators) - have male SD listed as a possible side effect. Ideally, the active comparator should be known to have no effect on the event of interest since it is used to represent the background risk in the disease. (Yoshida et al., 2015) However, impotence is listed as a rare side effect for

lansoprazole as well as for H2RAs, and decreased libido is listed as rare side effect for famotidine. (EMC, 2024a, 2024b, 2024c) Therefore, we opted to also include a non-user comparator (non-initiators), to gain insight into the background risk for sexual dysfunction. Of note, it was also of interest for the signal evaluation to investigate the effect of omeprazole (i.e. the racemate of esomeprazole and R-omeprazole), considering the partly identical structure shared by esomeprazole and omeprazole. Hence, this study also examined whether being prescribed omeprazole is associated with an increased risk of SD when compared to the abovementioned comparators.

In view of the differences in the definition of SD and risk factors between female and male individuals, that the reported cases which occurred mostly in men and that the majority of primary care recording of SD occurs in males, this study focused on SD in male individuals only. It is noteworthy that for the signal assessment it is relevant to investigate not only erectile dysfunction but other forms of SD as well. Thus, we used a composite outcome including several forms of sexual dysfunction.

3. Research question and objectives

Among male patients, is the prescription of:

1) **Esomeprazole** associated with increased risk of sexual dysfunction (SD) when compared to patients who are:
    a) prescribed other PPIs (namely omeprazole, pantoprazole and lansoprazole)?
    b) prescribed H2RAs?
    c) not prescribed either PPIs or H2RAs?
2) **Omeprazole** associated with increased risk of sexual dysfunction when compared to patients who are:
    a) prescribed other PPIs (namely esomeprazole, pantoprazole and lansoprazole)?
    b) prescribed H2RAs?
    c) not prescribed either PPIs or H2RAs?

Box *1* provides the rationale for the selection of multiple comparator groups.

Box 1. Rationale for the selection of multiple comparator groups and limitations

A. Active comparators (other PPIs, H2RA)

- Active comparators are alternatives for the target treatment within the same indication. They enable to indirectly restrict the study population to patients with a comparable indication to the target drug. If alternative treatments for the same indication can be identified and are assumed to be used interchangeably, i.e., prescribed with clinical equipoise, then confounding by indication is reduced.
- For this study, the most suitable active comparators would be either other PPIs or H2RAs which have similar indications. However, some shortcomings should be considered.
    - Lansoprazole and pantoprazole are the most common PPIs prescribed in the selected databases after esomeprazole and omeprazole. However, for lansoprazole erectile dysfunction is already listed in the product information as a rare side effect. Yet, the comparison with other PPIs might provide insights into potential differences within the drug class.

- H2RAs also have erectile dysfunction listed in the product information as a rare adverse effect and famotidine has also decreased libido listed. Yet, the comparison with H2RAs might provide insights into whether there is an increased risk of sexual dysfunction in esomeprazole/omeprazole users.
- The availability of over the counter (OTC) PPIs has increased over time and, subsequently their OTC use, which is not captured in electronic health records databases. Hence, exposure misclassification is expected.
- The prescribing of H2RAs has decreased over time (see Annex II, Excel file), particularly after the suspension of all ranitidine medicines in the European Union due to the presence of low levels of an impurity called N-nitrosodimethylamine (NDMA) in April, 2020.

- Other treatment alternatives which could have been considered as active comparators such as alginates - which are indicated for treatment of peptic ulcers, dyspepsia, mild forms of GERD, etc. as an adjunct to other drugs - are widely used OTC. Thus, the potential for exposure misclassification may be greater than for H2RA considering their wide use.

B. Non-treated comparators (non-initiators of either PPIs or H2RAs treatments)

- If the indication for treatment is a risk factor for the study outcome, then treated patients, who are more likely to have the indication than non-treated patients, are at a higher risk for adverse health outcomes associated with the indication, leading to confounding by indication. In this respect, the non-treated/non-user comparator is not the preferable comparator for safety studies.
- However, to our knowledge, the main treatment indications for PPIs (e.g., GERD, duodenal and gastric ulcers) have not been associated with SD. Thus, in this study, it is not expected that the estimate of the effect will be strongly biased by confounding by indication, which makes the comparison with non-treated patients acceptable. Additionally, the comparison with a non-treated group might provide insights into the background risk for SD, which will not be gained with the comparison with the selected active comparators in view of their potential risk for erectile dysfunction as mentioned above.
- The non-initiator group in this study might be a mixed group of non-users and [PPIs, H2RAs, alginates] OTC users for which a prescribing for either PPIs or H2RAs treatment is not required probably because of the presence of milder gastroduodenal conditions potentially requiring short term, occasional treatment in low doses.

Conclusion: In view of the above-mentioned advantages and disadvantages, we chose to use multiple comparators which when combined could aid interpretation of the findings.

4. Methods

Box 2. Summary of study methods	
Recruitment period	01/01/2005 - 31/12/2020
Data sources	IQVIA™ Disease Analyser (DA) Germany IQVIA™ Medical Research Data (IMRD) UK
Eligibility criteria	• Eligibility criteria were applied at cohort entry (index-date, see definition below) *Inclusion criteria:*

Box 2. Summary of study methods	
	• Men aged 18 years or older; • With a recorded diagnosis for any of the following, prior to index date: GERD, gastric and duodenal ulcers, chronic gastroduodenitis, Zolliger-Elison syndrome, OR with a recorded recent history of comedication with any of the following: NSAIDs, acetyl salicylic and derivatives, glucocorticoids, or antithrombotic treatments; • With at least one year of recorded medical history prior index-date. *Exclusion criteria:* • Those with recorded prescription of any PPIs or H2RAs within one year before index-date; • Those with recorded history of SD OR treatment for SD at any time prior index-date; • Those with recorded history of selected severe central nervous system comorbidities (Section 5.3, Table 1) prior to index-date; • Those with history of Helicobacter pylori (H. pylori) infection or use of fixed PPI-antibiotic treatments for this indication. Of note, this eligibility criterion was applied to both treated and non-treated individuals only in the analysis including the non-initiator comparator.
Treatment protocols	Initiate any of the following substances (or none of them in the "non-initiators" cohort) at index-date (see definition below), as monotherapy (i.e., not in combination with another PPI or H2RA). *Target arms:* • esomeprazole (target arm [Cohort 1]) • omeprazole (target arm [Cohort 2]) *Comparator arms:* • pantoprazole (comparator arm [Cohort 3] in the IQVIA™ Disease Analyser (DA) Germany database) • lansoprazole (comparator arm [Cohort 4] in the IQVIA™ Medical Research Data (IMRD) UK database) • H2RAs, all combined (comparator arm [Cohort 5]) • non-initiators of either PPIs or H2RAs (comparator arm [Cohort 6])
Assignment procedures	We assumed treatments are randomly assigned conditional on measured potential confounding factors [see Section 5.6, Potential confounding factors]
Index-date (cohort entry, beginning of follow-up)	**Active treatment arms** (including PPIs and H2RAs [Cohort 1 to 5])**:** The index-date was the date of the initiation of treatment defined as a prescription date for PPIs/H2RAs after a washout window of at least 365 days in which no previous prescription with any PPIs or H2RAs was recorded. **Non-initiator arm** [Cohort 6]**:** Non-initiator comparators were selected on each date of the recruitment period when esomeprazole/omeprazole initiators start treatment, matched on birth-year. This date was the non-initiator comparators **index-date**. Thus,

Box 2. Summary of study methods	
	with regards to treatment, the active treatment arms initiated a treatment on index-date and non-initiator comparators did not.
Outcome	First recorded occurrence of SD, including the following ICD-10 codes: F52.0, F52.1, F52.2, F52.3, F52.6, F52.8, F52.9, N48.4, N94.1, N48.3 [See section 5.6, Outcome]
Follow-up	Patients were followed-up from index-date up to maximum 1 year. Thus, patients were followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up, death (only available in IMRD UK), end of follow-up (1 year) or end of the study period [See Section 5.5, Follow-up period]
Causal contrast of interest	Intention to treat effect, i.e., patients were followed up irrespective of treatment change (main analysis).
Statistical methods	• Inverse probability of treatment weighting (IPTW) was used to adjust for confounders measured at cohort entry. • Incidence rates (IR) and cumulative incidence proportions was estimated for each treatment cohort. • Hazard ratios (HRs) were estimated using a Cox proportional hazards model. • Cumulative incidence proportions were estimated for each treatment arm using the Kaplan-Meier estimator. • Supplementary analyses included a **"Per-protocol"** analytical strategy. [See Section 5.7. Statistical analyses]

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4.1. Study design

Comparative cohort design, including:

a) Active comparator, new user design:

- Esomeprazole initiators (target treatment [Cohort 1]) were compared to the following comparators: pantoprazole [Cohort 3 – only in IQVIA™ Disease Analyser (DA) Germany], lansoprazole [Cohort 4 – only in IQVIA™ Medical Research Data (IMRD) UK], and H2RAs [Cohort 5] initiators.
- Omeprazole initiators (target treatment [Cohort 2]) were compared to the following comparators: pantoprazole [Cohort 3 – only in IQVIA™ Disease Analyser (DA) Germany], lansoprazole [Cohort 4 – only in IQVIA™ Medical Research Data (IMRD) UK], and H2RAs [Cohort 5] initiators.

Treatment initiation was defined as the prescription date for PPIs/H2RAs after a washout window of at least 365 days in which no previous prescription with any PPIs or H2RAs has been recorded. This date coincided with the cohort entry or start of follow-up in the study, which we refer to as **index-date**.

b) Non-initiator comparator:

- Esomeprazole initiators (target treatment [Cohort 1]) were also compared to patients who did not have a prescription for either PPIs or H2RA despite having a recorded indication (see Section 5.3, eligibility criteria) for theses treatment (non-initiator comparator [Cohort 6]).
- Omeprazole initiators (target treatment [Cohort 2]) were also compared to patients who did not have a prescription for either PPIs or H2RA despite having a recorded indication (see Section 5.3, eligibility criteria) for theses treatment (non-initiator comparator [Cohort 6]).

As above, treatment initiation was defined as the prescription date for esomeprazole/omeprazole after a washout window of at least 365 days in which no previous prescriptions with any PPIs or H2RAs have been recorded. This date coincides with the start of follow-up in the study, which we refer to as **index-date**.

Non-initiator comparators were selected on each date of the recruitment period when esomeprazole/omeprazole initiators started treatment, matched on birth-year. This date was the non-initiator comparators index-date. Thus, with regards to treatment, the active treatment arms initiated a treatment on index-date and non-initiator comparators did not.

A graphical representation of the study design including the assessment windows for inclusion–exclusion criteria, covariates and follow-up relative to index-date is shown in Figure *1*. Further details for each component of the diagram are provided in the respective sections below.

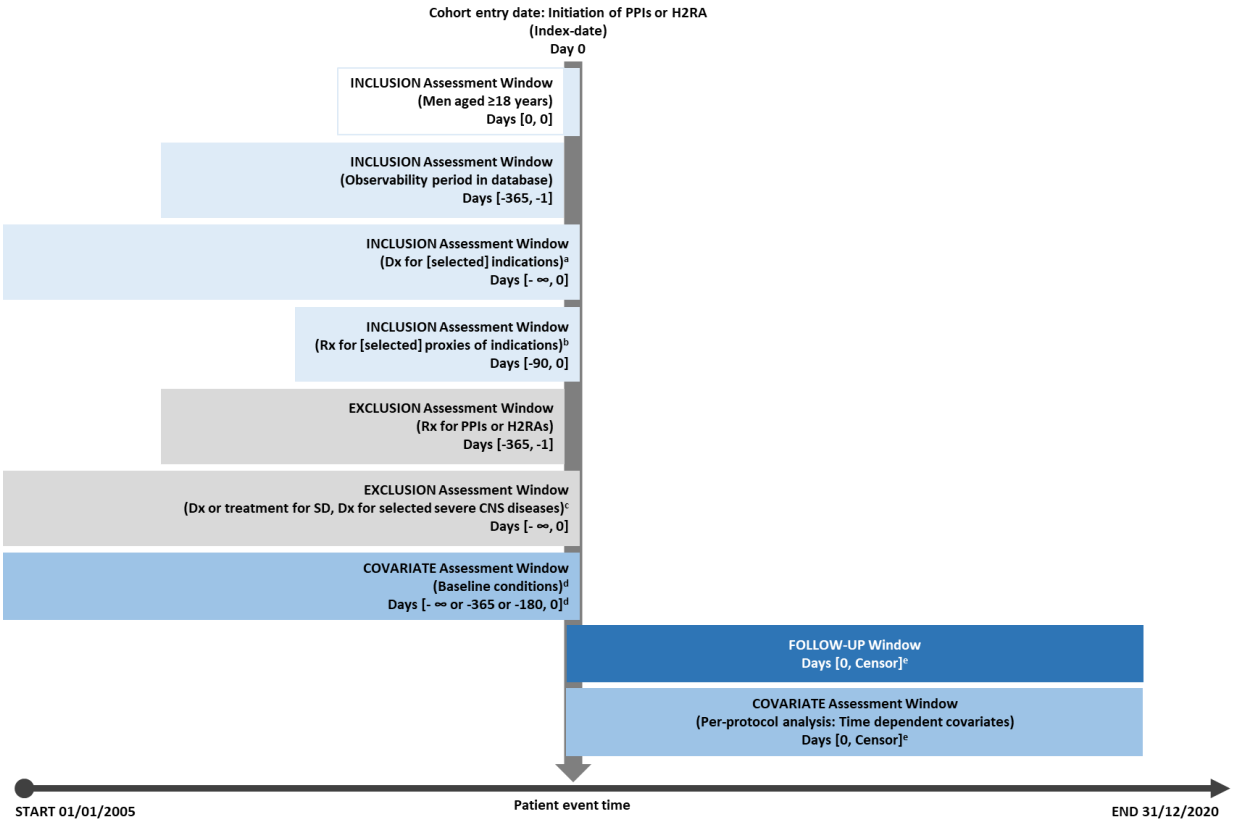

Figure 1. Study design diagram

Dx: diagnosis; Rx: prescription; SD: sexual dysfunction.

[a] For the analyses of active treatments only, no restriction to indication was applied. For the analysis including a non-initiator comparator, indications for chronic conditions were selected: GERD, gastric and duodenal ulcers, chronic forms of gastroduodenitis, and Zollinger-Ellison syndrome and excluding patients with history of H. pylori.

[b] For the analysis including a non-initiator comparator, selected proxies of indications were also considered as follows: recent comedication with NSAID, acetyl salicylic and derivatives, glucocorticoids, and antithrombotic treatments.

[c] Selected severe CNS diseases: Hereditary ataxia (mainly hereditary spastic paraplegia), Huntington disease, spinal muscular atrophy and related syndromes, cerebral palsy, hemiplegia, paraplegia and tetraplegia, other paralytic syndromes (monoplegia of lower limb, cauda equina syndrome, locked-in syndrome), dependence on wheelchair.

[d] Baseline conditions: See Section 5.6 on potential confounding factors.

[e] Censoring: Patients were censored at the earliest of the following events: first occurrence of outcome, loss to follow-up (e.g., transfer out date from the general practice in IMRD or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), death (only available in IMRD UK), end of follow-up (1 year) or end of the study period.

4.2. Data sources

The following databases were used: IQVIA™ Disease Analyser (DA) Germany, and IQVIA™ Medical Research Data (IMRD) UK. Brief descriptions of these databases are provided in **Annex 1**.

4.3. Study population

The population eligible for the study was selected based on the inclusion and exclusion criteria listed in Table *1*, which were measured at baseline (i.e., index-date). Figure *1* above provides details on the assessment windows for these eligibility criteria in relation to the index-date.

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
• Patients registered with a general practice (GP) covered by IMRD UK or patients visiting GP in IQVIA™ DA Germany;	• Recorded prescription of any PPIs or H2RAs within one year before index-date;
• Male; AND • Aged ≥18 years;	• Recorded history of SD OR treatment for SD (e.g., Viagra) prior index-date;
• At least one year of recorded medical history prior to index-date.	• Those with recorded history of selected severe CNS diseases prior index-date, namely: Hereditary ataxia (mainly hereditary spastic paraplegia), Huntington disease, spinal muscular atrophy and related syndromes, cerebral palsy, hemiplegia, paraplegia and tetraplegia, other paralytic syndromes (monoplegia of lower limb, cauda equina syndrome, locked-in syndrome), dependence on wheelchair.
Only applicable to the analysis including a non-initiator comparator: • Recorded diagnosis for GERD, gastric and duodenal ulcers, chronic gastroduodenitis, and Zollinger-Ellison syndrome[1]; OR • History of comedication with NSAID, acetyl salicylic and derivatives, glucocorticoids, and antithrombotic treatments [1, 2]	*Only applicable to the analysis including a non-initiator comparator:* • No diagnosis of H. pylori or fixed combination treatment for H. pylori with PPI and antibiotics.

[1] These indications are selected indications for PPIs and H2RAs. We restricted the study population to patients with chronic indications, for which treatment is likely chronic. The rationale for this is explained in Limitations (first paragraph)

[2] These are assumed to be proxies of indications (e.g., PPIs are indicated to patients requiring continued NSAID or antithrombotic therapy).

4.4. Recruitment period

The recruitment period started on January 1st, 2005, and ended on December 31st, 2020, in both IQVIA™ DA Germany and IMRD UK.

Although the first use of esomeprazole dates to September 2000, in IMRD UK and October 2000, in IQVIA™ DA Germany, we opted to include data from 2005, the year when the distribution of male sexual dysfunction events started being consistent.

Additionally, we opted to limit the recruitment period up to 2020 because the use of H2RAs is very limited in IQVIA™ DA Germany after 2020. Of note, the suspension of all ranitidine medicines in the European Union due to the presence of low levels of an impurity called N-nitrosodimethylamine (NDMA) in April, 2020 (European Medicines Agency, 2020) led to the suspension of ranitidine, the dominant H2RA in Europe.

4.5. Follow-up period

Patients were followed-up from index-date up to maximum one year. For instance, patients recruited in 2020 could have been followed up to 2021. Thus, patients were followed-up from index-date to the earliest of: date of first occurrence of outcome, loss to follow-up (e.g., transfer out date from the general practice in IMRD or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), death (only available in IMRD UK), end of follow-up (1 year) or end of the study period.

Considering the recommended duration for these treatments (4-8 weeks for PPIs and 8-12 weeks for H2RAs), a patient may have participated with several treatment episodes - and consequently index-dates - during the study period. For example, a patient may have received a prescription for 8 weeks after which the medication was discontinued to assess the need for ongoing therapy (on-demand or intermittent use). After 15 months of discontinuing this therapy, the patient may have received another prescription for the same therapy and duration. Therefore, this patient entered the study twice and contributed with two treatment episodes. Of note, eligibility criteria were evaluated at each index-date every time the patient contributed with a treatment episode. Figure *2* illustrates examples of patient exposure to treatments for four different patients according to calendar time (in months).

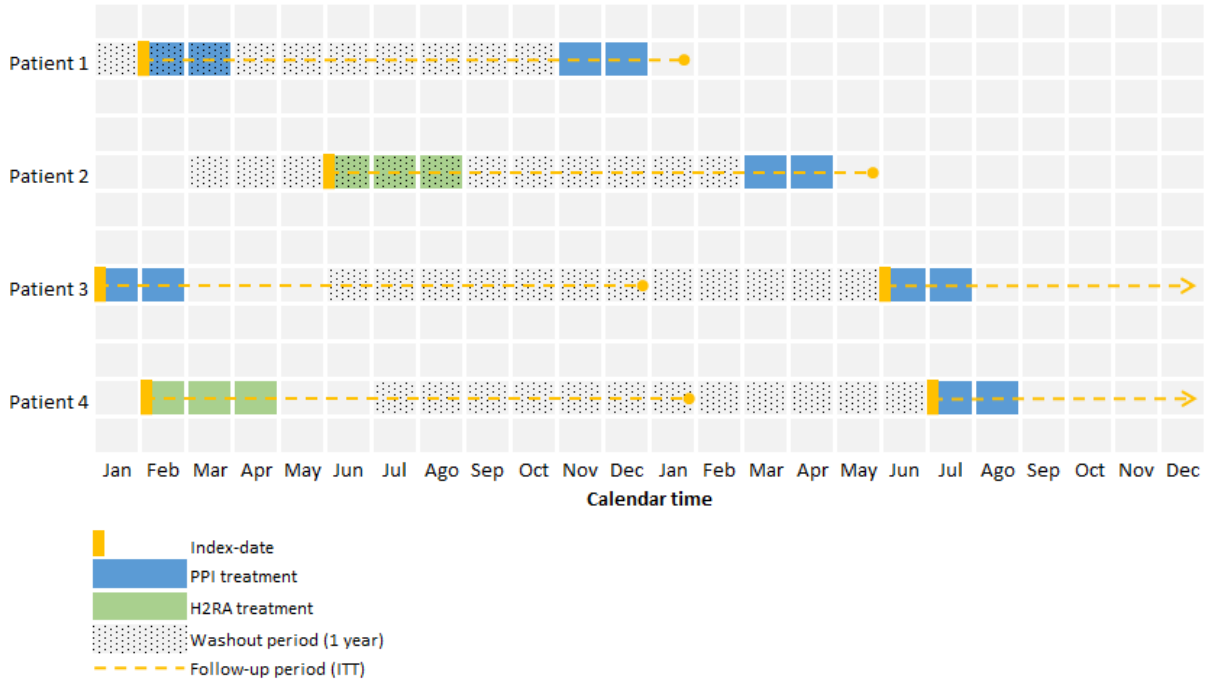

Figure 2. Patient exposure to treatments according to calendar time

Patient 1: Patient contributed with 1 treatment episode (first episode). The second episode did not meet the criterion of 1 year washout before index-date.

Patient 2: Patient contributed with 1 treatment episode (first episode). The second episode did not meet the criterion of 1 year washout before index-date.

Patient 3: Patient contributed with 2 treatment episodes. The second episode met the criterion of 1 year washout before index-date.

Patient 4: Patient contributed with 2 treatment episodes. The second episode met the criterion of 1 year washout before index-date.

The follow-up period illustrated here corresponds to the 12-month follow-up for the ITT analysis (in case of no earlier outcome event or censoring).

4.6. Variables

Exposure

a) Active treatment arm (cohorts):

Patients who **initiated treatment** with either target treatments (esomeprazole or omeprazole) or active comparators (pantoprazole, lansoprazole, H2RAs) during the study period were identified based on the dates of prescriptions in the database and considering a washout period (See Figure *2* above) of 1 year before index-date in which no previous prescription with any PPIs or H2RAs had been recorded.

Only initiation of target treatments and active comparators as **monotherapy** were included in the study. Initiating treatment with more than one PPI or H2RA or any combination of the two on the same day were not allowed. However, combinations with treatments other than PPIs and H2RAs were allowed (e.g., alginates and antacid basic salts).

Table 2 shows the treatment assignment by target/comparator treatment arm.

Of note, considering that these treatments have been long available on the market, their prescribing pattern (on-demand or intermittent use) and widespread OTC use, it is not possible to identify the first prescription ever (i.e., first use or incident exposure) with any certainty. Electronic health records may not capture the entire patient history of utilisation of these treatments. In addition, these treatments are used interchangeably which would mean that a substantial number of individuals would have been excluded from the study population if the study would have focused only on first use ever of any of these substances. Therefore, the study assessed initiation of treatment after a washout window of at least 365 days.

Prescriptions were identified through keyword searches using international non-proprietary names (INNs) in several prescription-related variables (e.g., "Therapy Name", "Product Name", "Molecule"). Detailed list of keywords used are provided in **Annex 2**.

PPIs included the most prescribed substances in each database, i.e., esomeprazole, omeprazole, and pantoprazole in IQVIA™ DA Germany, and esomeprazole, omeprazole, and lansoprazole in IMRD UK. Other PPIs such as dexlansoprazole and rabeprazole were less commonly recorded in the selected databases and, therefore, were not included in this study.

Products containing H2RAs included the following substances (ordered by frequency of prescribing): ranitidine, famotidine, cimetidine, nizatidine in IQVIA™ DA Germany ranitidine, and famotidine, nizatidine, cimetidine in IMRD UK.

Annex 2 provides details on the prescribing of PPI and H2RA over time in each database.

b) Non-initiators arm (cohort)

Non-initiator comparators were randomly sampled and selected on each date of the recruitment period when esomeprazole/omeprazole initiators started treatment, **matched on birth-year**. This date was the non-initiator comparators index-date. Thus, with regards to treatment, the active arms initiated a treatment on index-date and non-initiator comparators did not. Matching on index-date and on year of birth was meant to ensure a similar distribution of calendar time and age at index-date, both of which are considered important potential confounders.

It should be noted that *non-initiators* refer to patients who have selected indications (see Table 1 above, inclusion criteria) recorded in the databases but who did not initiate therapy (i.e., did not have a recorded PPIs or H2RA prescription within 12 months before index-date or on index date).

Table *2* summarises the treatment assignments by cohorts.

Table 2. Treatment assignment by cohorts

Target treatments:	Active comparators:	Non-initiator comparator:
• Treatment initiation as monotherapy* with: ○ Esomeprazole [Cohort 1] ○ Omeprazole [Cohort 2]	• Treatment initiation as monotherapy* with: ○ Selected PPIs: ▪ Omeprazole [Cohort 2], when esomeprazole was the target treatment; ▪ Esomeprazole [Cohort 1], when omeprazole was the target treatment; ▪ Pantoprazole in IQVIA™ DA Germany [Cohort 3], or ▪ Lansoprazole in IMRD UK [Cohort 4] ○ Selected H2RAs [Cohort 5]: ranitidine, famotidine, cimetidine, nizatidine in IQVIA™ DA Germany, and ranitidine, famotidine, nizatidine, cimetidine in IMRD UK.	• Prior diagnosis of indication but no treatment initiation with either PPIs nor H2RAs within previous 12-month or on index date [Cohort 6].

* **Note:** Treatment initiation with any combination with other PPIs or H2RAs on the index-date was not part of the study.

Outcome

Sexual dysfunction (SD) was defined as the first recorded occurrence of any of the following conditions (WHO ICD-10 code): lack or loss of sexual desire (F52.0); sexual aversion and lack of sexual enjoyment (F52.1); failure of genital response (F52.2); orgasmic dysfunction (F52.3); nonorganic dyspareunia (F52.6); other sexual dysfunction, not caused by organic disorder or disease (F52.8); unspecified sexual dysfunction, not caused by organic disorder or disease (F52.9); impotence of organic origin (N48.4); dyspareunia (N94.1), priapism, painful erection (N48.3).

Annex 2 provides the list of WHO ICD-10 codes used to identify outcome events in IQVIA™ DA Germany. READ codes were used to identify these conditions in IMRD UK (Annex 2). Of note, SD as defined here was mostly driven by erectile dysfunction/impotence, which was the most frequent condition recorded in both databases.

Potential confounding factors

Analyses accounted for the following baseline covariates measured before index-date, which are considered risk factors for the outcome, particularly for erectile dysfunction (DynaMed, 2023; La Torre et al., 2013; Razdan et al., 2018; Shamloul & Ghanem, 2013; Trinchieri et al., 2021; Yogarajah & Mula, 2017):

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(i) Main organic causes of sexual dysfunction
Neurogenic
Multiple sclerosis and other demyelinating disorders
Parkinson's disease
Alzheimer's disease and other dementias (e.g., vascular)
Stroke
Autonomic neuropathies
Endocrinological
Diabetes mellitus
Hypogonadism
Hyperprolactinaemia
Hypothyroidism
Testosterone deficiency
Vasculogenic
Atherosclerosis
Systematic diseases and general ill health
Myocardial infarction
Cardiac failure
Chronic kidney disease
Severe chronic respiratory diseases: COPD, emphysema, sleep apnoea (Budweiser et al., 2009)
Major pelvic surgery: prostatectomy, urethroplasty or surgery for urethral structure, cystectomy, aorto-iliac surgery
Malignancy, and radiation in the pelvic region

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(ii) Factors related to the development of psychogenic sexual dysfunction
Depression
Anxiety
Stress disorders
Behaviour and sexuality disorders

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(iii) Drugs reported to be associated with sexual dysfunction
Cytostatic anti-androgens (prostate cancer)
Cytostatic anti-androgens (e.g., bicalutamide, cyproterone)
Cytostatic gonadotrophin-releasing hormone analogue (e.g. leuprorelin)
Antihypertensives
Diuretics
Potassium-sparing diuretics (e.g., spironolactone)
Thiazides and analogues (e.g., hydrochlorothiazide, indapamide) Loop diuretics (e.g., torasemide, furosemide)
Beta-blockers
Beta-blockers (e.g. metoprolol, bisoprolol, carvedilol)
Anti-adrenergic agents

(iii) Drugs reported to be associated with sexual dysfunction

Alpha-adrenoreceptor blockers (doxazosin, prazosin, indoramin, trimazosin, bunazosin, urapidil)
Guanidine derivatives (guanethidine, betanidine, guanoxan, debrisoquine, guanoclor, guanazodine, guanoxabenz)
Cardiovascular drugs acting on the renin-angiotensin system

ACE inhibitors (e.g., ramipril, enalapril, lisinopril)
Angiotensin II receptor blockers (e.g., losartan, irbesartan)
Centrally Acting Anti-hypertensives

Antihypertensives centrally acting (e.g., moxonidine, clonidine, methyldopa, reserpine)

Antiarrhythmics

Digitalis glycosides

Cardiac glycosides (e.g., digoxin, digitoxin)

Other antiarrhythmics

Amiodarone, Disopyramide

Benign Prostatic Hypertrophy drugs

Alpha-adrenergic antagonists (e.g., tamsulosin, terazosin)

5-alpha testosterone reductase inhibitors (5-ARI) (e.g., finasteride, dutasteride)

Antifungal drugs

Ketoconazole, Terbinafine

Antidepressants and Mood Stabilizers

Antidepressants that negatively affect sexual function

SSRI antidepressants (e.g., citalopram, sertraline, fluoxetine)

SNRI antidepressants (e.g., venlafaxine)

Other antidepressants including tricyclics (e.g., clomipramine, amitriptyline, imipramine, doxepin) and MAOIs (e.g., phenelzine, tranylcypromine, moclobemide) and excluding bupropion, mirtazapine, agomelatine, nefazodone, trazodone and tianeptine (included below)
Antidepressants that may improve sexual function

Mirtazapine, bupropion, agomelatine, lamotrigine

Antipsychotic Drugs

Atypical antipsychotics (e.g., olanzapine, quetiapine, risperidone, aripiprazole)

Conventional antipsychotics (e.g., haloperidol, flupentixol, sulpiride)

Anxiolytic Drugs

Anxiolytics that negatively affect sexual function

e.g., benzodiazepines, hydroxyzine, meprobamate

Anxiolytics that may improve sexual function

Buspirone, Piper Methysticum (Kava)

Antiepileptic Drugs

Antiepileptics that negatively affect sexual function

Carbamazepine, phenobarbital, valproic acid and phenytoin

Antiepileptics that may improve sexual function

Lamotrigine, levetiracetam

Opioids

Lipid lowering drugs

Statins (e.g., simvastatin, atorvastatin, rosuvastatin)

Fibrates (e.g., bezafibrate, clofibrate)

Combinations of statins and fibrates with other agents (mainly ezetimibe)

Anti-Parkinsonian Drugs

Prolactin inhibitors

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(iv) Risk factors associated with sexual dysfunction
Age **Lifestyle factors** ○ Cigarette smoking (yes/no) ○ Substance abuse (including alcohol) **Metabolic risk factors** ○ Overweight > 25 Kg/m^2 ○ BMI > 30 Kg/m^2

(v) Other potential confounders
History of PPIs or H2RAs use - To account for the potential effect of past exposure (>12 months) on the likelihood of receiving subsequent PPI/H2RA therapy and the risk of outcome.
Calendar year - To account for changes in prescribing and diagnosis recording practices over time.

4.7. Statistical analysis

4.7.1. Brief summary of the analysis method (for publication HMA-EMA Catalogue of RWD studies)

In this study, the estimated treatment effect was the comparison of the risk of sexual dysfunction, over one year, between patients who initiated (i.e., were prescribed treatment after the specified washout) esomeprazole versus patients who: a) initiated other proton pump inhibitors (PPIs, namely omeprazole, pantoprazole/lansoprazole); b) initiated histamine type 2 receptor antagonists (H2RA)) and c) patients who did not initiate treatment with either PPIs or H2RA but had received a diagnostic for a PPI or H2RA indication (i.e. non-initiators comparators). Outcome events were attributed to the baseline treatment protocol regardless of treatment change during follow-up. (i.e., **intention-to-treat analysis** (**ITT**)).

4.7.2. Descriptive analysis

Analyses were performed to describe the study cohorts at baseline in terms of demographic characteristics, lifestyle factors, potential indications, comorbidities, and history of treatment with drugs commonly associated with sexual dysfunction.

4.7.3. Main statistical analysis

Inverse probability of treatment weighting (IPTW)

Inverse probability of treatment weighting (IPTW) was used to render the assignment of study treatments independent of the baseline measured covariates, thus minimising the potential confounding effect of these covariates.

Using IPTW, the average treatment effect (ATE) in the entire study population was estimated, assuming that all important confounding variables have been accounted for. For each observation in the study population, the IPTW is the inverse of the probability of receiving the observed treatment

conditional on all variables considered sufficient for confounding adjustment. In order to stabilize the weights (i.e., less extreme weights, that are closer to the mean weight of one), the numerator of one was replaced by the marginal probability of receiving the observed treatment in the study population (i.e., the proportion of observations in the study population with the respective treatment). (Hernan & Robins, 2006) Extreme weights were truncated to the 99th percentile of the distribution, if above this upper threshold or to the 1st percentile of the distribution if below this lower threshold. All analyses were conducted in the re-weighted population, without additional confounding adjustment, on the assumption of no unmeasured confounding. To account for weighting the population (essentially multiplying observations by the weight coefficient) robust standard error estimators were used.

The distributions of baseline covariates before and after weighting was compared between esomeprazole and the other treatment arms by calculating and plotting standardized mean differences (SMD), with a SMD of <10 used to determine appropriate covariate balance. For each variable, the SMD was the difference in mean (for continuous variables) or proportion (for binary variables) between each treatment arms and the entire study population (which is the target population in the ATE to which the composition of covariates distribution in each treatment arm is standardized), divided by the study population standard deviation of the variable.(McCaffrey et al., 2013)

Intention-to-treat (ITT) analysis

The ITT approach chosen for the main analysis involved following patients from the date of an intention to initiate a study treatment (i.e., index date = first prescription after washout) until the earliest of any of the following: first outcome event date, loss to follow-up (e.g., transfer out date from the general practice in IMRD UK or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), date of death (only available in IMRD UK) or the end of the study. Consequently, outcome events were attributed to the baseline treatment regardless of treatment change during follow-up. Moreover, it was assumed that intercurrent events that may occur during follow-up are independent of the risk of the outcome (i.e., the risk of experiencing the outcome among individuals remaining in the analysis over the course of follow-up is representative of the risk among censored individuals).

Incidence rates (IRs)

IRs were calculated as the number of events occurring during follow-up divided by the total person-time in each treatment-arm. IRs are presented as number of events per 100 person-years.

Cumulative incidence (Incidence proportion)

Survival (i.e., the proportion of the patients included at baseline who have not yet experienced a sexual dysfunction event) over the course of follow-up, was estimated by treatment arm using the Kaplan-Meier method. (Bland & Altman, 1998) The cumulative incidence was calculated as the complement of survival (i.e., the proportion of the patients included at baseline who have experienced a sexual dysfunction event) at each follow-up time and is presented as number of events per 100 patients.

Cox proportional hazards model

Hazard ratios of sexual dysfunction associated with treatment of interest (esomeprazole) versus comparators were estimated using a Cox proportional hazards model.

4.7.4. Supplementary analysis

The following supplementary analysis was performed to test the robustness of the study findings:

Applying "per-protocol" (PP) approach: In this analysis, the follow-up of patients was censored at the initiation of a PPI or H2RA other than the baseline treatment (i.e., treatment switch or addition). Assuming that such censoring is independent of the risk of SD (i.e., non-informative censoring), this analysis estimated the treatment effect had patients remained on the baseline treatment for the entire follow-up or discontinued the baseline treatment but without initiating an alternative PPI/H2RA.

Thus, we considered a patient to respect the baseline treatment protocol from index-date to the date of initiation of an alternative treatment. Patients were censored at the earliest of the following events:, initiating an alternative treatment, first outcome event date, loss to follow-up (e.g., transfer out date from the general practice in IMRD UK or end of continuous observation of the patient by the practice in IQVIA™ DA Germany, or date of last data collection from the practice), date of death (only available in IMRD UK) or at the end of the study period.

This approach addresses the situation in which a patient initiates another PPI/H2RA after index-date, which might be problematic if the other PPI/H2RA initiated after index-date and within the 1-year follow-up might cause the outcome event instead of the baseline treatment.

It should be noted that the difference between the ITT and PP approach lies in the follow-up period. The same baseline conditions such as eligibility criteria and washout period before index-date were applied for both analytical approaches.

Analyses were performed using SAS Enterprise Guide 7.1 software.

4.7.5. Sample size

The sample size was driven by the availability of individuals with exposures and outcomes within each database and no *a priori* sample size requirement was stipulated.

4.8. Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance were adhered to for the conduct of the study. These procedures included rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents underwent at least one round of review by an experienced reviewer, while the results from the statistical analysis were reviewed.

The quality control of the data is the responsibility of the data holder.

5. Deviation from the protocol

- Study population:
    - No restriction was applied by indications when selecting the treatment cohorts for the analyses comparing esomeprazole/omeprazole with other alternative treatments (i.e., pantoprazole, lansoprazole, H2RAs). This was done to potentially avoid substantial drop-off in the study population as some of the selected indications for PPIs/H2RAs might not be well-recorded in the databases. It should be noted that this recommendation was made by the Scientific Research Committee of IMRD UK.
    - For the analyses comparing esomeprazole/omeprazole cohorts with non-initiator of treatment cohort, the study population was restricted to selected indications as described in Table 1 (Section 5.3 Study population) and as per original protocol.
- Supplementary analysis: Adjustment for informative censoring at treatment discontinuation was not conducted as results for the PP analyses were similar to those for the ITT analyses.

6. Results

Note: In accordance with IMRD UK database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report. Additional cells have been redacted (events/patients typically being rounded up to the nearest 10) if needed in order to ensure that the aforementioned low cell counts cannot be re-identified. This may include both events/patients and follow-up times.

6.1. Comparison between esomeprazole/omeprazole and active treatment cohorts

6.1.1. Descriptive results

Figure *3* and Figure *4* show details of the patient attrition for the treatment cohorts in the IQVIA™ DA Germany and the IMRD UK databases, respectively. Overall, 1,101,439 and 528,841 patients who were prescribed PPIs or H2RAs from January 1st, 2005, to December 31st, 2020, were identified in IQVIA™ DA Germany and IMRD UK, respectively. After excluding patients who were prescribed more than one study treatment on index-date or PPIs not included in this study, and patients who did not meet the eligibility criteria, 442,259 and 244,063 patients were included in the study for IQVIA™ DA Germany and for IMRD UK, respectively. These patients comprised the study population for the analyses comparing esomeprazole/omeprazole with other alternative treatments (i.e., pantoprazole, lansoprazole, H2RAs).

A total of 2,974 and 4,022 incident cases of SD were identified within the 1-year follow-up period, in IQVIA™ DA Germany and for IMRD UK, respectively.

In IQVIA™ DA Germany, the clinical terms (WHO ICD10) which most contributed to the SD definition were failure of genital response (90%), and impotence of organic origin (4%). In IMRD UK, erectile dysfunction (67%), impotence (15%) and complains of erectile dysfunction (12%) were the clinical terms (READ) that most contributed to the SD definition (Annex 3, Table A1 and Table A2).

Table *3* shows the baseline characteristics for the four treatment cohorts in IQVIA™ DA Germany. Before IPTW:

- Patients initiating esomeprazole were slightly older and more likely to have received their prescription in more recent years than patients initiating omeprazole and H2RAs. In addition, they were more likely to have a diagnosis of GERD, other esophageal disease, or diaphragmatic hernia, and to have received a previous prescription for other PPIs than patients initiating omeprazole, pantoprazole or H2RAs.
- Patients initiating pantoprazole were slightly older and more likely to have received their prescription in later years than patients initiating omeprazole and H2RAs. Besides, they were more likely to have received a diagnosis for heart disease, chronic kidney disease, Alzheimer's or other dementia disease, diabetes mellitus, and cerebrocardiovascular disease than patients initiating esomeprazole, omeprazole or H2RAs. They were also more likely to have received a previous prescription for anti-thrombotic treatment, diuretics, β-blockers, ACEi/ARBs, and lipid lowering treatment compared to esomeprazole, omeprazole and H2RAs initiators.
- Patients initiating H2RAs were more likely to have received a diagnosis for gastrointestinal infection or acute gastro-duodenitis and less like to have received a diagnosis for GERD or diaphragmatic hernia than patients initiating esomeprazole, omeprazole, or pantoprazole. Also, they were more likely to have received a prescription for glucocorticoids, anxiolytics or a

previous H2RA, and less likely to have received a prescription for NSAIDs and PPIs compared to esomeprazole, omeprazole, or pantoprazole initiators.

Table *4* shows the baseline characteristics for the four treatment cohorts in IMRD UK. Before IPTW:

- Patients initiating esomeprazole were slightly younger than patients initiating omeprazole, lansoprazole or H2RAs. In addition, they were more likely to have received a diagnosis of GERD, gastro-duodenal ulcer, esophagitis, other esophageal disease, or diaphragmatic hernia, and less likely to have received a diagnosis of atherosclerosis, heart disease, chronic prostate condition, chronic kidney disease, or cerebrovascular disease. They were also more likely to have received a prescription for NSAIDs, or other PPIs and less likely to have received a prescription for salicylate derivatives, glucocorticoids, anti-thrombotic treatment, diuretics, β-blockers, ACEi/ARBs, prostatic hypertrophy treatment, anxiolytics, lipid lowering treatment and hypothyroidism treatment.
- Patients initiating omeprazole were also less likely to have been prescribed with a H2RAs before index-date.
- Patients initiating lansoprazole were slightly more likely to have been diagnosed with a substance abuse problem and to have been prescribed with opioids than patients initiating esomeprazole, omeprazole or H2RAs.
- Patients initiating H2RAs were more likely to have received their prescription in earlier years than patients initiating esomeprazole, omeprazole or lansoprazole. Besides, they were more likely to have been diagnosed with gastro-intestinal infection, dyspepsia, gastro-duodenal symptoms, atherosclerosis, heart disease and to be smokers than patients initiating esomeprazole, omeprazole and lansoprazole. They were also more likely to have been prescribed with anti-thrombotic treatment, other H2RAs, β-blockers, or digitalis glycoside, and less likely to have been prescribed with NSAIDs, or other PPIs.

The absolute standardized differences between treatment arms for each baseline covariate before and after stabilized IPTW are shown in Figure A*1* and Figure A*2* for IQVIA™ DA Germany and in Figure A*3* and Figure A*4* for IMRD UK. The treatment groups were well balanced across all covariates after IPTW, with most of absolute standardized differences <10, except for index-year, prescription of NSAIDs, other PPIs or H2RAs before index-date.

6.1.2. Intention-to-treat (ITT) analysis

Incidence rates (IR)

In IQVIA™ DA Germany, the unadjusted IR per 100 person-years of SD varied from 0.49 [95% CI: 0.42; 0.57] in the esomeprazole cohort to 0.56 [95% CI: 0.52; 0.60] in the omeprazole cohort (Table *5*). Differences in IRs across treatment cohorts were slightly attenuated after IPTW adjustment, varying from 0.50 [95% CI: 0.42; 0.59] in the esomeprazole cohort to 0.54 [95% CI: 0.40; 0.72] in the H2RAs cohort.

In IMRD UK, the unadjusted IR per 100 person-years of SD were higher than in IQVIA™ DA Germany and varied from 1.06 [95% CI: 0.73; 1.54] in the esomeprazole cohort to 1.48 [95% CI: 1.31; 1.68] in the H2RAs cohort (Table *5*). Differences in the IRs across treatment cohorts slightly increased after IPTW adjustment, varying from 0.97 [95% CI: 0.65; 1.45] in the esomeprazole cohort to 1.53 [95% CI: 1.33; 1.77] in the H2RAs cohort.

Cumulative incidence (Incidence proportion)

The unadjusted and IPTW adjusted cumulative incidence curves of SD by treatment cohort are displayed in Figure *5* for IQVIA™ DA Germany. The unadjusted cumulative incidence curves of all treatment cohorts exhibited a trend of gradual, approximately linear increase over time, crossing at different points throughout the 1-year follow-up period. The adjusted IPTW cumulative incidence curves showed a similar pattern. While the adjusted cumulative incidence of SD in the H2RA cohort was the highest during the first 3-month follow-up, the cumulative risk for SD in the esomeprazole cohort remained the highest of the four treatment cohorts between the 4- and 9-follow-up months. Of note, the number of events and follow-up time of the H2RA cohort were limited.

The unadjusted and IPTW adjusted cumulative incidence curves of SD by treatment cohort are displayed in Figure *6* for IMRD UK. The unadjusted cumulative incidence curves of all treatment cohorts exhibited a trend of gradual, approximately linear increase over time. The adjusted cumulative risk for SD in the H2RA cohort remained the highest from the 3-month follow-up to the end of the follow-up period. Of note, the number of events and follow-up time of the esomeprazole cohort were very limited. A similar pattern was observed in the IPTW adjusted cumulative incidence curves of SD, with accentuated differences between the H2RA and the esomeprazole cohorts.

Hazard ratios (HR)

Table *6* shows the unadjusted and IPTW adjusted HRs of SD for both databases.

In IQVIA™ DA Germany, a slightly increased risk for SD was observed in the H2RAs, omeprazole and pantoprazole cohorts when compared to esomeprazole cohort in the unadjusted analysis. The increased risk remained in the H2RA and pantoprazole cohorts and was attenuated in the omeprazole cohort after IPTW adjustment, all point estimates being very close to one. However, the associated uncertainty reflected by the 95% confidence intervals indicated results compatible with similar, higher and lower risk of SD in H2RAs, omeprazole and pantoprazole initiators in comparison to esomeprazole initiators. Conversely, a slightly decreased risk for SD was observed in the H2RAs, esomeprazole and pantoprazole cohorts when compared to omeprazole cohort in the unadjusted analysis, but all hazard ratios approach the value of one after adjustment. The associated uncertainty of the unadjusted and IPTW adjusted HRs indicated results also compatible with similar, higher and lower risk of SD in H2RAs, esomeprazole and pantoprazole initiators in comparison to omeprazole initiators.

In IMRD UK, the unadjusted risk for SD was 13% (omeprazole, lansoprazole) to 40% (H2RAs) higher in the alternative treatment cohorts than in the esomeprazole cohort. These contrasts were accentuated after adjustment for IPTW to the following: 20% increased risk in lansoprazole, 26% increased risk in omeprazole and 59% increased risk in H2RA initiators compared to esomeprazole cohort. However, the associated uncertainty also indicated results compatible with similar, higher and lower risk of SD in the omeprazole and lansoprazole initiators compared to the risk in esomeprazole initiators. The associated uncertainty for H2RA initiators indicated results compatible with higher risk of SD and incompatible with lower risk compared to the esomeprazole initiators.

A higher risk of SD was observed in the H2RA cohort and lower risk in the esomeprazole cohort when compared to omeprazole cohort in the unadjusted analysis. While the associated uncertainty of the unadjusted and IPTW adjusted HRs in the H2RA cohort was compatible with higher risk but incompatible with lower risk of SD when compared to the omeprazole cohort, that for the esomeprazole cohort was compatible with lower, similar or higher risk of SD compared to the omeprazole cohort.

6.1.3. Supplementary analysis (Per-protocol analysis)

A total of 2,853 and 2,512 incident cases of SD were identified in IQVIA™ DA Germany and IMRD UK, respectively, following patients from treatment initiation to treatment change or censoring. The clinical terms which most contributed to the SD case definition were failure of genital response (90%), and impotence of organic origin (4%) in IQVIA™ DA Germany (Annex 3, Table A1). In IMRD UK, erectile dysfunction (67%), impotence (15%) and complains of erectile dysfunction (12%) were the clinical terms that most contributed to the SD definition (Annex 3, Table A*2*).

Table A*5* and Table A*6* show IRs per 100 person-years and HRs of SD, respectively, for the four treatment cohorts in both databases. Figure A*5* and Figure A*6* display cumulative incidence of SD for the four treatment cohorts in both databases, respectively. Results were consistent with those of the main analyses.

In IQVIA™ DA Germany, the percentage of patients followed until the end of the 1-year follow-up period without changing the baseline treatment varied between 75% in H2RA cohort and 85% in pantoprazole cohort. In IMRD UK, the percentage of patients followed until the end of the 1-year follow-up period without changing the baseline treatment varied between 70% in H2RA cohort and 85% in omeprazole cohort.

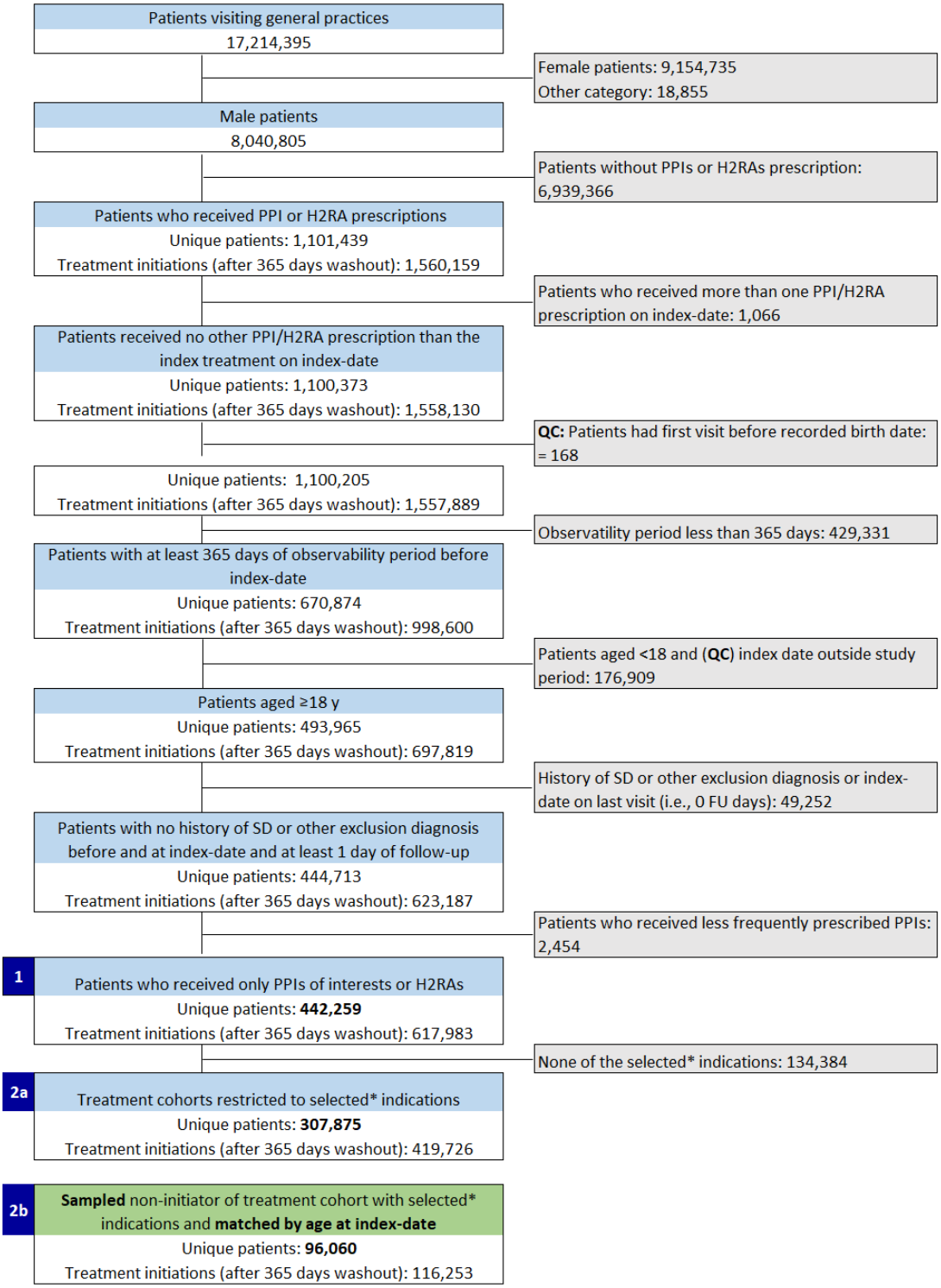

Figure 3. Patient attrition diagram in the IQVIA™ DA Germany database

Study population 1: Treatment cohorts for the analyses comparing target treatment arms (esomeprazole/omeprazole) and active treatment arms (pantoprazole, H2RAs).
Study population 2: Treatment cohorts [**2a**] AND non-initiator of treatment cohort [**2b**] for the analyses comparing target treatment arms (esomeprazole/omeprazole) and non-initiator of treatment arm.
*Selected indications (treatments considered proxies of indications): GERD, gastric and duodenal ulcers, gastroduodenitis, history of prescription of NSAID, acetyl salicylic and derivatives, glucocorticoids, and antithrombotic treatments.
QC: Quality control check of data consistency.

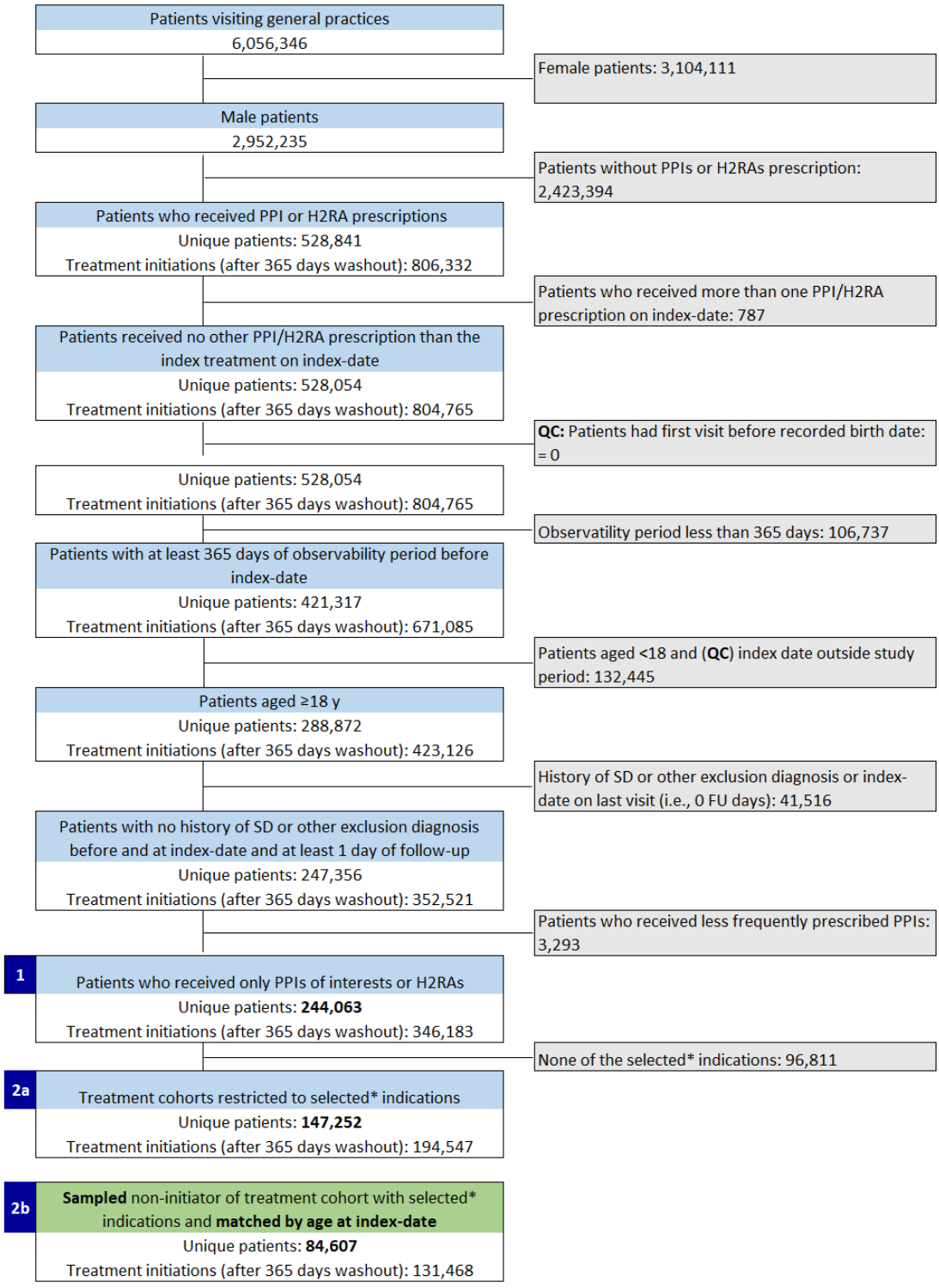

Figure 4. Patient attrition diagram in the IMRD UK database

Study population 1: Treatment cohorts for the analyses comparing target treatment arms (esomeprazole/omeprazole) and active treatment arms (pantoprazole, H2RAs).
Study population 2: Treatment cohorts [**2a**] AND non-initiator of treatment cohort [**2b**] for the analyses comparing target treatment arms (esomeprazole/omeprazole) and non-initiator of treatment arm.
*Selected indications (treatments considered proxies of indications): GERD, gastric and duodenal ulcers, gastroduodenitis, history of prescription of NSAID, acetyl salicylic and derivatives, glucocorticoids, and antithrombotic treatments.
QC: Quality control check of data consistency

645 Table 3. Baseline characteristics of the study population in IQVIA™ DA Germany

Covariates	Before IPTW (unadjusted)				After stabilized IPTW (adjusted)			
	Esomeprazole	Omeprazole	Pantoprazole	H2RAs	Esomeprazole	Omeprazole	Pantoprazole	H2RAs
N	**33469**	**138943**	**429075**	**16496**	**33903.4**	**139631.3**	**424813.6**	**14294.3**
Age at index-date, median (IQR)	56.0 (44.0-68.0)	54.0 (41.0-67.0)	56.0 (42.0-69.0)	53.0 (36.0-68.0)	55.0 (42.0-69.0)	55.0 (41.0-68.0)	55.0 (42.0-69.0)	54.0 (40.0-68.0)
Index year, median (IQR)	2015 (2012-2018)	2013 (2009-2017)	2016 (2014-2019)	2012 (2008-2016)	2016 (2013-2019)	2016 (2012-2019)	2016 (2013-2018)	2016 (2011-2018)
GERD before index-date (any time), N (%)	12870.0 (38.5)	44206.0 (31.8)	123171.0 (28.7)	4109.0 (24.9)	10139.6 (29.9)	42691.9 (30.6)	127356.8 (30.0)	4220.2 (29.5)
Gastro-duodenal ulcer before index-date (any time), N (%)	2229.0 (6.7)	9736.0 (7.0)	25865.0 (6.0)	968.0 (5.9)	2117.9 (6.2)	8750.6 (6.3)	26574.2 (6.3)	884.1 (6.2)
Chronic gastro-duodenitis before index-date (any time), N (%)	3389.0 (10.1)	13286.0 (9.6)	34615.0 (8.1)	1797.0 (10.9)	2949.6 (8.7)	12420.0 (8.9)	36626.6 (8.6)	1357.9 (9.5)
Zollinger-Ellison syndrome before index-date (any time), N (%)	<6.0 (<0.1)	8.0 (0.0)	33.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	12.2 (0.0)	31.9 (0.0)	<6.0 (<0.1)
Gastrointestinal infection before index-date (90 days), N (%)	1768.0 (5.3)	10904.0 (7.8)	28142.0 (6.6)	2409.0 (14.6)	2345.2 (6.9)	10011.5 (7.2)	29396.0 (6.9)	1343.1 (9.4)
H. pylori diagnosis or treatment before index-date (90 days), N (%)	6.0 (0.0)	536.0 (0.4)	4189.0 (1.0)	0.0 (0.0)	15.4 (0.0)	1253.2 (0.9)	3337.2 (0.8)	0.0 (0.0)
Esophagitis before index-date (365 days), N (%)	258.0 (0.8)	674.0 (0.5)	1749.0 (0.4)	64.0 (0.4)	151.7 (0.4)	616.5 (0.4)	1869.6 (0.4)	82.6 (0.6)
Other esophageal disease before index-date (any time), N (%)	1379.0 (4.1)	3349.0 (2.4)	9752.0 (2.3)	184.0 (1.1)	809.1 (2.4)	3616.0 (2.6)	10380.0 (2.4)	274.1 (1.9)
Acute gastro-duodenitis before index-date (90 days), N (%)	6515.0 (19.5)	32893.0 (23.7)	88079.0 (20.5)	4490.0 (27.2)	7190.3 (21.2)	30262.0 (21.7)	90046.5 (21.2)	3408.1 (23.8)
Dyspepsia before index-date (90 days), N (%)	226.0 (0.7)	781.0 (0.6)	2400.0 (0.6)	149.0 (0.9)	200.7 (0.6)	835.0 (0.6)	2427.7 (0.6)	101.1 (0.7)
Gastro-duodenal symptoms before index-date (90 days), N (%)	3619.0 (10.8)	14572.0 (10.5)	43134.0 (10.1)	1994.0 (12.1)	3539.9 (10.4)	14800.7 (10.6)	43672.2 (10.3)	1767.7 (12.4)
Other gastro-duodenal diseases before index-date (any time), N (%)	1195.0 (3.6)	4964.0 (3.6)	13347.0 (3.1)	627.0 (3.8)	1086.4 (3.2)	4717.3 (3.4)	13900.9 (3.3)	510.0 (3.6)
Inflammatory bowel disease before index-date (any time), N (%)	3094.0 (9.2)	11558.0 (8.3)	38659.0 (9.0)	1244.0 (7.5)	3146.6 (9.3)	12606.0 (9.0)	37838.9 (8.9)	1305.7 (9.1)
Gastro-duodenal bleeding before index-date (90 days), N (%)	283.0 (0.8)	907.0 (0.7)	4954.0 (1.2)	43.0 (0.3)	309.0 (0.9)	1224.3 (0.9)	4263.4 (1.0)	75.2 (0.5)
Diaphragmatic hernia before index-date (any time), N (%)	2676.0 (8.0)	7090.0 (5.1)	19657.0 (4.6)	469.0 (2.8)	1647.1 (4.9)	7447.7 (5.3)	21134.3 (5.0)	598.8 (4.2)
Post-surgical gastric syndromes before index-date (any time), N (%)	21.0 (0.1)	80.0 (0.1)	232.0 (0.1)	11.0 (0.1)	18.9 (0.1)	80.7 (0.1)	235.5 (0.1)	13.4 (0.1)
Gastrointestinal malignancy before index-date (any time), N (%)	249.0 (0.7)	451.0 (0.3)	1770.0 (0.4)	41.0 (0.2)	146.8 (0.4)	522.6 (0.4)	1731.2 (0.4)	62.3 (0.4)

Atherosclerosis before index-date (any time), N (%)	7060.0 (21.1)	28157.0 (20.3)	99864.0 (23.3)	3596.0 (21.8)	7738.9 (22.8)	30086.4 (21.5)	95220.4 (22.4)	3277.1 (22.9)
Heart disease before index-date (any time), N (%)	3137.0 (9.4)	12643.0 (9.1)	51125.0 (11.9)	1666.0 (10.1)	3859.8 (11.4)	14491.1 (10.4)	47189.2 (11.1)	1625.3 (11.4)
Acute prostate condition before index-date (365 days), N (%)	212.0 (0.6)	791.0 (0.6)	2285.0 (0.5)	88.0 (0.5)	184.2 (0.5)	743.6 (0.5)	2292.6 (0.5)	82.6 (0.6)
Chronic prostate condition before index-date (any time), N (%)	4740.0 (14.2)	18483.0 (13.3)	63568.0 (14.8)	2093.0 (12.7)	4961.3 (14.6)	19672.5 (14.1)	61281.9 (14.4)	2023.4 (14.2)
Genito-urinary disease before index-date (365 days), N (%)	139.0 (0.4)	552.0 (0.4)	1765.0 (0.4)	55.0 (0.3)	149.0 (0.4)	559.0 (0.4)	1730.5 (0.4)	53.6 (0.4)
Chronic kidney disease before index-date (any time), N (%)	587.0 (1.8)	2055.0 (1.5)	11091.0 (2.6)	255.0 (1.5)	799.5 (2.4)	2933.8 (2.1)	9702.3 (2.3)	328.9 (2.3)
Malignancy in pelvic region before index-date (365 days), N (%)	425.0 (1.3)	1798.0 (1.3)	6739.0 (1.6)	213.0 (1.3)	490.3 (1.4)	1996.2 (1.4)	6319.2 (1.5)	203.6 (1.4)
Chronic obstructive respiratory disease before index-date (any time), N (%)	7341.0 (21.9)	31394.0 (22.6)	100079.0 (23.3)	3695.0 (22.4)	8011.7 (23.6)	31900.6 (22.8)	98048.3 (23.1)	3492.5 (24.4)
Depression before index-date (365 days), N (%)	1822.0 (5.4)	8338.0 (6.0)	26608.0 (6.2)	995.0 (6.0)	2173.2 (6.4)	8555.1 (6.1)	26085.8 (6.1)	985.6 (6.9)
Anxiety before index-date (any time), N (%)	6552.0 (19.6)	30240.0 (21.8)	97303.0 (22.7)	3487.0 (21.1)	7703.1 (22.7)	31140.7 (22.3)	94827.9 (22.3)	3410.4 (23.9)
Behaviour and sexuality disorders before index-date (any time), N (%)	325.0 (1.0)	1797.0 (1.3)	6877.0 (1.6)	235.0 (1.4)	525.5 (1.6)	2083.9 (1.5)	6397.0 (1.5)	263.8 (1.8)
Alzheimer's or other dementia before index-date (any time), N (%)	723.0 (2.2)	2528.0 (1.8)	11110.0 (2.6)	307.0 (1.9)	846.2 (2.5)	3058.3 (2.2)	10109.6 (2.4)	352.1 (2.5)
Autonomic neuropathies before index-date (any time), N (%)	750.0 (2.2)	3227.0 (2.3)	13211.0 (3.1)	392.0 (2.4)	996.3 (2.9)	3853.8 (2.8)	12130.1 (2.9)	407.6 (2.9)
Diabetes before index-date (any time), N (%)	5910.0 (17.7)	25731.0 (18.5)	86110.0 (20.1)	3041.0 (18.4)	6793.0 (20.0)	26741.3 (19.2)	83128.7 (19.6)	2776.8 (19.4)
Hyperprolactinaemia before index-date (any time), N (%)	<6.0 (<0.1)	21.0 (0.0)	53.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	16.0 (0.0)	51.8 (0.0)	<6.0 (<0.1)
Hypogonadism disorders before index-date (any time), N (%)	208.0 (0.6)	576.0 (0.4)	2270.0 (0.5)	63.0 (0.4)	174.9 (0.5)	693.7 (0.5)	2162.6 (0.5)	68.5 (0.5)
Hypothyroidism before index-date (any time), N (%)	1025.0 (3.1)	4343.0 (3.1)	15242.0 (3.6)	434.0 (2.6)	1183.1 (3.5)	4765.9 (3.4)	14586.8 (3.4)	464.7 (3.3)
Demyelinating disorders before index-date (any time), N (%)	92.0 (0.3)	398.0 (0.3)	1359.0 (0.3)	52.0 (0.3)	111.7 (0.3)	433.6 (0.3)	1315.7 (0.3)	54.5 (0.4)
Parkinson’s (or related) disorders before index-date (any time), N (%)	327.0 (1.0)	1040.0 (0.7)	4338.0 (1.0)	113.0 (0.7)	329.7 (1.0)	1227.3 (0.9)	4010.0 (0.9)	141.9 (1.0)
Cerebrovascular disease before index-date (any time), N (%)	1769.0 (5.3)	6746.0 (4.9)	24502.0 (5.7)	805.0 (4.9)	1912.6 (5.6)	7299.1 (5.2)	23275.5 (5.5)	819.1 (5.7)
NSAIDs before index-date (90 days), N (%)	7851.0 (23.5)	38182.0 (27.5)	121713.0 (28.4)	3200.0 (19.4)	9612.0 (28.4)	38282.6 (27.4)	117447.5 (27.6)	3223.0 (22.5)
NSAIDs before index (90 days) or NSAIDs treatment, N (%)	7885.0 (23.6)	38182.0 (27.5)	121713.0 (28.4)	3200.0 (19.4)	9647.3 (28.5)	38282.6 (27.4)	117447.5 (27.6)	3223.0 (22.5)

Salicylate derivatives before index-date (90 days), N (%)	2605.0 (7.8)	9741.0 (7.0)	40402.0 (9.4)	1460.0 (8.9)	3020.9 (8.9)	11300.9 (8.1)	37134.8 (8.7)	1366.1 (9.6)
Glucocorticoids before index-date (90 days), N (%)	1320.0 (3.9)	5815.0 (4.2)	23873.0 (5.6)	1056.0 (6.4)	1801.8 (5.3)	6731.2 (4.8)	22034.1 (5.2)	963.9 (6.7)
Anti-thrombotics before index-date (90 days), N (%)	4372.0 (13.1)	16006.0 (11.5)	79035.0 (18.4)	2171.0 (13.2)	5581.7 (16.5)	20663.9 (14.8)	69843.5 (16.4)	2334.9 (16.3)
Anti-infectives before index-date (90 days), N (%)	3531.0 (10.6)	15806.0 (11.4)	52236.0 (12.2)	1930.0 (11.7)	4097.9 (12.1)	16011.2 (11.5)	50346.3 (11.9)	1839.4 (12.9)
Any antineoplastics before index-date (90 days), N (%)	35.0 (0.1)	116.0 (0.1)	419.0 (0.1)	24.0 (0.1)	34.9 (0.1)	122.5 (0.1)	409.6 (0.1)	16.6 (0.1)
PPIs before index-date (any time), N (%)	15596.0 (46.6)	61755.0 (44.4)	176610.0 (41.2)	4154.0 (25.2)	14230.7 (42.0)	60007.7 (43.0)	179037.2 (42.1)	5283.3 (37.0)
H2RAs before index-date (any time), N (%)	1329.0 (4.0)	7946.0 (5.7)	13646.0 (3.2)	5373.0 (32.6)	1601.6 (4.7)	6251.7 (4.5)	18593.5 (4.4)	1682.4 (11.8)
Cytostatic anti-androgens before index-date (180 days), N (%)	20.0 (0.1)	49.0 (0.0)	280.0 (0.1)	10.0 (0.1)	18.8 (0.1)	61.9 (0.0)	245.4 (0.1)	10.2 (0.1)
Diuretics before index-date (180 days), N (%)	2191.0 (6.5)	10193.0 (7.3)	38548.0 (9.0)	1236.0 (7.5)	2911.5 (8.6)	11012.7 (7.9)	35769.2 (8.4)	1166.1 (8.2)
Beta-blockers before index-date (180 days), N (%)	5126.0 (15.3)	22607.0 (16.3)	76649.0 (17.9)	2717.0 (16.5)	5954.3 (17.6)	23183.6 (16.6)	73473.9 (17.3)	2441.6 (17.1)
Anti-adrenergics before index-date (180 days)	194.0 (0.6)	801.0 (0.6)	2827.0 (0.7)	129.0 (0.8)	216.4 (0.6)	868.9 (0.6)	2710.4 (0.6)	90.3 (0.6)
ACEi/ARBs before index-date (180 days), N (%)	7855.0 (23.5)	33438.0 (24.1)	117391.0 (27.4)	3605.0 (21.9)	9083.9 (26.8)	35664.8 (25.5)	111755.3 (26.3)	3492.1 (24.4)
Centrally acting anti-hypertensives before index-date (180 days), N (%)	297.0 (0.9)	1261.0 (0.9)	4394.0 (1.0)	172.0 (1.0)	343.2 (1.0)	1340.0 (1.0)	4217.2 (1.0)	141.5 (1.0)
Digitalis glycosides before index-date (180 days), N (%)	291.0 (0.9)	1292.0 (0.9)	4073.0 (0.9)	176.0 (1.1)	314.7 (0.9)	1227.3 (0.9)	3972.4 (0.9)	136.7 (1.0)
Amiodarone, Disopyramide before Index-date (180 days), N (%)	108.0 (0.3)	463.0 (0.3)	2010.0 (0.5)	59.0 (0.4)	138.8 (0.4)	539.7 (0.4)	1819.0 (0.4)	50.5 (0.4)
Prostatic hypertrophy treatment before index-date (180 days), N (%)	863.0 (2.6)	3266.0 (2.4)	12866.0 (3.0)	339.0 (2.1)	963.0 (2.8)	3830.9 (2.7)	11979.8 (2.8)	382.1 (2.7)
Ketoconazole, terbinafine before index-date (180 days), N (%)	44.0 (0.1)	144.0 (0.1)	457.0 (0.1)	15.0 (0.1)	35.4 (0.1)	159.2 (0.1)	458.0 (0.1)	10.2 (0.1)
Antidepressants (negative) before index-date (180 days), N (%)	1013.0 (3.0)	4271.0 (3.1)	13359.0 (3.1)	545.0 (3.3)	1114.6 (3.3)	4252.1 (3.0)	13200.3 (3.1)	476.6 (3.3)
Antidepressants (positive) before index-date (180 days), N (%)	258.0 (0.8)	918.0 (0.7)	3918.0 (0.9)	90.0 (0.5)	304.2 (0.9)	1164.4 (0.8)	3604.0 (0.8)	129.9 (0.9)
Antipsychotics before index-date (180 days), N (%)	378.0 (1.1)	1431.0 (1.0)	5404.0 (1.3)	220.0 (1.3)	416.5 (1.2)	1579.5 (1.1)	5107.5 (1.2)	201.4 (1.4)
Anxiolytics (negative) before index-date (180 days) , N (%)	619.0 (1.8)	2320.0 (1.7)	6392.0 (1.5)	417.0 (2.5)	532.6 (1.6)	2215.7 (1.6)	6667.3 (1.6)	264.4 (1.8)
Anxiolytics (positive) before index-date (180 days), N (%)	<6.0 (0.0)	<6.0 (0.0)	8.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	<6.0 (<0.1)	11.2 (0.0)	<6.0 (<0.1)
Antiepileptics (negative) before index-date (180 days), N (%)	136.0 (0.4)	530.0 (0.4)	1523.0 (0.4)	72.0 (0.4)	131.7 (0.4)	496.7 (0.4)	1544.5 (0.4)	66.7 (0.5)

Antiepileptics (positive) before index-date (180 days), N (%)	81.0 (0.2)	189.0 (0.1)	1088.0 (0.3)	30.0 (0.2)	71.3 (0.2)	293.7 (0.2)	962.9 (0.2)	39.8 (0.3)
Opioids before index-date (180 days), N (%)	399.0 (1.2)	1333.0 (1.0)	5352.0 (1.2)	174.0 (1.1)	409.4 (1.2)	1526.5 (1.1)	5006.7 (1.2)	183.8 (1.3)
Lipid lowering treatment before index-date (180 days), N (%)	4070.0 (12.2)	16962.0 (12.2)	60706.0 (14.1)	1899.0 (11.5)	4702.9 (13.9)	18327.9 (13.1)	57564.2 (13.6)	1780.0 (12.5)
Anti-parkinsonian drugs before index-date (180 days), N (%)	216.0 (0.6)	708.0 (0.5)	2749.0 (0.6)	84.0 (0.5)	221.8 (0.7)	801.5 (0.6)	2595.2 (0.6)	84.6 (0.6)
Prolactin inhibitors before index-date (180 days), N (%)	<6.0 (<0.1)	24.0 (0.0)	41.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	16.3 (0.0)	47.4 (0.0)	<6.0 (<0.1)
Selected antineoplastics before index-date (180 days), N (%)	6.0 (0.0)	8.0 (0.0)	67.0 (0.0)	<6.0 (<0.1)	7.7 (0.0)	7.7 (0.0)	62.5 (0.0)	<6.0 (<0.1)
Hypothyroidism treatment before index-date (365 days), N (%)	1945.0 (5.8)	7417.0 (5.3)	25225.0 (5.9)	748.0 (4.5)	1984.7 (5.9)	7920.0 (5.7)	24372.4 (5.7)	778.9 (5.4)
Acetazolamide, aminocaproic acid before index-date (180 days), N (%)	<6.0 (<0.1)	8.0 (0.0)	42.0 (0.0)	0.0 (0.0)	<6.0 (<0.1)	7.6 (0.0)	38.6 (0.0)	0.0 (0.0)
Obesity diagnosis, treatment, adiposity measure or BMI >25 Kg/m^2 before index-date (365 days), N (%)	2832.0 (8.5)	13020.0 (9.4)	41288.0 (9.6)	1513.0 (9.2)	3249.4 (9.6)	13074.4 (9.4)	40294.1 (9.5)	1467.2 (10.3)
BMI >30 Kg/m^2 before index-date (365 days)	816.0 (2.4)	3958.0 (2.8)	13210.0 (3.1)	445.0 (2.7)	1032.5 (3.0)	4128.4 (3.0)	12704.7 (3.0)	469.8 (3.3)
Current smoker (365 days), N (%)	382.0 (1.1)	1761.0 (1.3)	5150.0 (1.2)	217.0 (1.3)	420.9 (1.2)	1667.3 (1.2)	5140.8 (1.2)	149.7 (1.0)
Substance abuse diagnosis (including alcoholism) before index-date (365 days), N (%)	446.0 (1.3)	2360.0 (1.7)	8512.0 (2.0)	273.0 (1.7)	649.7 (1.9)	2530.2 (1.8)	7949.4 (1.9)	290.7 (2.0)

IPTW: inverse probability of treatment weighting; GERD: Gastroesophageal reflux disease; PPIs: Proton pump inhibitors; H2RA: Histamine type 2 receptor antagonists; ACEi/ARBs: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs); NSAIDs: nonsteroidal anti-inflammatory drugs, BMI: body mass index.

Note: In accordance with IMRD database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

652 Table 4. Baseline characteristics of the study population in IMRD UK

Covariates	Before IPTW (unadjusted)				After stabilized IPTW (adjusted)			
	Esomeprazole	Omeprazole	Lansoprazole	H2RAs	Esomeprazole	Omeprazole	Lansoprazole	H2RAs
N	**2748**	**228505**	**99726**	**17952**	**2531.8**	**228464.7**	**99676.8**	**14950.4**
Age at index-date, median (IQR)	47.0 (37.0-59.0)	52.0 (39.0-65.0)	52.0 (39.0-66.0)	51.0 (37.0-66.0)	50.0 (38.0-63.0)	51.0 (39.0-65.0)	51.0 (39.0-65.0)	52.0 (38.0-66.0)
Index year, median (IQR)	2013 (2006-2018)	2014 (2010-2017)	2013 (2009-2017)	2010 (2006-2014)	2014 (2007-2018)	2013 (2010-2017)	2013 (2009-2017)	2012 (2008-2016)
GERD before index-date (any time), N (%)	556.0 (20.2)	29202.0 (12.8)	13451.0 (13.5)	2169.0 (12.1)	376.2 (14.9)	29752.0 (13.0)	13000.0 (13.0)	2057.6 (13.8)
Gastro-duodenal ulcer before index-date (any time), N (%)	106.0 (3.9)	6547.0 (2.9)	3229.0 (3.2)	598.0 (3.3)	95.0 (3.8)	6869.4 (3.0)	2997.8 (3.0)	450.3 (3.0)
Chronic gastro-duodenitis before index-date (any time), N (%)	11.0 (0.4)	866.0 (0.4)	502.0 (0.5)	90.0 (0.5)	11.5 (0.5)	966.9 (0.4)	421.3 (0.4)	69.6 (0.5)
Zollinger-Ellison syndrome before index-date (any time), N (%)	0.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	0.0 (0.0)	0.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	0.0 (0.0)
Gastrointestinal infection before index-date (90 days), N (%)	38.0 (1.4)	3967.0 (1.7)	1725.0 (1.7)	429.0 (2.4)	41.5 (1.6)	4049.5 (1.8)	1765.5 (1.8)	308.2 (2.1)
H. pylori diagnosis or treatment before index-date (90 days), N (%)	24.0 (0.9)	956.0 (0.4)	982.0 (1.0)	8.0 (0.0)	17.6 (0.7)	1266.0 (0.6)	557.2 (0.6)	13.5 (0.1)
Esophagitis before index-date (365 days), N (%)	59.0 (2.1)	2151.0 (0.9)	974.0 (1.0)	115.0 (0.6)	34.5 (1.4)	2160.0 (0.9)	944.3 (0.9)	104.5 (0.7)
Other esophageal disease before index-date (any time), N (%)	114.0 (4.1)	2658.0 (1.2)	1324.0 (1.3)	125.0 (0.7)	48.3 (1.9)	2763.3 (1.2)	1206.7 (1.2)	150.4 (1.0)
Acute gastro-duodenitis before index-date (90 days), N (%)	92.0 (3.3)	5705.0 (2.5)	2788.0 (2.8)	521.0 (2.9)	72.0 (2.8)	5942.7 (2.6)	2603.2 (2.6)	403.3 (2.7)
Dyspepsia before index-date (90 days), N (%)	33.0 (1.2)	4182.0 (1.8)	2136.0 (2.1)	538.0 (3.0)	47.1 (1.9)	4513.2 (2.0)	1972.9 (2.0)	361.9 (2.4)
Gastro-duodenal symptoms before index-date (90 days), N (%)	391.0 (14.2)	41462.0 (18.1)	19287.0 (19.3)	4389.0 (24.4)	452.2 (17.9)	42924.0 (18.8)	18745.1 (18.8)	3319.5 (22.2)
Other gastro-duodenal diseases before index-date (any time), N (%)	22.0 (0.8)	832.0 (0.4)	414.0 (0.4)	92.0 (0.5)	14.6 (0.6)	891.9 (0.4)	390.7 (0.4)	68.7 (0.5)
Inflammatory bowel disease before index-date (any time), N (%)	37.0 (1.3)	4085.0 (1.8)	1675.0 (1.7)	341.0 (1.9)	40.6 (1.6)	4022.7 (1.8)	1761.6 (1.8)	296.3 (2.0)
Gastro-duodenal bleeding before index-date (90 days), N (%)	27.0 (1.0)	1861.0 (0.8)	597.0 (0.6)	72.0 (0.4)	26.5 (1.0)	1679.8 (0.7)	739.4 (0.7)	92.4 (0.6)
Diaphragmatic hernia before index-date (any time), N (%)	257.0 (9.4)	10565.0 (4.6)	4993.0 (5.0)	765.0 (4.3)	135.9 (5.4)	10872.5 (4.8)	4759.6 (4.8)	683.5 (4.6)
Post-surgical gastric syndromes before index-date (any time), N (%)	0.0 (0.0)	15.0 (0.0)	38.0 (0.0)	<6.0 (<0.1)	0.0 (0.0)	25.3 (0.0)	15.3 (0.0)	<6.0 (<1.0)

Gastrointestinal malignancy before index-date (any time), N (%)	13.0 (0.5)	540.0 (0.2)	372.0 (0.4)	34.0 (0.2)	9.0 (0.4)	635.7 (0.3)	281.1 (0.3)	36.2 (0.2)
Atherosclerosis before index-date (any time), N (%)	178.0 (6.5)	19553.0 (8.6)	11291.0 (11.3)	2613.0 (14.6)	205.2 (8.1)	22140.2 (9.7)	9653.7 (9.7)	1852.3 (12.4)
Heart disease before index-date (any time)	88.0 (3.2)	11528.0 (5.0)	6905.0 (6.9)	1911.0 (10.6)	115.6 (4.6)	13437.0 (5.9)	5849.0 (5.9)	1237.6 (8.3)
Acute prostate condition before index-date (365 days), N (%)	20.0 (0.7)	2156.0 (0.9)	942.0 (0.9)	185.0 (1.0)	21.1 (0.8)	2171.5 (1.0)	959.1 (1.0)	154.2 (1.0)
Chronic prostate condition before index-date (any time), N (%)	115.0 (4.2)	14692.0 (6.4)	6731.0 (6.7)	1180.0 (6.6)	135.5 (5.4)	14916.6 (6.5)	6486.4 (6.5)	1055.4 (7.1)
Genito-urinary disease before index-date (365 days), N (%)	15.0 (0.5)	1457.0 (0.6)	616.0 (0.6)	93.0 (0.5)	15.9 (0.6)	1427.1 (0.6)	626.3 (0.6)	84.1 (0.6)
Chronic kidney disease before index-date (any time), N (%)	65.0 (2.4)	10976.0 (4.8)	4985.0 (5.0)	1025.0 (5.7)	90.1 (3.6)	11232.6 (4.9)	4901.9 (4.9)	902.1 (6.0)
Malignancy in pelvic region before index-date (365 days), N (%)	24.0 (0.9)	2847.0 (1.2)	1223.0 (1.2)	185.0 (1.0)	24.5 (1.0)	2818.7 (1.2)	1226.6 (1.2)	191.2 (1.3)
Chronic obstructive respiratory disease before index-date (any time), N (%)	303.0 (11.0)	30795.0 (13.5)	13146.0 (13.2)	2251.0 (12.5)	332.3 (13.1)	30503.8 (13.4)	13321.6 (13.4)	2070.3 (13.8)
Depression before index-date (365 days)	85.0 (3.1)	7895.0 (3.5)	3378.0 (3.4)	633.0 (3.5)	92.8 (3.7)	7864.0 (3.4)	3448.4 (3.5)	536.7 (3.6)
Anxiety before index-date (any time), N (%)	458.0 (16.7)	40766.0 (17.8)	17540.0 (17.6)	2907.0 (16.2)	437.3 (17.3)	40416.0 (17.7)	17659.0 (17.7)	2636.4 (17.6)
Behaviour and sexuality disorders before index-date (any time), N (%)	28.0 (1.0)	3832.0 (1.7)	1498.0 (1.5)	297.0 (1.7)	36.0 (1.4)	3706.5 (1.6)	1608.6 (1.6)	239.4 (1.6)
Alzheimer's or other dementia before index-date (any time), N (%)	44.0 (1.6)	3719.0 (1.6)	2179.0 (2.2)	283.0 (1.6)	38.4 (1.5)	4082.5 (1.8)	1772.2 (1.8)	286.0 (1.9)
Autonomic neuropathies before index-date (any time), N (%)	9.0 (0.3)	821.0 (0.4)	424.0 (0.4)	76.0 (0.4)	8.9 (0.4)	866.3 (0.4)	378.7 (0.4)	65.0 (0.4)
Diabetes before index-date (any time), N (%)	186.0 (6.8)	17696.0 (7.7)	8476.0 (8.5)	1476.0 (8.2)	189.9 (7.5)	18242.4 (8.0)	7935.1 (8.0)	1259.0 (8.4)
Hyperprolactinaemia before index-date (any time), N (%)	0.0 (0.0)	15.0 (0.0)	10.0 (0.0)	<6.0 (<0.1)	0.0 (0.0)	16.6 (0.0)	6.8 (0.0)	<6.0 (<0.1)
Hypogonadism disorders before index-date (any time), N (%)	<6.0 (<0.2)	433.0 (0.2)	229.0 (0.2)	35.0 (0.2)	<6.0 (<0.3)	458.9 (0.2)	199.0 (0.2)	29.8 (0.2)
Hypothyroidism before index-date (any time), N (%)	34.0 (1.2)	3321.0 (1.5)	1420.0 (1.4)	280.0 (1.6)	41.8 (1.7)	3310.5 (1.4)	1446.4 (1.5)	237.4 (1.6)
Demyelinating disorders before index-date (any time), N (%)	<6.0 (<0.2)	309.0 (0.1)	147.0 (0.1)	33.0 (0.2)	<6.0 (<0.2)	322.4 (0.1)	141.7 (0.1)	26.0 (0.2)
Parkinson's (or related) disorders before index-date (any time), N (%)	12.0 (0.4)	1243.0 (0.5)	617.0 (0.6)	92.0 (0.5)	8.8 (0.3)	1288.3 (0.6)	562.9 (0.6)	96.3 (0.6)
Cerebrovascular disease before index-date (any time), N (%)	55.0 (2.0)	7219.0 (3.2)	4575.0 (4.6)	739.0 (4.1)	70.7 (2.8)	8288.5 (3.6)	3593.7 (3.6)	660.7 (4.4)
NSAIDs before index-date (90 days), N (%)	948.0 (34.5)	73594.0 (32.2)	24807.0 (24.9)	2326.0 (13.0)	824.1 (32.5)	66521.9 (29.1)	29009.1 (29.1)	2807.9 (18.8)

NSAIDs before index (90 days) or NSAIDs treatment, N (%)	948.0 (34.5)	73594.0 (32.2)	24807.0 (24.9)	2326.0 (13.0)	824.1 (32.5)	66521.9 (29.1)	29009.1 (29.1)	2807.9 (18.8)
Salicylate derivatives before index-date (90 days), N (%)	213.0 (7.8)	25243.0 (11.0)	13535.0 (13.6)	2878.0 (16.0)	262.7 (10.4)	27554.6 (12.1)	12038.2 (12.1)	2207.3 (14.8)
Glucocorticoids before index-date (90 days), N (%)	75.0 (2.7)	11864.0 (5.2)	5237.0 (5.3)	1048.0 (5.8)	97.4 (3.8)	11966.4 (5.2)	5216.4 (5.2)	902.6 (6.0)
Anti-thrombotics before index-date (90 days), N (%)	269.0 (9.8)	31859.0 (13.9)	18205.0 (18.3)	3846.0 (21.4)	328.7 (13.0)	35632.6 (15.6)	15527.8 (15.6)	2948.6 (19.7)
Anti-infectives before index-date (90 days), N (%)	429.0 (15.6)	35249.0 (15.4)	16586.0 (16.6)	2904.0 (16.2)	375.0 (14.8)	36186.6 (15.8)	15849.7 (15.9)	2493.1 (16.7)
Any antineoplastics before index-date (90 days), N (%)	<6.0 (<0.3)	1192.0 (0.5)	551.0 (0.6)	129.0 (0.7)	7.5 (0.3)	1234.7 (0.5)	533.9 (0.5)	117.4 (0.8)
PPIs before index-date (any time), N (%)	1353.0 (49.2)	92913.0 (40.7)	41876.0 (42.0)	5386.0 (30.0)	1078.9 (42.6)	92698.2 (40.6)	40396.1 (40.5)	5703.0 (38.1)
H2RAs before index-date (any time), N (%)	393.0 (14.3)	25210.0 (11.0)	12961.0 (13.0)	4929.0 (27.5)	338.3 (13.4)	28496.6 (12.5)	12418.4 (12.5)	2572.6 (17.2)
Cytostatic anti-androgens before index-date (180 days), N (%)	18.0 (0.7)	1904.0 (0.8)	929.0 (0.9)	108.0 (0.6)	18.1 (0.7)	1957.5 (0.9)	857.7 (0.9)	120.6 (0.8)
Diuretics before index-date (180 days), N (%)	144.0 (5.2)	18761.0 (8.2)	9175.0 (9.2)	1906.0 (10.6)	181.2 (7.2)	19719.3 (8.6)	8615.6 (8.6)	1540.8 (10.3)
Beta-blockers before index-date (180 days), N (%)	194.0 (7.1)	21142.0 (9.3)	10697.0 (10.7)	2339.0 (13.0)	227.6 (9.0)	22582.8 (9.9)	9860.4 (9.9)	1770.5 (11.8)
Anti-adrenergics before index-date (180 days), N (%)	43.0 (1.6)	4329.0 (1.9)	2091.0 (2.1)	456.0 (2.5)	47.2 (1.9)	4552.5 (2.0)	1986.0 (2.0)	363.5 (2.4)
ACEi/ARBs before index-date (180 days), N (%)	324.0 (11.8)	39063.0 (17.1)	18289.0 (18.3)	3458.0 (19.3)	388.6 (15.3)	40152.6 (17.6)	17534.0 (17.6)	2861.7 (19.1)
Centrally acting anti-hypertensives before index-date (180 days), N (%)	<6.0 (<0.2)	274.0 (0.1)	192.0 (0.2)	27.0 (0.2)	<6.0 (<0.2)	328.6 (0.1)	143.0 (0.1)	24.8 (0.2)
Digitalis glycosides before index-date (180 days), N (%)	14.0 (0.5)	1675.0 (0.7)	926.0 (0.9)	230.0 (1.3)	17.9 (0.7)	1878.0 (0.8)	815.0 (0.8)	173.0 (1.2)
Amiodarone, Disopyramide before Index-date (180 days), N (%)	<6.0 (<0.2)	514.0 (0.2)	298.0 (0.3)	85.0 (0.5)	<6.0 (<0.3)	594.5 (0.3)	259.3 (0.3)	56.3 (0.4)
Prostatic hypertrophy treatment before index-date (180 days), N (%)	73.0 (2.7)	9582.0 (4.2)	4258.0 (4.3)	741.0 (4.1)	88.1 (3.5)	9633.3 (4.2)	4193.6 (4.2)	674.6 (4.5)
Ketoconazole, terbinafine before index-date (180 days), N (%)	10.0 (0.4)	980.0 (0.4)	396.0 (0.4)	80.0 (0.4)	9.9 (0.4)	959.9 (0.4)	419.3 (0.4)	68.0 (0.5)
Antidepressants (negative) before index-date (180 days), N (%)	218.0 (7.9)	23162.0 (10.1)	10031.0 (10.1)	1637.0 (9.1)	246.8 (9.7)	22999.7 (10.1)	10056.8 (10.1)	1534.6 (10.3)
Antidepressants (positive) before index-date (180 days), N (%)	38.0 (1.4)	4153.0 (1.8)	1720.0 (1.7)	288.0 (1.6)	41.4 (1.6)	4067.0 (1.8)	1777.1 (1.8)	276.9 (1.9)
Antipsychotics before index-date (180 days), N (%)	27.0 (1.0)	3118.0 (1.4)	1512.0 (1.5)	261.0 (1.5)	34.5 (1.4)	3232.0 (1.4)	1413.1 (1.4)	228.5 (1.5)
Anxiolytics (negative) before index-date (180 days), N (%)	52.0 (1.9)	5844.0 (2.6)	2510.0 (2.5)	495.0 (2.8)	56.6 (2.2)	5851.5 (2.6)	2566.6 (2.6)	413.1 (2.8)

Anxiolytics (positive) before index-date (180 days), N (%)	<6.0 (<0.2)	131.0 (0.1)	58.0 (0.1)	7.0 (0.0)	<6.0 (<0.2)	133.0 (0.1)	59.6 (0.1)	7.3 (0.0)
Antiepileptics (negative) before index-date (180 days), N (%)	27.0 (1.0)	2533.0 (1.1)	1187.0 (1.2)	254.0 (1.4)	29.1 (1.1)	2630.2 (1.2)	1153.6 (1.2)	192.9 (1.3)
Antiepileptics (positive) before index-date (180 days), N (%)	6.0 (0.2)	865.0 (0.4)	426.0 (0.4)	78.0 (0.4)	7.8 (0.3)	901.3 (0.4)	391.9 (0.4)	69.4 (0.5)
Opioids before index-date (180 days)	30.0 (1.1)	3737.0 (1.6)	2015.0 (2.0)	240.0 (1.3)	33.5 (1.3)	3972.5 (1.7)	1744.8 (1.8)	267.7 (1.8)
Lipid lowering treatment before index-date (180 days), N (%)	392.0 (14.3)	42966.0 (18.8)	21183.0 (21.2)	3900.0 (21.7)	436.2 (17.2)	44951.5 (19.7)	19656.3 (19.7)	3232.2 (21.6)
Anti-parkinsonian drugs before index-date (180 days), N (%)	8.0 (0.3)	1350.0 (0.6)	652.0 (0.7)	94.0 (0.5)	11.4 (0.4)	1377.9 (0.6)	602.7 (0.6)	94.4 (0.6)
Prolactin inhibitors before index-date (180 days), N (%)	0.0 (0.0)	30.0 (0.0)	14.0 (0.0)	<6.0 (<0.1)	0.0 (0.0)	30.5 (0.0)	13.7 (0.0)	<6.0 (<0.1)
Selected antineoplastics before index-date (180 days), N (%)	0.0 (0.0)	338.0 (0.1)	140.0 (0.1)	28.0 (0.2)	0.0 (0.0)	346.2 (0.2)	134.8 (0.1)	26.5 (0.2)
Hypothyroidism treatment before index-date (365 days), N (%)	45.0 (1.6)	4956.0 (2.2)	2226.0 (2.2)	422.0 (2.4)	56.4 (2.2)	5012.5 (2.2)	2179.5 (2.2)	360.5 (2.4)
Acetazolamide, aminocaproic acid before index-date (180 days), N (%)	<6.0 (<0.1)	40.0 (0.0)	23.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.2)	39.8 (0.0)	20.9 (0.0)	<6.0 (<0.1)
Obesity diagnosis, treatment, adiposity measure or BMI >25 Kg/m^2 before index-date (365 days), N (%)	583.0 (21.2)	50150.0 (21.9)	23954.0 (24.0)	4019.0 (22.4)	567.6 (22.4)	51596.8 (22.6)	22583.3 (22.7)	3415.7 (22.8)
BMI >30 Kg/m^2 before index-date (365 days), N (%)	258.0 (9.4)	22222.0 (9.7)	10491.0 (10.5)	1601.0 (8.9)	239.9 (9.5)	22664.0 (9.9)	9924.5 (10.0)	1457.4 (9.7)
Current smoker (365 days), N (%)	418.0 (15.2)	34168.0 (15.0)	16663.0 (16.7)	3289.0 (18.3)	404.2 (16.0)	35726.8 (15.6)	15647.6 (15.7)	2525.4 (16.9)
Substance abuse diagnosis (including alcoholism) before index-date (365 days), N (%)	363.0 (13.2)	26819.0 (11.7)	14768.0 (14.8)	2333.0 (13.0)	336.0 (13.3)	29126.6 (12.7)	12793.9 (12.8)	1989.2 (13.3)

IPTW: inverse probability of treatment weighting; GERD: Gastroesophageal reflux disease; PPIs: Proton pump inhibitors; H2RA: Histamine type 2 receptor antagonists; ACEi/ARBs: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs); NSAIDs: nonsteroidal anti-inflammatory drugs; BMI: body mass index.

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

Table 5. Unadjusted and adjusted incidence rates (IR) per 100 person-years of sexual dysfunction by treatment arm and database using ITT analytical approach

	Treatment arm	N (persons)	N index-dates	Follow-up (person-years)	n events	Unadjusted			Stabilized IPTW adjusted		
						IR	95% CI		IR	95% CI	
IQVIA™ DA Germany	H2RAs	14038	16496	15651.12	83	**0.53**	0.43	0.66	**0.54**	0.40	0.72
	Esomeprazole	28702	33469	31081.77	152	**0.49**	0.42	0.57	**0.50**	0.42	0.59
	Omeprazole	109553	138943	130896.90	730	**0.56**	0.52	0.60	**0.52**	0.48	0.57
	Pantoprazole	332811	429075	400557.80	2009	**0.50**	0.48	0.52	**0.52**	0.49	0.54
IMRD UK	H2RAs	16432	17952	17083.49	253	**1.48**	1.31	1.68	**1.53**	1.33	1.77
	Esomeprazole	2553	2748	2639.35	28	**1.06**	0.73	1.54	**0.97**	0.65	1.45
	Omeprazole	172555	228505	217956.70	2608	**1.20**	1.15	1.24	**1.22**	1.17	1.27
	Lansoprazole	81310	99726	94475.83	1133	**1.20**	1.13	1.27	**1.16**	1.09	1.23

ITT: intention-to-treat analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

Table 6. Unadjusted and adjusted hazard ratios (HR) of sexual dysfunction by treatment arm and database using ITT analytical approach

		Target arm: Esomeprazole						Target arm: Omeprazole					
		Unadjusted			Stabilized IPTW adjusted			Unadjusted			Stabilized IPTW adjusted		
	Treatment arm	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
IQVIA™ DA Germany	H2RAs	**1.08**	0.83	1.42	**1.08**	0.77	1.51	**0.95**	0.76	1.19	**1.03**	0.76	1.39
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.88**	0.74	1.05	**0.96**	0.79	1.16
	Omeprazole	**1.14**	0.96	1.36	**1.05**	0.86	1.27	**1.00**	[Reference]		**1.00**	[Reference]	
	Pantoprazole	**1.03**	0.87	1.21	**1.04**	0.87	1.24	**0.90**	0.83	0.98	**0.99**	0.90	1.09
IMRD UK	H2RAs	**1.40**	0.95	2.06	**1.59**	1.03	2.43	**1.24**	1.09	1.41	**1.26**	1.08	1.46
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.89**	0.61	1.29	**0.79**	0.53	1.19
	Omeprazole	**1.13**	0.78	1.64	**1.26**	0.84	1.90	**1.00**	[Reference]		**1.00**	[Reference]	
	Lansoprazole	**1.13**	0.78	1.64	**1.20**	0.80	1.80	**1.00**	0.93	1.07	**0.95**	0.88	1.02

ITT: intention-to-treat analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

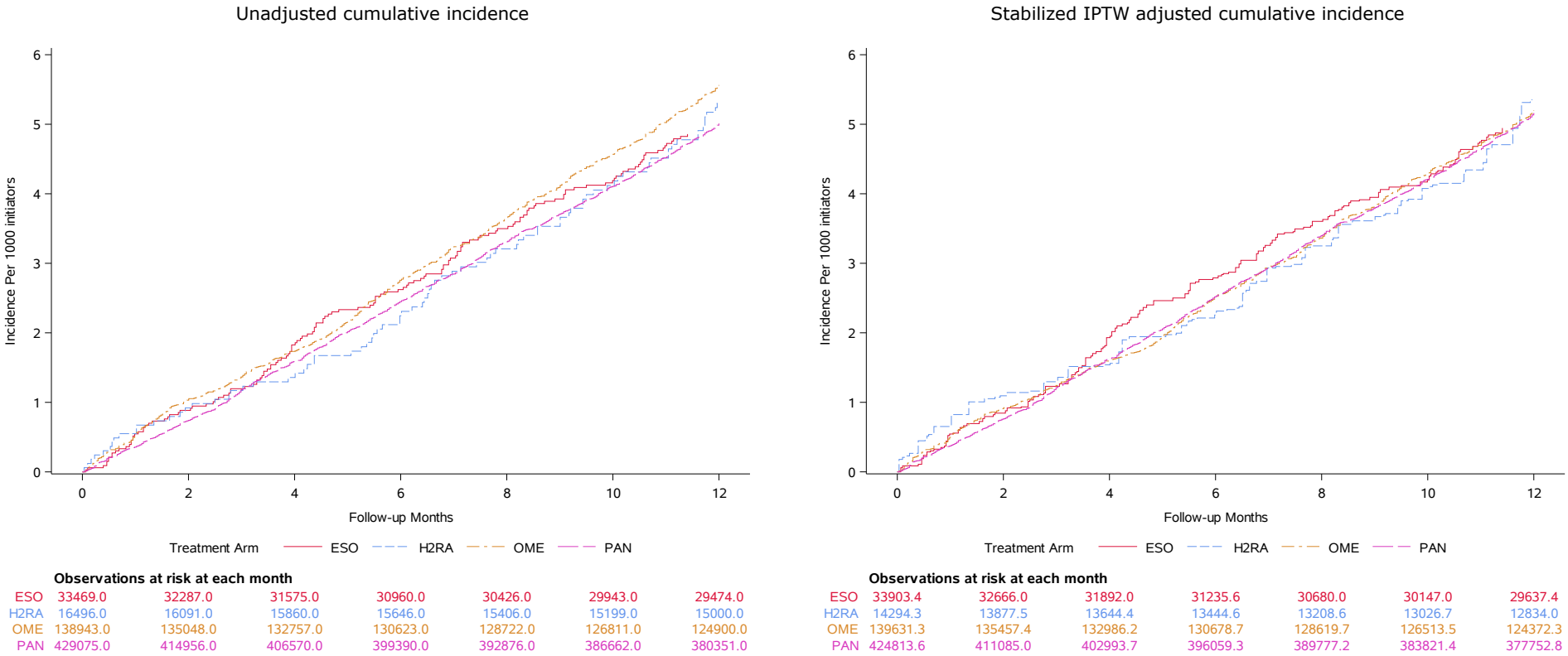

Figure 5. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IQVIA™ DA Germany using ITT analytical approach

ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; PAN: Pantoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-to-treat analysis.

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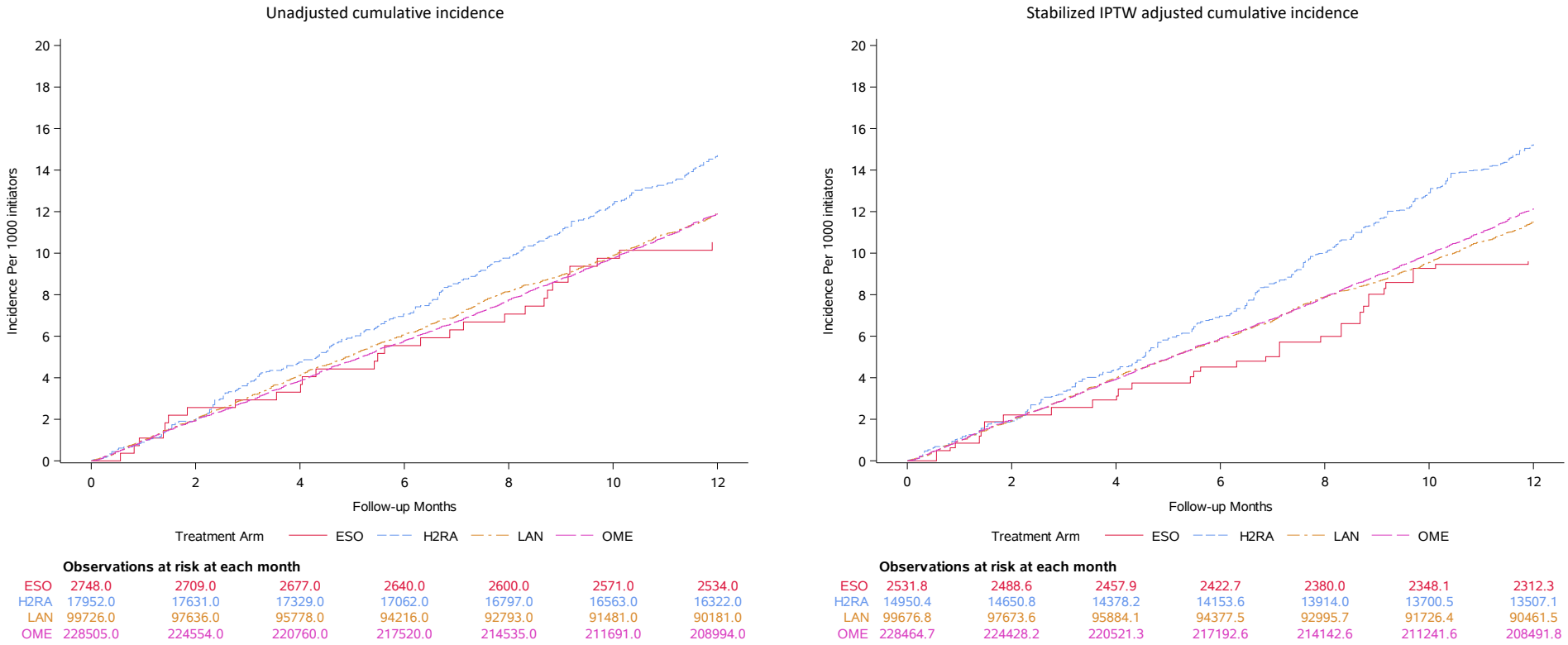

670 Figure 6. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IMRD UK using ITT analytical approach

671 ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; LAN: Lansoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-
672 to-treat analysis.

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6.2. Comparison between esomeprazole/omeprazole and non-initiators of treatment cohort

6.2.1. Descriptive results

Of the 442,259 and 244,063 patients included in the study comparing treatment cohorts in IQVIA™ DA Germany and IMRD UK, respectively, 307,875 and 147,252 remained after restricting to selected indications of interest for which treatment is likely to be chronic (Figure *3* and Figure *4*). Additionally, a sample of patients with the selected indications who did not initiate treatment with PPIs or H2RA on index-date was identified, matching by age and index-date to the patients with selected indications who initiated esomeprazole or omeprazole. Thus, 96,060 and 84,607 patients from IQVIA™ DA Germany and IMRD UK, respectively, were included in the study compromising the non-initiator of treatment cohort (Figure *3* and Figure *4*).

A total of 2,608 and 3,996 incident cases of SD were identified within the 1-year follow-up period, in IQVIA™ DA Germany and for IMRD UK, respectively. The clinical terms which most contributed to the SD definition were failure of genital response (90%), and impotence of organic origin (5%) in IQVIA™ DA Germany. In IMRD UK, erectile dysfunction (62%), complains of erectile dysfunction (16%) and impotence (15%) were the clinical terms that most contributed to the SD definition (Annex 3, Table A*3* and Table A*4*).

Table *7*shows the baseline characteristics for the four treatment cohorts and the non-initiator of treatment cohort in IQVIA™ DA Germany. Before IPTW:

- Patients who did not have a prescription for PPIs/H2RAs (non-initiator cohort) were less likely to have received a diagnosis of GERD, gastrointestinal infection, chronic prostate condition, chronic obstructive respiratory disease, and depression than patients initiating treatment with PPIs or H2RAS. They were also less likely to have received a prescription for NSAIDs, anti-infectives, antidepressants, and hypothyroidism treatment.

Table 8 shows the baseline characteristics for the four treatment cohorts and the non-initiator of treatment cohort in IMRD UK. Before IPTW:

- Patients who did not have a prescription for PPIs/H2RAs (non-initiator cohort) were less likely to be current smokers and to have received a diagnosis of gastrointestinal infection, esophagitis, other esophageal disease, acute gastro-duodenitis, dyspepsia, and gastro-duodenal symptoms than patients initiating treatment with PPIs or H2RAS. They were also less likely to have received a prescription for NSAIDs, anti-infectives, and opioids. In addition, they were more likely to have received a prescription for anti-trombotics, ACEi/ARBs, and lipid lowering treatment than patients initiating PPIs.

The absolute standardized differences between treatment arms for each baseline covariate before and after stabilized IPTW are shown in Figure A*7* and Figure A*8* for IQVIA™ DA Germany and in Figure A*9* and Figure A*10* for IMRD UK. The treatment groups were well balanced across all covariates after IPTW, with most of absolute standardized differences <10, except for index-year, diagnosis of acute gastro-duodenitis, and prescription of H2RAs before index-date in IQVIA™ DA Germany. Of note, the median of index-year was 2015-2016 for the four treatment cohorts and the non-initiator cohort after IPTW adjustment.

In IMRD UK, treatment groups were well balanced across all covariates after IPTW, with most of absolute standardized differences <10, except for index-year, diagnosis of gastroduodenal symptoms, atherosclerosis, and heart disease, and prescription of NSAIDs, antithrombotics, and glucocorticoids,

H2RAs before index-date. Of note, the median of index-year was 2014 for the four treatment cohorts and the non-initiator cohort after IPTW adjustment.

6.2.2. Intention-to-treat (ITT) analysis

Incidence rates (IR)

In IQVIA™ DA Germany, the unadjusted IR per 100 person-years of SD varied from 0.43 [95% CI: 0.39; 0.47] in the non-initiator cohort to 0.64 [95% CI: 0.49; 0.83] in the H2RAs cohort (Table *9*). Differences in IRs across treatment cohorts remained similar after IPTW adjustment.

In IMRD UK, the unadjusted IR per 100 person-years of SD were higher than in IQVIA™ DA Germany and varied from 1.15 [95% CI: 0.73; 1.81] in the esomeprazole cohort to 1.69 [95% CI: 1.43; 2.00] in the H2RAs cohort (Table *9*). Differences in the IRs across treatment cohorts slightly increased after IPTW adjustment, varying from 1.17 [95% CI: 1.10; 1.25] in the non-initiator cohort to 1.72 [95% CI: 1.40; 2.12] in the H2RAs cohort.

Cumulative incidence (Incidence proportion)

The unadjusted and IPTW adjusted cumulative incidence curves of SD by cohort are displayed in Figure *7* for IQVIA™ DA Germany. The unadjusted cumulative incidence curves of all treatment cohorts exhibited a trend of gradual and approximately linear increase over time, crossing at different points throughout the 1-year follow-up period. The cumulative risk for SD in the non-initiator cohort was the lowest from the 7-month follow-up of the five cohorts. The adjusted IPTW cumulative incidence curves showed a similar pattern of gradual increase and crossing at different points throughout the 1-year follow-up period. While the cumulative risk for SD in the H2RA was the highest during the first 3-month follow-up, that of the non-initiator cohort was the lowest from the 6-month follow-up. Of note, the number of events and follow-up time of the H2RA cohort were limited.

The unadjusted and IPTW adjusted cumulative incidence curves of SD by cohort are displayed in Figure *8* for IMRD UK. The unadjusted cumulative incidence curves of all cohorts exhibited a trend of gradual increase over time. The cumulative risk for SD in the H2RA and lansoprazole cohorts remained higher than the cumulative incidence of the other cohorts from the 4-month follow-up. Of note, the number of events and follow-up time of the esomeprazole cohort were very limited. A similar pattern was observed in the IPTW adjusted cumulative incidence curves of SD, with accentuated differences between the H2RA and the non-initiator cohorts.

Hazard ratios (HR)

Table *10* shows the unadjusted and IPTW adjusted HRs of SD for both databases. In IQVIA™ DA Germany, a slightly increased risk for SD was observed in the H2RAs, omeprazole and pantoprazole cohorts and lower risk in the non-initiator cohort when compared to esomeprazole cohort in the unadjusted analysis. The increased risk remained in the H2RA and pantoprazole cohorts, was attenuated in the omeprazole cohort and remained the same in the non-initiator cohort after IPTW adjustment. However, the associated uncertainty reflected by the 95% confidence intervals was compatible with similar, higher and lower risk of SD in H2RAs, omeprazole and pantoprazole initiators in comparison to esomeprazole initiators.

A slightly increased risk for SD was observed in the H2RAs cohort and lower risk in the esomeprazole, pantoprazole and non-initiator cohorts when compared to omeprazole cohort in the unadjusted analysis. The associated uncertainty of the unadjusted and IPTW adjusted HRs was also compatible with similar, higher and lower risk of SD in H2RAs, esomeprazole and pantoprazole initiators in

comparison to omeprazole initiators, but compatible with lower risk and incompatible with higher risk in the non-initiator cohort.

In IMRD UK, the unadjusted risk for SD was 3% (non-initiators) to 47% (H2RAs) higher in the alternative treatment cohorts than in the esomeprazole cohort. These risks were attenuated after adjustment for IPTW: 5% lower risk in the non-initiator cohort and 40% higher risk in the H2RA initiators compared to esomeprazole cohort. However, the associated uncertainty was also compatible with similar, higher and lower risk of SD in alternative treatment and non-initiator cohorts compared to the esomeprazole cohort.

A higher risk of SD was observed in the H2RAs and lansoprazole cohorts, and lower risk in the esomeprazole, and non-initiator cohorts when compared to omeprazole cohort in the unadjusted analysis. While the associated uncertainty of the unadjusted and IPTW adjusted HRs in the H2RA cohort was compatible with higher risk but incompatible with lower risk of SD when compared to the omeprazole cohort, that for the non-initiator cohort was compatible with lower risk but incompatible with higher risk of SD.

6.2.3. Supplementary analysis (Per-protocol analysis)

A total of 2,489 and 3,759 incident cases of SD were identified in IQVIA™ DA Germany and IMRD UK, respectively, following patients from treatment initiation to treatment change or censoring. The clinical terms which most contributed to the SD case definition were failure of genital response (90%), and impotence of organic origin (5%) in IQVIA™ DA Germany (Annex 3, Table A*3*). In IMRD UK, erectile dysfunction (62%), complains of erectile dysfunction (16%) and impotence (15%) were the clinical terms that most contributed to the SD definition (Annex 3, Table A*4*).

Table A*7* and Table A*8* show IRs per 100 person-years and HRs of SD, respectively, for the four treatment cohorts and the non-initiator cohort in both databases. Figure A*11* and Figure A*12* display cumulative incidence of SD for the five cohorts in both databases, respectively. Results were consistent with those of the main analyses. It should be noted that in this population restricted to selected indications, the adjusted point estimate HRs (Table A8) were very similar between IQVIA™ DA Germany and IMRD UK.

In IQVIA™ DA Germany, the percentage of patients followed until the end of the 1-year follow-up period without changing the baseline treatment varied between 73% in H2RA cohort and 86% in pantoprazole cohort. The percentage of those who switched treatment during the 1-year follow-up were slightly lower on the PPI cohorts (4-13%) and the non-initiator cohort (11%) compared to H2I cohort (19%). In IMRD UK, the percentage of patients followed until the end of the 1-year follow-up period without changing the baseline treatment varied between 70% in H2RA cohort and 85% in omeprazole cohort.

Table 7. Baseline characteristics of the study population in IQVIA™ DA Germany

Covariates	Before stabilized IPTW (unadjusted)					After stabilized IPTW (adjusted)				
	Esomeprazole	Omeprazole	Pantoprazole	H2RAs	Non-initiators	Esomeprazole	Omeprazole	Pantoprazole	H2RAs	Non-initiators
N	23660	92596	293874	9596	116253	24002.7	92903.6	288850.7	9396.8	101240.1
Age at index-date, median (IQR)	57.0 (46.0-69.0)	56.0 (44.0-69.0)	58.0 (45.0-71.0)	57.0 (43.0-70.0)	56.0 (44.0-69.0)	57.0 (45.0-70.0)	57.0 (45.0-70.0)	57.0 (45.0-70.0)	57.0 (44.0-70.0)	57.0 (45.0-70.0)
Index year, median (IQR)	2015 (2012-2018)	2013 (2009-2017)	2016 (2014-2019)	2012 (2008-2016)	2014 (2009-2017)	2016 (2012-2019)	2016 (2012-2019)	2015 (2012-2018)	2015 (2010-2018)	2016 (2011-2018)
GERD before index-date (any time), N (%)	12866.0 (54.4)	44072.0 (47.6)	122291.0 (41.6)	4109.0 (42.8)	46223.0 (39.8)	10380.2 (43.2)	40615.3 (43.7)	125479.4 (43.4)	4243.6 (45.2)	43403.3 (42.9)
Gastro-duodenal ulcer before index-date (any time), N (%)	2229.0 (9.4)	9680.0 (10.5)	25386.0 (8.6)	968.0 (10.1)	13203.0 (11.4)	2300.0 (9.6)	9003.4 (9.7)	27278.0 (9.4)	949.4 (10.1)	9570.9 (9.5)
Chronic gastro-duodenitis before index-date (any time), N (%)	3387.0 (14.3)	13182.0 (14.2)	33900.0 (11.5)	1797.0 (18.7)	16649.0 (14.3)	3161.0 (13.2)	12386.7 (13.3)	37472.4 (13.0)	1401.2 (14.9)	13429.9 (13.3)
Zollinger-Ellison syndrome before index-date (any time), N (%)	<6.0 (<0.1)	8.0 (0.0)	33.0 (0.0)	<6.0 (<0.1)	<6.0 (0.0)	<6.0 (<0.1)	11.7 (0.0)	27.2 (0.0)	<6.0 (<0.1)	7.7 (0.0)
Gastrointestinal infection before index-date (90 days), N (%)	963.0 (4.1)	4871.0 (5.3)	13277.0 (4.5)	816.0 (8.5)	1996.0 (1.7)	999.1 (4.2)	3886.8 (4.2)	11881.6 (4.1)	532.4 (5.7)	3901.1 (3.9)
Esophagitis before index-date (365 days), N (%)	179.0 (0.8)	343.0 (0.4)	923.0 (0.3)	31.0 (0.3)	77.0 (0.1)	74.5 (0.3)	277.0 (0.3)	846.0 (0.3)	47.2 (0.5)	200.8 (0.2)
Other esophageal disease before index-date (any time), N (%)	1138.0 (4.8)	2711.0 (2.9)	7848.0 (2.7)	144.0 (1.5)	3690.0 (3.2)	706.6 (2.9)	2930.9 (3.2)	8770.3 (3.0)	237.8 (2.5)	3017.2 (3.0)
Acute gastro-duodenitis before index-date (90 days), N (%)	3246.0 (13.7)	15598.0 (16.8)	42069.0 (14.3)	1937.0 (20.2)	736.0 (0.6)	2833.5 (11.8)	11253.0 (12.1)	34402.2 (11.9)	1359.9 (14.5)	2510.9 (2.5)
Dyspepsia before index-date (90 days), N (%)	123.0 (0.5)	439.0 (0.5)	1250.0 (0.4)	72.0 (0.8)	84.0 (0.1)	86.5 (0.4)	369.0 (0.4)	1063.3 (0.4)	52.2 (0.6)	235.9 (0.2)
Gastro-duodenal symptoms before index-date (90 days), N (%)	1983.0 (8.4)	7007.0 (7.6)	21846.0 (7.4)	837.0 (8.7)	1296.0 (1.1)	1527.2 (6.4)	5935.5 (6.4)	18006.8 (6.2)	762.8 (8.1)	3920.2 (3.9)
Other gastro-duodenal diseases before index-date (any time), N (%)	850.0 (3.6)	3058.0 (3.3)	8706.0 (3.0)	328.0 (3.4)	2658.0 (2.3)	695.3 (2.9)	2797.1 (3.0)	8510.3 (2.9)	329.8 (3.5)	3018.5 (3.0)
Inflammatory bowel disease before index-date (any time), N (%)	2283.0 (9.6)	7738.0 (8.4)	26705.0 (9.1)	727.0 (7.6)	8566.0 (7.4)	2173.0 (9.1)	8160.5 (8.8)	25268.9 (8.7)	892.6 (9.5)	8541.2 (8.4)
Gastro-duodenal bleeding before index-date (90 days), N (%)	190.0 (0.8)	596.0 (0.6)	3371.0 (1.1)	27.0 (0.3)	140.0 (0.1)	175.7 (0.7)	707.7 (0.8)	2354.4 (0.8)	49.0 (0.5)	429.1 (0.4)
Diaphragmatic hernia before index-date (any time), N (%)	2332.0 (9.9)	5907.0 (6.4)	16818.0 (5.7)	380.0 (4.0)	9339.0 (8.0)	1567.8 (6.5)	6478.2 (7.0)	19516.9 (6.8)	553.2 (5.9)	6554.3 (6.5)
Post-surgical gastric syndromes before index-date (any time), N (%)	11.0 (0.0)	60.0 (0.1)	157.0 (0.1)	7.0 (0.1)	34.0 (0.0)	12.0 (0.1)	49.9 (0.1)	145.0 (0.1)	11.4 (0.1)	52.7 (0.1)

Gastrointestinal malignancy before index-date (any time), N (%)	170.0 (0.7)	308.0 (0.3)	1225.0 (0.4)	29.0 (0.3)	374.0 (0.3)	99.5 (0.4)	354.4 (0.4)	1146.3 (0.4)	46.5 (0.5)	400.8 (0.4)
Atherosclerosis before index-date (any time), N (%)	5682.0 (24.0)	21949.0 (23.7)	79952.0 (27.2)	2757.0 (28.7)	28811.0 (24.8)	6266.2 (26.1)	23563.0 (25.4)	74806.1 (25.9)	2638.3 (28.1)	26239.4 (25.9)
Heart disease before index-date (any time), N (%)	2497.0 (10.6)	10063.0 (10.9)	41306.0 (14.1)	1325.0 (13.8)	14159.0 (12.2)	3160.8 (13.2)	11534.2 (12.4)	37474.6 (13.0)	1312.8 (14.0)	13130.7 (13.0)
Acute prostate condition before index-date (365 days), N (%)	154.0 (0.7)	610.0 (0.7)	1652.0 (0.6)	59.0 (0.6)	436.0 (0.4)	129.9 (0.5)	483.3 (0.5)	1577.4 (0.5)	61.3 (0.7)	542.3 (0.5)
Chronic prostate condition before index-date (any time), N (%)	3682.0 (15.6)	14204.0 (15.3)	49412.0 (16.8)	1558.0 (16.2)	15187.0 (13.1)	3768.9 (15.7)	14507.7 (15.6)	45625.6 (15.8)	1588.8 (16.9)	15815.4 (15.6)
Genito-urinary disease before index-date (365 days), N (%)	101.0 (0.4)	376.0 (0.4)	1260.0 (0.4)	33.0 (0.3)	343.0 (0.3)	102.5 (0.4)	371.3 (0.4)	1164.6 (0.4)	36.5 (0.4)	400.9 (0.4)
Chronic kidney disease before index-date (any time), N (%)	477.0 (2.0)	1578.0 (1.7)	8714.0 (3.0)	188.0 (2.0)	2123.0 (1.8)	601.6 (2.5)	2162.7 (2.3)	7193.2 (2.5)	260.1 (2.8)	2514.8 (2.5)
Malignancy in pelvic region before index-date (365 days), N (%)	326.0 (1.4)	1312.0 (1.4)	5118.0 (1.7)	142.0 (1.5)	1179.0 (1.0)	348.8 (1.5)	1375.1 (1.5)	4411.9 (1.5)	150.8 (1.6)	1489.3 (1.5)
Chronic obstructive respiratory disease before index-date (any time), N (%)	5642.0 (23.8)	23337.0 (25.2)	75276.0 (25.6)	2588.0 (27.0)	23969.0 (20.6)	5968.7 (24.9)	22598.7 (24.3)	70911.2 (24.5)	2580.1 (27.5)	25010.2 (24.7)
Depression before index-date (365 days), N (%)	1316.0 (5.6)	5683.0 (6.1)	18573.0 (6.3)	650.0 (6.8)	4539.0 (3.9)	1431.0 (6.0)	5366.2 (5.8)	16865.3 (5.8)	675.2 (7.2)	5974.6 (5.9)
Anxiety before index-date (any time), N (%)	4905.0 (20.7)	21082.0 (22.8)	68913.0 (23.4)	2277.0 (23.7)	21777.0 (18.7)	5460.2 (22.7)	20679.9 (22.3)	64729.9 (22.4)	2380.0 (25.3)	22589.0 (22.3)
Behaviour and sexuality disorders before index-date (any time), N (%)	241.0 (1.0)	1216.0 (1.3)	4686.0 (1.6)	136.0 (1.4)	1357.0 (1.2)	361.5 (1.5)	1316.5 (1.4)	4180.2 (1.4)	166.3 (1.8)	1434.6 (1.4)
Alzheimer's or other dementia before index-date (any time), N (%)	569.0 (2.4)	1934.0 (2.1)	8607.0 (2.9)	233.0 (2.4)	2327.0 (2.0)	650.6 (2.7)	2292.4 (2.5)	7444.8 (2.6)	285.0 (3.0)	2629.9 (2.6)
Autonomic neuropathies before index-date (any time), N (%)	565.0 (2.4)	2390.0 (2.6)	10107.0 (3.4)	294.0 (3.1)	3042.0 (2.6)	759.6 (3.2)	2854.4 (3.1)	8905.4 (3.1)	319.4 (3.4)	3156.4 (3.1)
Diabetes before index-date (any time), N (%)	4429.0 (18.7)	18933.0 (20.4)	64761.0 (22.0)	2113.0 (22.0)	22479.0 (19.3)	5149.6 (21.5)	19359.4 (20.8)	60927.2 (21.1)	2067.6 (22.0)	21488.7 (21.2)
Hyperprolactinaemia before index-date (any time), N (%)	<6.0 (<0.1)	19.0 (0.0)	38.0 (0.0)	<6.0 (<0.1))	17.0 (0.0)	<6.0 (<0.1)	11.7 (0.0)	39.3 (0.0)	<6.0 (<0.1)	15.0 (0.0)
Hypogonadism disorders before index-date (any time), N (%)	157.0 (0.7)	418.0 (0.5)	1698.0 (0.6)	46.0 (0.5)	501.0 (0.4)	128.4 (0.5)	472.4 (0.5)	1548.9 (0.5)	51.3 (0.5)	554.1 (0.5)
Hypothyroidism before index-date (any time), N (%)	786.0 (3.3)	3083.0 (3.3)	11010.0 (3.7)	279.0 (2.9)	3120.0 (2.7)	830.1 (3.5)	3148.6 (3.4)	10065.1 (3.5)	331.6 (3.5)	3484.5 (3.4)
Demyelinating disorders before index-date (any time), N (%)	73.0 (0.3)	283.0 (0.3)	983.0 (0.3)	40.0 (0.4)	285.0 (0.2)	84.0 (0.4)	292.7 (0.3)	911.1 (0.3)	35.2 (0.4)	326.9 (0.3)

Parkinson's (or related) disorders before index-date (any time), N (%)	241.0 (1.0)	779.0 (0.8)	3284.0 (1.1)	87.0 (0.9)	909.0 (0.8)	242.0 (1.0)	925.7 (1.0)	2854.7 (1.0)	118.7 (1.3)	978.9 (1.0)
Cerebrovascular disease before index-date (any time), N (%)	1435.0 (6.1)	5505.0 (5.9)	20216.0 (6.9)	654.0 (6.8)	7206.0 (6.2)	1603.7 (6.7)	5870.6 (6.3)	18895.0 (6.5)	683.3 (7.3)	6580.5 (6.5)
NSAIDs before index-date (90 days), N (%)	7850.0 (33.2)	38149.0 (41.2)	121397.0 (41.3)	3200.0 (33.3)	28919.0 (24.9)	9058.6 (37.7)	35047.4 (37.7)	107211.0 (37.1)	3126.0 (33.3)	36353.8 (35.9)
Salicylate derivatives before index-date (90 days), N (%)	2605.0 (11.0)	9719.0 (10.5)	40179.0 (13.7)	1460.0 (15.2)	15444.0 (13.3)	3051.4 (12.7)	11360.4 (12.2)	36864.3 (12.8)	1373.5 (14.6)	12929.9 (12.8)
Glucocorticoids before index-date (90 days), N (%)	1320.0 (5.6)	5812.0 (6.3)	23815.0 (8.1)	1056.0 (11.0)	5236.0 (4.5)	1690.5 (7.0)	6224.1 (6.7)	20128.3 (7.0)	847.2 (9.0)	6728.7 (6.6)
Anti-thrombotics before index-date (90 days), N (%)	4372.0 (18.5)	15966.0 (17.2)	78659.0 (26.8)	2171.0 (22.6)	26135.0 (22.5)	5620.5 (23.4)	20780.6 (22.4)	68086.2 (23.6)	2399.6 (25.5)	23220.2 (22.9)
Anti-infectives before index-date (90 days), N (%)	2505.0 (10.6)	10636.0 (11.5)	35677.0 (12.1)	1155.0 (12.0)	7804.0 (6.7)	2610.6 (10.9)	9785.2 (10.5)	31326.9 (10.8)	1160.3 (12.3)	10894.2 (10.8)
Any antineoplastics before index-date (90 days), N (%)	26.0 (0.1)	90.0 (0.1)	322.0 (0.1)	18.0 (0.2)	70.0 (0.1)	26.3 (0.1)	88.7 (0.1)	289.7 (0.1)	12.5 (0.1)	104.1 (0.1)
PPIs before index-date (any time), N (%)	12085.0 (51.1)	46605.0 (50.3)	134074.0 (45.6)	3057.0 (31.9)	47450.0 (40.8)	11024.2 (45.9)	43566.1 (46.9)	132289.3 (45.8)	4222.6 (44.9)	45609.0 (45.1)
H2RAs before index-date (any time), N (%)	1104.0 (4.7)	6372.0 (6.9)	11288.0 (3.8)	3689.0 (38.4)	7417.0 (6.4)	1369.9 (5.7)	5107.5 (5.5)	15066.6 (5.2)	1199.8 (12.8)	5493.4 (5.4)
Cytostatic anti-androgens before index-date (180 days), N (%)	17.0 (0.1)	40.0 (0.0)	222.0 (0.1)	7.0 (0.1)	40.0 (0.0)	14.2 (0.1)	48.6 (0.1)	176.9 (0.1)	6.3 (0.1)	67.0 (0.1)
Diuretics before index-date (180 days), N (%)	1758.0 (7.4)	7962.0 (8.6)	30837.0 (10.5)	969.0 (10.1)	10325.0 (8.9)	2346.9 (9.8)	8628.9 (9.3)	27896.4 (9.7)	972.9 (10.4)	9988.0 (9.9)
Beta-blockers before index-date (180 days), N (%)	3988.0 (16.9)	17206.0 (18.6)	60493.0 (20.6)	1991.0 (20.7)	22612.0 (19.5)	4767.4 (19.9)	17732.6 (19.1)	57311.2 (19.8)	1907.3 (20.3)	20333.4 (20.1)
Anti-adrenergics before index-date (180 days), N (%)	144.0 (0.6)	618.0 (0.7)	2174.0 (0.7)	100.0 (1.0)	786.0 (0.7)	167.9 (0.7)	651.6 (0.7)	2071.4 (0.7)	70.4 (0.7)	774.9 (0.8)
ACEi/ARBs before index-date (180 days), N (%)	6011.0 (25.4)	24942.0 (26.9)	89953.0 (30.6)	2560.0 (26.7)	31159.0 (26.8)	6970.5 (29.0)	26141.1 (28.1)	83769.7 (29.0)	2664.3 (28.4)	29491.4 (29.1)
Centrally acting anti-hypertensives before index-date (180 days), N (%)	232.0 (1.0)	966.0 (1.0)	3399.0 (1.2)	132.0 (1.4)	1162.0 (1.0)	266.8 (1.1)	995.7 (1.1)	3185.0 (1.1)	106.5 (1.1)	1118.1 (1.1)
Digitalis glycosides before index-date (180 days), N (%)	247.0 (1.0)	1074.0 (1.2)	3463.0 (1.2)	149.0 (1.6)	1968.0 (1.7)	310.1 (1.3)	1135.3 (1.2)	3613.3 (1.3)	131.9 (1.4)	1342.1 (1.3)
Amiodarone, disopyramide before Index-date (180 days), N (%)	85.0 (0.4)	391.0 (0.4)	1710.0 (0.6)	52.0 (0.5)	592.0 (0.5)	119.6 (0.5)	460.9 (0.5)	1532.0 (0.5)	42.5 (0.5)	529.6 (0.5)
Prostatic hypertrophy treatment before index-date (180 days), N (%)	655.0 (2.8)	2517.0 (2.7)	10013.0 (3.4)	265.0 (2.8)	2777.0 (2.4)	714.3 (3.0)	2815.7 (3.0)	8875.3 (3.1)	309.7 (3.3)	3104.5 (3.1)

Ketoconazole, terbinafine before index-date (180 days), N (%)	36.0 (0.2)	99.0 (0.1)	335.0 (0.1)	7.0 (0.1)	105.0 (0.1)	24.3 (0.1)	109.9 (0.1)	322.4 (0.1)	5.8 (0.1)	101.0 (0.1)
Antidepressants (negative) before index-date (180 days), N (%)	744.0 (3.1)	3001.0 (3.2)	9597.0 (3.3)	374.0 (3.9)	2635.0 (2.3)	760.8 (3.2)	2834.2 (3.1)	8920.0 (3.1)	315.9 (3.4)	3272.5 (3.2)
Antidepressants (positive) before index-date (180 days), N (%)	188.0 (0.8)	655.0 (0.7)	2860.0 (1.0)	63.0 (0.7)	697.0 (0.6)	213.3 (0.9)	785.2 (0.8)	2484.7 (0.9)	109.6 (1.2)	894.6 (0.9)
Antipsychotics before index-date (180 days), N (%)	265.0 (1.1)	986.0 (1.1)	3835.0 (1.3)	166.0 (1.7)	1035.0 (0.9)	282.9 (1.2)	1063.0 (1.1)	3433.1 (1.2)	151.8 (1.6)	1300.4 (1.3)
Anxiolytics (negative) before index-date (180 days), N (%)	461.0 (1.9)	1659.0 (1.8)	4683.0 (1.6)	308.0 (3.2)	1373.0 (1.2)	378.3 (1.6)	1513.9 (1.6)	4606.9 (1.6)	178.6 (1.9)	1667.5 (1.6)
Anxiolytics (positive) before index-date (180 days), N (%)	<6.0 (<0.1)	<6.0 (<0.1)	7.0 (0.0)	0.0 (0.0)	<6.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	6.4 (0.0)	0.0 (0.0)	<6.0 (<0.1)
Antiepileptics (negative) before index-date (180 days), N (%)	109.0 (0.5)	369.0 (0.4)	1100.0 (0.4)	52.0 (0.5)	414.0 (0.4)	96.0 (0.4)	360.2 (0.4)	1089.4 (0.4)	48.4 (0.5)	386.5 (0.4)
Antiepileptics (positive) before index-date (180 days), N (%)	53.0 (0.2)	125.0 (0.1)	810.0 (0.3)	20.0 (0.2)	182.0 (0.2)	48.2 (0.2)	201.9 (0.2)	657.9 (0.2)	28.2 (0.3)	240.6 (0.2)
Opioids before index-date (180 days), N (%)	296.0 (1.3)	1017.0 (1.1)	4222.0 (1.4)	131.0 (1.4)	685.0 (0.6)	292.5 (1.2)	1060.1 (1.1)	3483.2 (1.2)	131.3 (1.4)	1204.2 (1.2)
Lipid lowering treatment before index-date (180 days), N (%)	3278.0 (13.9)	13341.0 (14.4)	48777.0 (16.6)	1451.0 (15.1)	18556.0 (16.0)	3846.4 (16.0)	14376.2 (15.5)	46173.2 (16.0)	1499.1 (16.0)	16340.2 (16.1)
Anti-parkinsonian drugs before index-date (180 days), N (%)	161.0 (0.7)	520.0 (0.6)	2094.0 (0.7)	61.0 (0.6)	592.0 (0.5)	168.3 (0.7)	597.9 (0.6)	1875.6 (0.6)	67.2 (0.7)	655.9 (0.6)
Prolactin inhibitors before index-date (180 days), N (%)	<6.0 (<0.1)	18.0 (0.0)	32.0 (0.0)	<6 (<0.1)	13.0 (0.0)	<6.0 (<0.1)	11.5 (0.0)	34.6 (0.0)	<6.0 (<0.1)	12.4 (0.0)
Selected antineoplastics before index-date (180 days), N (%)	<6.0 (<0.1)	<6.0 (<0.1)	44.0 (0.0)	<6.0 (<0.1)	6.0 (0.0)	7.1 (0.0)	<6.0 (<0.1)	35.7 (0.0)	<6.0 (<0.1)	9.3 (0.0)
Hypothyroidism treatment before index-date (365 days), N (%)	1459.0 (6.2)	5308.0 (5.7)	18335.0 (6.2)	483.0 (5.0)	5647.0 (4.9)	1422.8 (5.9)	5411.3 (5.8)	17036.7 (5.9)	540.1 (5.7)	6100.1 (6.0)
Acetazolamide, aminocaproic acid before index-date (180 days), N (%)	<6.0 (<0.1)	<6.0 (<0.1)	29.0 (0.0)	0.0 (0.0)	6.0 (0.0)	<6.0 (<0.1)	<6.0 (<0.1)	24.9 (0.0)	0.0 (0.0)	5.9 (0.0)
Obesity diagnosis, treatment, adiposity measure or BMI >25 Kg/m^2 before index-date (365 days), N (%)	2106.0 (8.9)	9606.0 (10.4)	30809.0 (10.5)	1050.0 (10.9)	10414.0 (9.0)	2401.8 (10.0)	9244.4 (10.0)	29157.9 (10.1)	1067.5 (11.4)	10281.0 (10.2)
BMI >30 Kg/m^2 before index-date (365 days), N (%)	593.0 (2.5)	2957.0 (3.2)	9975.0 (3.4)	327.0 (3.4)	3371.0 (2.9)	762.8 (3.2)	2966.3 (3.2)	9317.3 (3.2)	337.9 (3.6)	3272.5 (3.2)
Current smoker (365 days), N (%)	303.0 (1.3)	1340.0 (1.4)	3884.0 (1.3)	163.0 (1.7)	1425.0 (1.2)	319.2 (1.3)	1212.6 (1.3)	3859.3 (1.3)	112.0 (1.2)	1367.0 (1.4)

Substance abuse diagnosis (including alcoholism) before index-date (365 days), N (%)	307.0 (1.3)	1494.0 (1.6)	5530.0 (1.9)	171.0 (1.8)	1202.0 (1.0)	405.9 (1.7)	1465.5 (1.6)	4739.1 (1.6)	190.5 (2.0)	1699.4 (1.7)

IPTW: inverse probability of treatment weighting; GERD: Gastroesophageal reflux disease; PPIs: Proton pump inhibitors; H2RA: Histamine type 2 receptor antagonists; ACEi/ARBs: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs); NSAIDs: nonsteroidal anti-inflammatory drugs.

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

800 Table 8. Baseline characteristics of the study population in IMRD UK

Covariates	Before IPTW (unadjusted)					After stabilized IPTW (adjusted)				
	Esomeprazole	Omeprazole	Lansoprazole	H2RAs	Non-initiators	Esomeprazole	Omeprazole	Lansoprazole	H2RAs	Non-initiators
N	1706	129761	54519	8561	131468	1615,9	128904,7	54376,6	8475,5	124517,5
Age at index-date, median (IQR)	48.0 (38.0-59.0)	57.0 (44.0-69.0)	58.0 (45.0-70.0)	60.0 (46.0-72.0)	57.0 (45.0-69.0)	56.0 (44.0-69.0)	57.0 (44.0-70.0)	57.0 (44.0-70.0)	60.0 (45.0-72.0)	57.0 (44.0-69.0)
Index year, median (IQR)	2014 (2008-2018)	2014 (2010-2017)	2013 (2009-2017)	2010 (2007-2014)	2014 (2010-2017)	2014 (2007-2018)	2014 (2010-2017)	2014 (2010-2018)	2014 (2009-2017)	2014 (2010-2017)
GERD before index-date (any time)	554.0 (32.5)	29103.0 (22.4)	13360.0 (24.5)	2168.0 (25.3)	35199.0 (26.8)	452.3 (28.0)	33093.3 (25.7)	13401.0 (24.6)	2138.9 (25.2)	30771.9 (24.7)
Gastro-duodenal ulcer before index-date (any time), N (%)	106.0 (6.2)	6458.0 (5.0)	3142.0 (5.8)	598.0 (7.0)	9757.0 (7.4)	134.3 (8.3)	7733.5 (6.0)	3229.8 (5.9)	507.1 (6.0)	7084.8 (5.7)
Chronic gastro-duodenitis before index-date (any time), N (%)	11.0 (0.6)	857.0 (0.7)	489.0 (0.9)	90.0 (1.1)	1518.0 (1.2)	14.7 (0.9)	1188.1 (0.9)	475.9 (0.9)	83.9 (1.0)	1066.2 (0.9)
Zollinger-Ellison syndrome before index-date (any time), N (%)	0.0 (0.0)	<6.0 (<0.1)	<6.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	<6 (0.0)	<6 (0.0)	0.0 (0.0)	0.0 (0.0)
Gastrointestinal infection before index-date (90 days), N (%)	20.0 (1.2)	1531.0 (1.2)	683.0 (1.3)	136.0 (1.6)	691.0 (0.5)	13.0 (0.8)	1280.6 (1.0)	524.3 (1.0)	103.5 (1.2)	1205.2 (1.0)
Esophagitis before index-date (365 days), N (%)	19.0 (1.1)	891.0 (0.7)	397.0 (0.7)	45.0 (0.5)	114.0 (0.1)	11.4 (0.7)	589.7 (0.5)	251.5 (0.5)	34.1 (0.4)	348.8 (0.3)
Other esophageal disease before index-date (any time), N (%)	58.0 (3.4)	1421.0 (1.1)	718.0 (1.3)	87.0 (1.0)	940.0 (0.7)	30.6 (1.9)	1307.8 (1.0)	551.7 (1.0)	90.5 (1.1)	1143.6 (0.9)
Acute gastro-duodenitis before index-date (90 days), N (%)	38.0 (2.2)	1807.0 (1.4)	917.0 (1.7)	138.0 (1.6)	58.0 (0.0)	20.7 (1.3)	1184.1 (0.9)	504.3 (0.9)	105.2 (1.2)	196.8 (0.2)
Dyspepsia before index-date (90 days), N (%)	12.0 (0.7)	1181.0 (0.9)	637.0 (1.2)	167.0 (2.0)	30.0 (0.0)	11.5 (0.7)	818.2 (0.6)	345.5 (0.6)	90.1 (1.1)	101.8 (0.1)
Gastro-duodenal symptoms before index-date (90 days), N (%)	145.0 (8.5)	10901.0 (8.4)	5411.0 (9.9)	1162.0 (13.6)	1104.0 (0.8)	111.1 (6.9)	7574.3 (5.9)	3156.9 (5.8)	737.2 (8.7)	3671.4 (2.9)
Other gastro-duodenal diseases before index-date (any time), N (%)	13.0 (0.8)	488.0 (0.4)	265.0 (0.5)	47.0 (0.5)	480.0 (0.4)	12.3 (0.8)	525.7 (0.4)	222.3 (0.4)	39.5 (0.5)	473.4 (0.4)
Inflammatory bowel disease before index-date (any time), N (%)	19.0 (1.1)	2409.0 (1.9)	924.0 (1.7)	200.0 (2.3)	2331.0 (1.8)	34.3 (2.1)	2390.1 (1.9)	970.4 (1.8)	171.9 (2.0)	2307.3 (1.9)
Gastro-duodenal bleeding before index-date (90 days), N (%)	17.0 (1.0)	947.0 (0.7)	306.0 (0.6)	29.0 (0.3)	68.0 (0.1)	11.5 (0.7)	549.9 (0.4)	233.5 (0.4)	47.4 (0.6)	219.9 (0.2)
Diaphragmatic hernia before index-date (any time), N (%)	172.0 (10.1)	6529.0 (5.0)	3114.0 (5.7)	465.0 (5.4)	5497.0 (4.2)	99.0 (6.1)	6366.4 (4.9)	2664.7 (4.9)	453.2 (5.3)	5745.4 (4.6)
Post-surgical gastric syndromes before index-date (any time), N (%)	0.0 (0.0)	6.0 (0.0)	15.0 (0.0)	0.0 (0.0)	2.0 (0.0)	0.0 (0.0)	7.8 (0.0)	6.4 (0.0)	0.0 (0.0)	6.8 (0.0)

Gastrointestinal malignancy before index-date (any time), N (%)	<6.0 (<0.4)	283.0 (0.2)	188.0 (0.3)	12.0 (0.1)	131.0 (0.1)	<6.0 (<0.4))	253.7 (0.2)	109.4 (0.2)	17.1 (0.2)	225.7 (0.2)
Atherosclerosis before index-date (any time), N (%)	157.0 (9.2)	17327.0 (13.4)	10158.0 (18.6)	2343.0 (27.4)	25374.0 (19.3)	249.1 (15.4)	21548.0 (16.7)	9447.0 (17.4)	1818.2 (21.5)	20888.6 (16.8)
Heart disease before index-date (any time), N (%)	77.0 (4.5)	10261.0 (7.9)	6246.0 (11.5)	1732.0 (20.2)	16024.0 (12.2)	143.6 (8.9)	13256.9 (10.3)	5824.7 (10.7)	1209.9 (14.3)	12997.8 (10.4)
Acute prostate condition before index-date (365 days), N (%)	14.0 (0.8)	1461.0 (1.1)	651.0 (1.2)	123.0 (1.4)	1151.0 (0.9)	17.2 (1.1)	1359.5 (1.1)	586.1 (1.1)	90.5 (1.1)	1236.7 (1.0)
Chronic prostate condition before index-date (any time), N (%)	73.0 (4.3)	10672.0 (8.2)	4910.0 (9.0)	794.0 (9.3)	9433.0 (7.2)	119.2 (7.4)	10157.1 (7.9)	4365.1 (8.0)	790.5 (9.3)	9450.6 (7.6)
Genito-urinary disease before index-date (365 days), N (%)	10.0 (0.6)	840.0 (0.6)	348.0 (0.6)	43.0 (0.5)	650.0 (0.5)	10.0 (0.6)	765.7 (0.6)	324.1 (0.6)	52.1 (0.6)	748.4 (0.6)
Chronic kidney disease before index-date (any time), N (%)	46.0 (2.7)	8506.0 (6.6)	3949.0 (7.2)	763.0 (8.9)	9906.0 (7.5)	93.4 (5.8)	9038.3 (7.0)	3906.8 (7.2)	764.8 (9.0)	8615.3 (6.9)
Malignancy in pelvic region before index-date (365 days), N (%)	15.0 (0.9)	2093.0 (1.6)	915.0 (1.7)	121.0 (1.4)	1427.0 (1.1)	21.1 (1.3)	1804.7 (1.4)	765.2 (1.4)	140.3 (1.7)	1600.9 (1.3)
Chronic obstructive respiratory disease before index-date (any time), N (%)	205.0 (12.0)	20391.0 (15.7)	8717.0 (16.0)	1328.0 (15.5)	18918.0 (14.4)	249.0 (15.4)	19773.3 (15.3)	8337.0 (15.3)	1411.2 (16.7)	18795.9 (15.1)
Depression before index-date (365 days), N (%)	52.0 (3.0)	4455.0 (3.4)	1859.0 (3.4)	304.0 (3.6)	3143.0 (2.4)	51.7 (3.2)	3968.3 (3.1)	1667.8 (3.1)	273.5 (3.2)	3742.0 (3.0)
Anxiety before index-date (any time), N (%)	293.0 (17.2)	23132.0 (17.8)	9737.0 (17.9)	1379.0 (16.1)	21107.0 (16.1)	274.5 (17.0)	22157.1 (17.2)	9290.5 (17.1)	1463.8 (17.3)	21055.4 (16.9)
Behaviour and sexuality disorders before index-date (any time), N (%)	11.0 (0.6)	2217.0 (1.7)	873.0 (1.6)	136.0 (1.6)	1986.0 (1.5)	22.1 (1.4)	2084.0 (1.6)	886.0 (1.6)	138.6 (1.6)	1995.5 (1.6)
Alzheimer's or other dementia before index-date (any time), N (%)	33.0 (1.9)	2793.0 (2.2)	1741.0 (3.2)	206.0 (2.4)	3998.0 (3.0)	32.3 (2.0)	3351.1 (2.6)	1501.3 (2.8)	264.2 (3.1)	3297.4 (2.6)
Autonomic neuropathies before index-date (any time), N (%)	8.0 (0.5)	637.0 (0.5)	342.0 (0.6)	56.0 (0.7)	658.0 (0.5)	10.8 (0.7)	668.4 (0.5)	288.4 (0.5)	53.2 (0.6)	609.1 (0.5)
Diabetes before index-date (any time), N (%)	139.0 (8.1)	12851.0 (9.9)	6094.0 (11.2)	1027.0 (12.0)	16802.0 (12.8)	186.1 (11.5)	14256.7 (11.1)	6170.2 (11.3)	1034.0 (12.2)	13935.7 (11.2)
Hyperprolactinaemia before index-date (any time), N (%)	0.0 (0.0)	6.0 (0.0)	7.0 (0.0)	<6.0 (0.0)	18.0 (0.0)	0.0 (0.0)	14.4 (0.0)	7.2 (0.0)	<6.0 (0.0)	14.5 (0.0)
Hypogonadism disorders before index-date (any time), N (%)	<6.0 (<0.4)	291.0 (0.2)	150.0 (0.3)	23.0 (0.3)	443.0 (0.3)	<6.0 (<0.4)	348.7 (0.3)	147.1 (0.3)	24.5 (0.3)	340.9 (0.3)
Hypothyroidism before index-date (any time), N (%)	25.0 (1.5)	2208.0 (1.7)	972.0 (1.8)	172.0 (2.0)	2325.0 (1.8)	38.1 (2.4)	2267.3 (1.8)	948.5 (1.7)	178.3 (2.1)	2188.8 (1.8)
Demyelinating disorders before index-date (any time), N (%)	<6.0 (<0.4)	202.0 (0.2)	97.0 (0.2)	17.0 (0.2)	170.0 (0.1)	<6.0 (<0.4)	199.1 (0.2)	83.0 (0.2)	13.5 (0.2)	205.2 (0.2)
Parkinson’s (or related) disorders before index-date (any time), N (%)	7.0 (0.4)	862.0 (0.7)	413.0 (0.8)	51.0 (0.6)	962.0 (0.7)	<6.0 (<0.4)	919.0 (0.7)	388.7 (0.7)	74.3 (0.9)	881.2 (0.7)

Cerebrovascular disease before index-date (any time), N (%)	48.0 (2.8)	6270.0 (4.8)	4076.0 (7.5)	643.0 (7.5)	10294.0 (7.8)	86.3 (5.3)	8027.2 (6.2)	3719.6 (6.8)	689.7 (8.1)	8059.3 (6.5)
NSAIDs before index-date (90 days), N (%)	946.0 (55.5)	73549.0 (56.7)	24750.0 (45.4)	2325.0 (27.2)	28630.0 (21.8)	674.5 (41.7)	51637.9 (40.1)	21886.3 (40.2)	2706.6 (31.9)	49718.7 (39.9)
Salicylate derivatives before index-date (90 days), N (%)	211.0 (12.4)	25159.0 (19.4)	13443.0 (24.7)	2876.0 (33.6)	37712.0 (28.7)	358.7 (22.2)	31010.6 (24.1)	13323.0 (24.5)	2443.2 (28.8)	30117.6 (24.2)
Glucocorticoids before index-date (90 days), N (%)	75.0 (4.4)	11848.0 (9.1)	5219.0 (9.6)	1048.0 (12.2)	9809.0 (7.5)	127.6 (7.9)	11388.6 (8.8)	4699.8 (8.6)	899.2 (10.6)	11033.9 (8.9)
Anti-thrombotics before index-date (90 days), N (%)	267.0 (15.7)	31757.0 (24.5)	18093.0 (33.2)	3844.0 (44.9)	54594.0 (41.5)	473.0 (29.3)	41830.2 (32.5)	18167.7 (33.4)	3442.4 (40.6)	41183.1 (33.1)
Anti-infectives before index-date (90 days), N (%)	260.0 (15.2)	20972.0 (16.2)	9468.0 (17.4)	1641.0 (19.2)	15366.0 (11.7)	251.4 (15.6)	19632.1 (15.2)	8114.3 (14.9)	1444.5 (17.0)	18742.7 (15.1)
Any antineoplastics before index-date (90 days), N (%)	<6.0 (<0.4)	891.0 (0.7)	418.0 (0.8)	88.0 (1.0)	870.0 (0.7)	<6.0 (<0.4)	950.7 (0.7)	388.2 (0.7)	86.6 (1.0)	937.9 (0.8)
PPIs before index-date (any time), N (%)	828.0 (48.5)	57715.0 (44.5)	25077.0 (46.0)	3023.0 (35.3)	53199.0 (40.5)	737.4 (45.6)	54812.8 (42.5)	23318.3 (42.9)	3697.0 (43.6)	50750.8 (40.8)
H2RAs before index-date (any time), N (%)	240.0 (14.1)	15843.0 (12.2)	8016.0 (14.7)	2585.0 (30.2)	16898.0 (12.9)	223.6 (13.8)	17371.7 (13.5)	7223.0 (13.3)	1496.6 (17.7)	15906.4 (12.8)
Cytostatic anti-androgens before index-date (180 days), N (%)	17.0 (1.0)	1478.0 (1.1)	733.0 (1.3)	79.0 (0.9)	990.0 (0.8)	17.2 (1.1)	1322.5 (1.0)	561.9 (1.0)	102.5 (1.2)	1200.4 (1.0)
Diuretics before index-date (180 days), N (%)	105.0 (6.2)	14486.0 (11.2)	7122.0 (13.1)	1410.0 (16.5)	18402.0 (14.0)	178.4 (11.0)	16357.7 (12.7)	6949.9 (12.8)	1337.4 (15.8)	15868.8 (12.7)
Beta-blockers before index-date (180 days), N (%)	144.0 (8.4)	16873.0 (13.0)	8663.0 (15.9)	1873.0 (21.9)	26548.0 (20.2)	229.8 (14.2)	20921.5 (16.2)	9071.1 (16.7)	1722.7 (20.3)	20370.9 (16.4)
Anti-adrenergics before index-date (180 days)	33.0 (1.9)	3234.0 (2.5)	1558.0 (2.9)	329.0 (3.8)	4340.0 (3.3)	41.8 (2.6)	3745.8 (2.9)	1608.3 (3.0)	306.4 (3.6)	3667.1 (2.9)
ACEi/ARBs before index-date (180 days), N (%)	234.0 (13.7)	29335.0 (22.6)	13774.0 (25.3)	2605.0 (30.4)	40239.0 (30.6)	377.2 (23.3)	33300.7 (25.8)	14357.2 (26.4)	2575.3 (30.4)	32528.8 (26.1)
Centrally acting anti-hypertensives before index-date (180 days), N (%)	<6.0 (<0.4)	210.0 (0.2)	151.0 (0.3)	19.0 (0.2)	316.0 (0.2)	<6.0 (<0.4)	278.3 (0.2)	119.8 (0.2)	21.1 (0.2)	260.1 (0.2)
Digitalis glycosides before index-date (180 days), N (%)	13.0 (0.8)	1519.0 (1.2)	863.0 (1.6)	214.0 (2.5)	3031.0 (2.3)	18.6 (1.2)	2116.1 (1.6)	914.2 (1.7)	199.9 (2.4)	2127.4 (1.7)
Amiodarone, Disopyramide before Index-date (180 days), N (%)	<6.0 (<0.4)	472.0 (0.4)	273.0 (0.5)	73.0 (0.9)	768.0 (0.6)	10.2 (0.6)	638.7 (0.5)	265.5 (0.5)	58.1 (0.7)	606.0 (0.5)
Prostatic hypertrophy treatment before index-date (180 days), N (%)	44.0 (2.6)	7074.0 (5.5)	3169.0 (5.8)	483.0 (5.6)	6581.0 (5.0)	87.6 (5.4)	6878.4 (5.3)	2952.5 (5.4)	498.2 (5.9)	6551.2 (5.3)
Ketoconazole, terbinafine before index-date (180 days), N (%)	6.0 (0.4)	587.0 (0.5)	225.0 (0.4)	40.0 (0.5)	591.0 (0.4)	8.6 (0.5)	577.6 (0.4)	247.8 (0.5)	34.2 (0.4)	567.0 (0.5)
Antidepressants (negative) before index-date (180 days), N (%)	140.0 (8.2)	14566.0 (11.2)	6155.0 (11.3)	909.0 (10.6)	11748.0 (8.9)	180.7 (11.2)	13539.0 (10.5)	5704.6 (10.5)	969.3 (11.4)	13017.2 (10.5)

Antidepressants (positive) before index-date (180 days), N (%)	21.0 (1.2)	2510.0 (1.9)	984.0 (1.8)	136.0 (1.6)	2196.0 (1.7)	22.1 (1.4)	2358.8 (1.8)	1010.6 (1.9)	156.7 (1.8)	2317.4 (1.9)
Antipsychotics before index-date (180 days), N (%)	15.0 (0.9)	1656.0 (1.3)	816.0 (1.5)	104.0 (1.2)	1771.0 (1.3)	23.3 (1.4)	1788.3 (1.4)	745.8 (1.4)	129.8 (1.5)	1727.2 (1.4)
Anxiolytics (negative) before index-date (180 days) , N (%)	32.0 (1.9)	3874.0 (3.0)	1600.0 (2.9)	264.0 (3.1)	3207.0 (2.4)	47.7 (3.0)	3790.6 (2.9)	1555.8 (2.9)	258.7 (3.1)	3666.6 (2.9)
Anxiolytics (positive) before index-date (180 days), N (%)	<6.0 (<0.4)	55.0 (0.0)	27.0 (0.0)	<6.0 (0.0)	57.0 (0.0)	<6.0 (<0.4)	66.8 (0.1)	23.1 (0.0)	<6.0 (0.0)	54.9 (0.0)
Antiepileptics (negative) before index-date (180 days), N (%)	16.0 (0.9)	1608.0 (1.2)	755.0 (1.4)	139.0 (1.6)	1874.0 (1.4)	21.7 (1.3)	1769.2 (1.4)	765.6 (1.4)	113.7 (1.3)	1755.7 (1.4)
Antiepileptics (positive) before index-date (180 days), N (%)	<6.0 (<0.4)	540.0 (0.4)	245.0 (0.4)	40.0 (0.5)	626.0 (0.5)	8.0 (0.5)	577.3 (0.4)	259.7 (0.5)	45.7 (0.5)	594.0 (0.5)
Opioids before index-date (180 days), N (%)	25.0 (1.5)	2779.0 (2.1)	1486.0 (2.7)	147.0 (1.7)	1641.0 (1.2)	26.7 (1.7)	2515.4 (2.0)	1049.4 (1.9)	189.6 (2.2)	2404.2 (1.9)
Lipid lowering treatment before index-date (180 days), N (%)	308.0 (18.1)	33649.0 (25.9)	16538.0 (30.3)	3040.0 (35.5)	47526.0 (36.2)	447.8 (27.7)	38894.8 (30.2)	16874.4 (31.0)	3022.5 (35.7)	37893.7 (30.4)
Anti-parkinsonian drugs before index-date (180 days), N (%)	<6.0 (<0.4)	902.0 (0.7)	420.0 (0.8)	46.0 (0.5)	979.0 (0.7)	9.3 (0.6)	934.7 (0.7)	400.5 (0.7)	61.3 (0.7)	903.0 (0.7)
Prolactin inhibitors before index-date (180 days), N (%)	0.0 (0.0)	22.0 (0.0)	12.0 (0.0)	<6.0 (0.0)	52.0 (0.0)	0.0 (0.0)	28.6 (0.0)	17.2 (0.0)	<6.0 (0.0)	33.8 (0.0)
Selected antineoplastics before index-date (180 days), N (%)	0.0 (0.0)	247.0 (0.2)	101.0 (0.2)	19.0 (0.2)	200.0 (0.2)	0.0 (0.0)	256.4 (0.2)	88.4 (0.2)	23.3 (0.3)	172.6 (0.1)
Hypothyroidism treatment before index-date (365 days), N (%)	32.0 (1.9)	3437.0 (2.6)	1577.0 (2.9)	252.0 (2.9)	3952.0 (3.0)	51.3 (3.2)	3671.5 (2.8)	1542.9 (2.8)	280.7 (3.3)	3560.4 (2.9)
Acetazolamide, aminocaproic acid before index-date (180 days), N (%)	<6.0 (<0.4)	27.0 (0.0)	14.0 (0.0)	<6.0 (0.0)	30.0 (0.0)	<6.0 (<0.4)	31.8 (0.0)	16.2 (0.0)	<6.0 (0.0)	33.0 (0.0)
Obesity diagnosis, treatment, adiposity measure or BMI >25 Kg/m^2 before index-date (365 days), N (%)	403.0 (23.6)	32445.0 (25.0)	15219.0 (27.9)	2457.0 (28.7)	36028.0 (27.4)	420.7 (26.0)	34104.8 (26.5)	14493.9 (26.7)	2383.8 (28.1)	33116.8 (26.6)
BMI >30 Kg/m^2 before index-date (365 days)	184.0 (10.8)	14845.0 (11.4)	6805.0 (12.5)	1015.0 (11.9)	16598.0 (12.6)	170.9 (10.6)	15443.4 (12.0)	6645.1 (12.2)	1049.2 (12.4)	15174.8 (12.2)
Current smoker (365 days), N (%)	247.0 (14.5)	18504.0 (14.3)	8804.0 (16.1)	1511.0 (17.6)	17001.0 (12.9)	240.6 (14.9)	18668.0 (14.5)	7779.6 (14.3)	1260.2 (14.9)	17891.1 (14.4)
Substance abuse diagnosis (including alcoholism) before index-date (365 days), N (%)	239.0 (14.0)	15160.0 (11.7)	8382.0 (15.4)	1216.0 (14.2)	15395.0 (11.7)	207.4 (12.8)	16372.7 (12.7)	6791.3 (12.5)	1151.5 (13.6)	15493.0 (12.4)

IPTW: inverse probability of treatment weighting; GERD: Gastroesophageal reflux disease; PPIs: Proton pump inhibitors; H2RA: Histamine type 2 receptor antagonists; ACEi/ARBs: Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs); NSAIDs: nonsteroidal anti-inflammatory drugs.

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

Table 9. Unadjusted and adjusted incidence rates (IR) per 100 person-years of sexual dysfunction by treatment arm and database using ITT approach

	Treatment arm	N	N index-dates	Follow-up (person-years)	n events	Unadjusted			Stabilized IPTW adjusted		
						IR	95% CI		IR	95% CI	
IQVIA™ DA Germany	H2RAs	8201	9596	9084.76	58	**0.64**	0.49	0.83	**0.64**	0.45	0.91
	Esomeprazole	20406	23660	22005.13	112	**0.51**	0.42	0.61	**0.52**	0.43	0.64
	Omeprazole	73513	92596	87451.34	519	**0.59**	0.54	0.65	**0.55**	0.50	0.60
	Pantoprazole	232637	293874	274676.70	1444	**0.53**	0.50	0.55	**0.54**	0.51	0.57
	Non-initiators	96060	116253	111746.40	475	**0.43**	0.39	0.47	**0.43**	0.38	0.48
IMRD UK	H2RAs	7940	8561	8099.75	137	**1.69**	1.43	2.00	**1.72**	1.40	2.12
	Esomeprazole	1601	1706	1648.98	19	**1.15**	0.73	1.81	**1.23**	0.74	2.06
	Omeprazole	103502	129761	123188.10	1622	**1.32**	1.25	1.38	**1.37**	1.30	1.45
	Lansoprazole	46311	54519	51227.32	713	**1.39**	1.29	1.50	**1.36**	1.26	1.47
	Non-initiators	131468	131468	8099.75	137	**1.19**	1.12	1.25	**1.17**	1.10	1.25

ITT: intention-to-treat analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

Table 10. Unadjusted and adjusted hazard ratios (HR) of sexual dysfunction by treatment arm and database using ITT approach

		Target arm: Esomeprazole						Target arm: Omeprazole					
		Unadjusted			Stabilized IPTW adjusted			Unadjusted			Stabilized IPTW adjusted		
	Treatment arm	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
IQVIA™DA Germany	H2RAs	**1.25**	0.91	1.72	**1.23**	0.82	1.85	**1.08**	0.82	1.41	**1.17**	0.81	1.69
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.86**	0.70	1.05	**0.95**	0.76	1.19
	Omeprazole	**1.17**	0.95	1.43	**1.05**	0.84	1.31	**1.00**	[Reference]		**1.00**	[Reference]	
	Pantoprazole	**1.03**	0.85	1.25	**1.03**	0.84	1.27	**0.89**	0.80	0.98	**0.98**	0.88	1.10
	Non-initiators	**0.84**	0.68	1.03	**0.83**	0.66	1.04	**0.72**	0.63	0.81	**0.79**	0.68	0.91
IMRD UK	H2RAs	**1.47**	0.91	2.38	**1.40**	0.80	2.44	**1.29**	1.08	1.53	**1.25**	1.01	1.55
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.88**	0.56	1.38	**0.90**	0.53	1.50
	Omeprazole	**1.14**	0.73	1.80	**1.12**	0.67	1.87	**1.00**	[Reference]		**1.00**	[Reference]	
	Lansoprazole	**1.21**	0.77	1.91	**1.10**	0.66	1.86	**1.06**	0.97	1.15	**0.99**	0.90	1.09
	Non-initiators	**1.03**	0.66	1.62	**0.95**	0.57	1.60	**0.90**	0.84	0.97	**0.85**	0.79	0.93

ITT: intention-to-treat analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

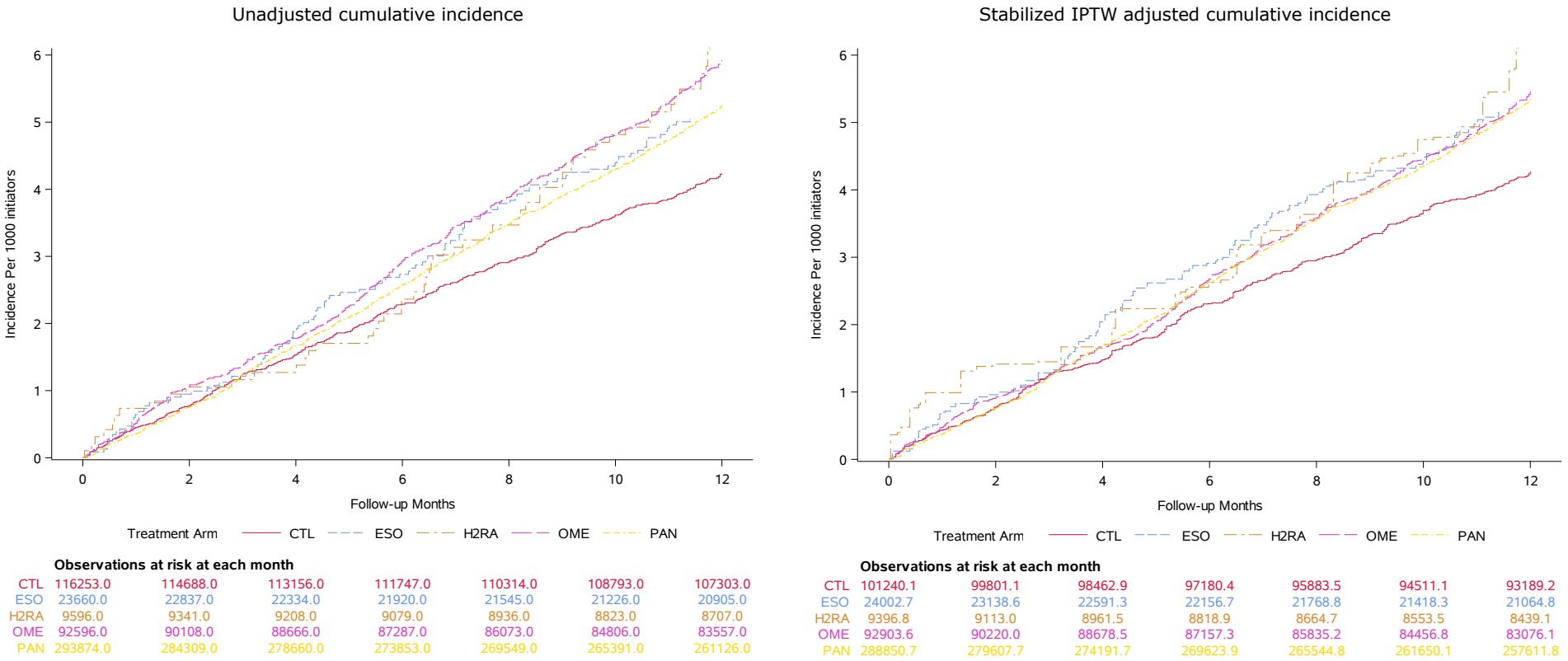

Figure 7. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IQVIA™ DA Germany using ITT analytical approach

CTL: Non-initiator of treatment cohort; ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; PAN: Pantoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-to-treat analysis.

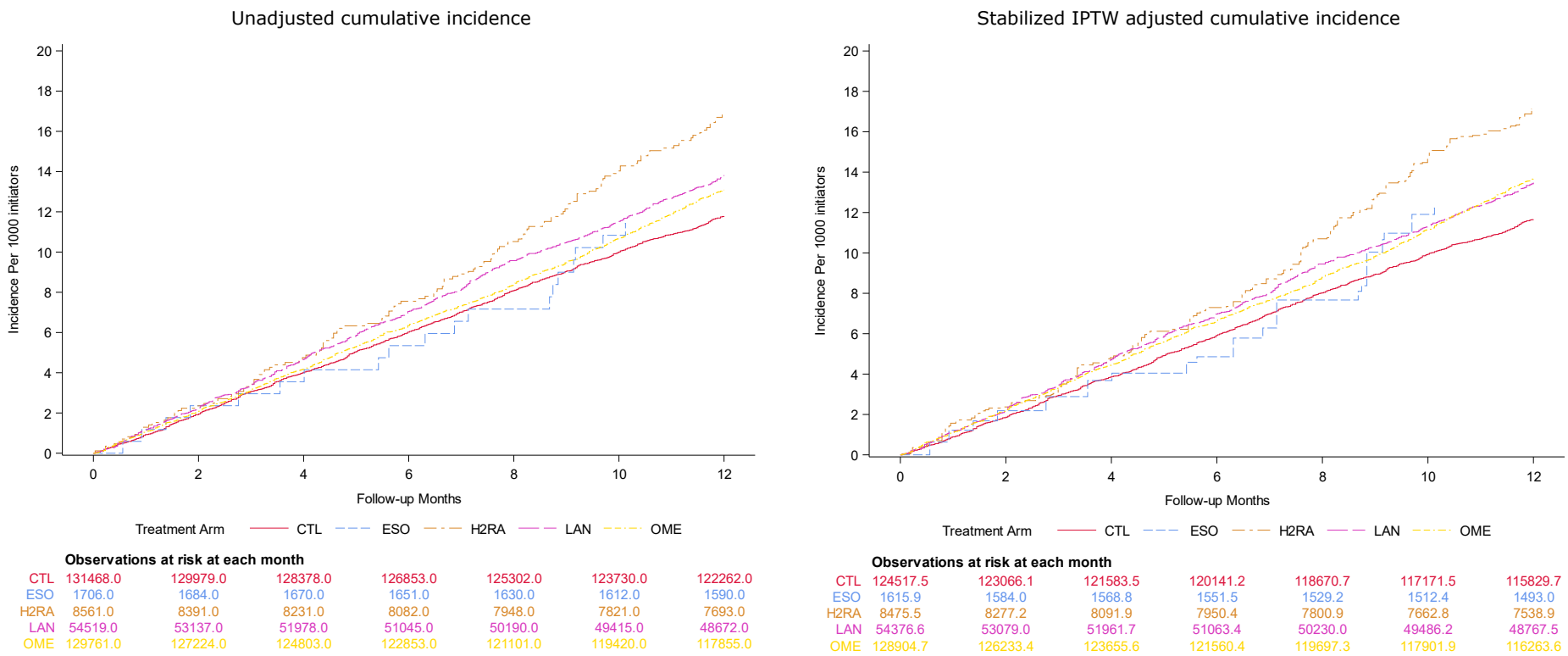

Figure 8. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IMRD UK using ITT analytical approach

CTL: Non-initiator of treatment cohort; ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; PAN: Pantoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-to-treat analysis.

7. Discussion

In the comparative cohort study among treatment cohorts (esomeprazole, omeprazole, pantoprazole/lansoprazole, and H2RAs):

- The IRs for SD were two to three times higher in IMRD UK than in IQVIA™ DA Germany. Previous studies have shown that the prevalence of erectile dysfunction (ED) varies markedly by country. (Kessler et al., 2019; Rosen et al., 2004) The MALES study which involved 27839 men aged 20-75years who were interviewed in eight countries (United States, United Kingdom, Germany, France, Italy, Spain, Mexico, and Brazil) using a standardized questionnaire found prevalences of ED that varied from 10% in Spain to 22% in the U.S. (Rosen et al., 2004) The study pointed out that among men who reported ED, only 58% had actively sought medical attention for their condition. (Rosen et al., 2004) In a comparison to men from the U.S, the study also showed that German men were less likely (OR: 0.46 95%CI: 0.29-0.75) to seek treatment with PDE5 inhibitors than British men (OR:1.32 95%CI: 0.89-1.97). (Fisher et al., 2004) Our study used electronic health records (EHRs) from two large primary care samples to capture SD based on recorded diagnosis. Therefore, these medical records would be expected to provide an underestimated depiction of the occurrence of SD in the general population and will represent only men with SD who seek medical care for their condition. It is well-known that not only characteristics of the underlying healthcare system might contribute to geographic variations in disease estimates based on EHRs, such as different clinical practices in relation to the application of diagnostic criteria, coding practices, or referral patterns, but also cultural and behavioural differences (e.g., healthcare seeking behaviour). Additionally, patients' medical history may be incomplete particularly in the German database where there is no national mandatory GP system and patients have free doctor choice. Consequently, specialists, such a urologist, can be consulted for conditions such a SD without referral from the GP which might lead to a lower sensitivity for capturing this diagnosis in IQVIA™ DA Germany GP data. It should also be noted that we used an outcome definition based on ICD-10 codes for IQVIA™ DA Germany, while for IMRD UK we adapted the ICD-10 definition to generate a definition based on READ codes. This adaption, which was required to allow for the different coding systems of the different data sources, may have introduced heterogeneity in the outcome definition. However, despite the likely incomplete ascertainment of the outcome, it is important to mention that this would be applied the same way in each comparison group within a database and so any bias of incidence rates would be expected to be non-differential between target and comparator groups. Thus, the causal contrasts remain valid.

- The lowest and the highest IRs for SD were found in the esomeprazole and omeprazole cohorts in IQVIA™ DA Germany and in the esomeprazole and H2RA cohorts in IMRD UK respectively.

- The unadjusted and IPTW adjusted cumulative incidence of SD showed a similar pattern in both databases, with gradual and approximately linear increase in the four treatment cohorts throughout the 1-year follow-up. In IQVIA™ DA Germany, the highest adjusted cumulative incidence was observed in the H2RA cohort during the 3-month follow-up and in the esomeprazole cohort between the 4- and 9-follow-up months. In IMRD UK, the adjusted cumulative risk in the H2RA cohort remained the highest from the 3-month follow-up to the end of the follow-up period. Of note, the number of events and follow-up time of the H2RA cohort and esomeprazole were limited in IQVIA™ DA Germany and IMRD UK, respectively.

- The unadjusted and IPTW adjusted point estimate HRs suggested a marginally increased risk of SD in the H2RAs, omeprazole and pantoprazole cohorts when compared to esomeprazole cohort in IQVIA™ DA Germany. However, the associated uncertainty indicates that the results were compatible with similar, higher and lower risk of SD in H2RAs, omeprazole and pantoprazole

initiators in comparison to esomeprazole initiators. A similar pattern but higher risk of SD was observed in IMRD UK in the H2RAs, omeprazole and lansoprazole cohorts when compared to esomeprazole cohort, however, the associated uncertainty for H2RA initiators was compatible with higher risk and incompatible with lower risk of SD compared to the esomeprazole initiators after IPTW adjustment. When using the omeprazole cohort as reference group, a consistent pattern to that for esomeprazole was observed in both databases.

- Of note, the number of events and follow-up time of the H2RA cohort and esomeprazole were limited in IQVIA™ DA Germany and IMRD UK, respectively.
- This pattern of results remained robust to the supplementary analysis performed using an PP analytical approach.

In the comparative cohort study among treatment cohorts (esomeprazole, omeprazole, pantoprazole/lansoprazole, and H2RAs) and non-initiator cohort:

- In both databases, the IR of SD was lower in the non-initiator cohort compared to the treated cohorts after adjustment for IPTW. Similarly, the cumulative incidence of SD tended to be the lowest/lower in the non-initiator cohort in comparison to the treatment cohorts throughout the follow-up period in both databases.
- IQVIA™ DA Germany, when using esomeprazole as reference group, a slightly lower risk for SD was observed in the non-initiator cohort. However, the associated uncertainty indicates results compatible with similar, higher and lower risk of SD in non-initiators in comparison to esomeprazole initiators after IPTW adjustment. When using omeprazole as reference group, the associated uncertainty indicates results compatible with lower risk and incompatible with higher risk in the non-initiator cohort after IPTW adjustment. A similar pattern was observed in IMRD UK.
- This pattern of results remained robust to the supplementary analysis performed using an PP analytical approach. It worth noting that in this analysis and when restricting the population to selected indications, the adjusted point estimate HRs were very similar between IQVIA™ DA Germany and IMRD UK.

7.1. Strengths and limitations

Exposure misclassification may exist since neither over-the-counter (OTC) drug use nor medication use during hospitalisation are captured in the included databases. This is a particular issue because of the availability of OTC PPIs has increased over time (Johnson et al., 2017) and, probably their OTC use. Additionally, information on the actual duration of treatment corresponding to each prescription is not available and is difficult to estimate since patients may be prescribed large packs and instructed to use the drug as needed, with possible discontinuation/restart and dose-variation over time. Moreover, whether patients collected their prescriptions or consumed the prescribed medication is unknown. Due to this uncertainty and considering information from individual case reports about the latency of effect, we chose to follow patients for a maximum of one year and attribute the entire follow-up to the index treatment. It should be noted that, in the analysis comparing with non-initiators, we restricted the study population to patients with chronic indications, for which treatment is likely chronic.

To our knowledge, the accuracy of diagnostic coding for sexual dysfunction has not been assessed in the primary care databases available. However, the nature of the diagnosis means that its recording in primary care records could be reasonably accurate, particularly for sexual dysfunction in male individuals. Nonetheless, this assumption should be treated cautiously. In the UK, the patent for Viagra expired in June 2013, which followed a drop by 93% in the price of generic preparations of sildenafil compared to the price of branded Viagra (Connelly, 2017). Besides, Sildenafil has been available OTC without

prescription from UK pharmacies since 2017 and, therefore, patients have no longer needed to see their doctor to get a diagnosis ever since. (MHRA, 2017) These events led to marked changes in diagnosis coding practices of erectile dysfunction during 2013-2014 and marked decrease of coding for impotence by GPs since 2017 which are reflected in the distribution of outcome events over calendar time. In IQVIA™ DA Germany the reporting of male sexual dysfunction appears stable after 2005. To account for uncertainties around potential misclassification due to changes in diagnostic criteria or coding practices over time, calendar period was adjusted for in the analysis.

It also needs to be considered that patient's medical history, as captured by GP practices included in the study, may be incomplete, particularly in the IQVIA™ DA Germany database. In Germany, there is no mandatory GP system and patients have free doctor choice. A specialist can be consulted without referral from the GP. As a result, data are collected from visits to various medical practices which are not linked by a unique patient identifier. Therefore, the entire medical history of patients might be fragmented and for that reason there is a risk of exposure, outcome and covariates misclassification. As mentioned above, this might partially explain the lower incidence rates of SD among male patients in IQVIA™ DA Germany compared to IMRD UK. It might also imply a higher degree of residual confounding.

Although confounding by indication represents a common source of bias, it is not likely that the main indications for PPIs (i.e., gastroesophageal reflux disease, esophagitis, and treatment for or prophylaxis against gastric or duodenal ulcer disease) are strongly associated with SD.

Ideally, the active comparator should be known to have no effect on the event of interest. Impotence is currently listed as a rare side effect in the UK product information for lansoprazole (EMC, 2023, 2024b), and for H2RAs. (EMC, 2024a, 2024c) Therefore, we used multiple comparators, including non-initiators, which were intended to capture (if possible) a "background risk" among patients with the indication but not under treatment. Even though we imposed the presence of at least one chronic indication for PPIs/H2RAs to both initiators and non-initiators, it is possible that non-initiators differ from initiators in the distribution of unmeasured outcome risk factors, which would leave residual unadjusted confounding. In addition, non-initiators might include patients misclassified as untreated but who were users of OTC drugs. However, we assume that OTC use is episodic, i.e., occurring occasionally at irregular intervals and therefore, individuals might be less exposed to long-term treatments. Given the greater methodological uncertainty, the risk contrasts against the non-initiator arm should be interpreted with more caution than contrasts between treatment initiator arms.

Finally, although more than 50 potential confounders were adjusted for, we cannot rule out the possibility of residual confounding as not all relevant potential confounders are captured in the selected databases (e.g., other comorbid conditions or severity of comorbidities) and there could be misclassification of measured covariates due to incomplete capture of some co-morbidities or co-medication in GP data.

8. Conclusion

In our study, the IR of SD was similar for patients initiating PPIs or H2RAs, when accounting for measured confounders in IQVIA™ DA Germany, and higher in patients initiating H2RAs in IMRD UK. In addition, the IR of SD in non-initiator cohort was consistently the lowest in both databases as expected.

Thus, our study did not find strong evidence of a substantial and clinically significant difference in the risk of SD between esomeprazole or omeprazole compared to H2RAs, lansoprazole, and pantoprazole. Even though there is evidence of a slightly higher risk of SD among PPIs and H2RA initiators compared to non-initiators, it is more likely that these contrasts are affected by residual confounding.

9. References

Bland, J. M., & Altman, D. G. (1998). Survival probabilities (the Kaplan-Meier method). *BMJ*, *317*(7172), 1572. https://doi.org/10.1136/bmj.317.7172.1572

Budweiser, S., Enderlein, S., Jorres, R. A., Hitzl, A. P., Wieland, W. F., Pfeifer, M., & Arzt, M. (2009). Sleep apnea is an independent correlate of erectile and sexual dysfunction. *J Sex Med*, *6*(11), 3147-3157. https://doi.org/10.1111/j.1743-6109.2009.01372.x

Calabro, R. S., Cacciola, A., Bruschetta, D., Milardi, D., Quattrini, F., Sciarrone, F., la Rosa, G., Bramanti, P., & Anastasi, G. (2019). Neuroanatomy and function of human sexual behavior: A neglected or unknown issue? *Brain Behav*, *9*(12), e01389. https://doi.org/10.1002/brb3.1389

Cao, F., Chen, C. X., Wang, M., Liao, H. R., Wang, M. X., Hua, S. Z., Huang, B., Xiong, Y., Zhang, J. Y., & Xu, Y. L. (2018). Updated meta-analysis of controlled observational studies: proton-pump inhibitors and risk of Clostridium difficile infection. *J Hosp Infect*, *98*(1), 4-13. https://doi.org/10.1016/j.jhin.2017.08.017

Connelly, D. (2017). Three decades of Viagra. *The Pharmaceutical Journal*, *298*(7901). https://doi.org/10.1211/PJ.2017.20202847

DynaMed. (2023). *Erectile Dysfunction*. Retrieved 05 March 2024 from https://www.dynamed.com/condition/erectile-dysfunction#LIKELY_RISK_FACTORS

EMC. (2023). *Lansoprazole 30 mg gastro-resistant capsules*. Retrieved 05 March 2024 from https://www.medicines.org.uk/emc/product/14551/smpc#gref

EMC. (2024a). *Famotidine: Side-effects*. Retrieved 18/03/2024 from https://www.medicinescomplete.com/#/content/bnf/_589364058

EMC. (2024b). *Lansoprazole: Side-effects*. Retrieved 18/03/2024 from https://www.medicinescomplete.com/#/content/bnf/_219012502#content%2Fbnf%2F_219012502%23pot-sideEffects

EMC. (2024c). *Ranitidine: Side-effects*. Retrieved 18/03/2024 from https://www.medicinescomplete.com/#/content/bnf/_726851766#content%2Fbnf%2F_726851766%23pot-sideEffects

European Medicines Agency. (2020). *Ranitidine-containing medicinal products - referral*. Retrieved 04/March/2024 from https://www.ema.europa.eu/en/medicines/human/referrals/ranitidine-containing-medicinal-products#ema-inpage-item-key-facts

Fisher, W. A., Rosen, R. C., Eardley, I., Niederberger, C., Nadel, A., Kaufman, J., & Sand, M. (2004). The multinational Men's Attitudes to Life Events and Sexuality (MALES) Study Phase II: understanding PDE5 inhibitor treatment seeking patterns, among men with erectile dysfunction. *J Sex Med*, *1*(2), 150-160. https://doi.org/10.1111/j.1743-6109.2004.04023.x

Hatzichristou, D., Kirana, P. S., Banner, L., Althof, S. E., Lonnee-Hoffmann, R. A., Dennerstein, L., & Rosen, R. C. (2016). Diagnosing Sexual Dysfunction in Men and Women: Sexual History Taking and the Role of Symptom Scales and Questionnaires. *J Sex Med*, *13*(8), 1166-1182. https://doi.org/10.1016/j.jsxm.2016.05.017

Hernan, M. A., & Robins, J. M. (2006). Estimating causal effects from epidemiological data. *J Epidemiol Community Health*, *60*(7), 578-586. https://doi.org/10.1136/jech.2004.029496

Johnson, D. A., Katz, P. O., Armstrong, D., Cohen, H., Delaney, B. C., Howden, C. W., Katelaris, P., Tutuian, R. I., & Castell, D. O. (2017). The Safety of Appropriate Use of Over-the-Counter Proton Pump Inhibitors: An Evidence-Based Review and Delphi Consensus. *Drugs*, *77*(5), 547-561. https://doi.org/10.1007/s40265-017-0712-6

Kessler, A., Sollie, S., Challacombe, B., Briggs, K., & Van Hemelrijck, M. (2019). The global prevalence of erectile dysfunction: a review. *BJU Int*, *124*(4), 587-599. https://doi.org/10.1111/bju.14813

La Torre, A., Giupponi, G., Duffy, D., & Conca, A. (2013). Sexual dysfunction related to psychotropic drugs: a critical review--part I: antidepressants. *Pharmacopsychiatry*, *46*(5), 191-199. https://doi.org/10.1055/s-0033-1345205

Laine, L., Ahnen, D., McClain, C., Solcia, E., & Walsh, J. H. (2000). Review article: potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. *Aliment Pharmacol Ther*, *14*(6), 651-668. https://doi.org/10.1046/j.1365-2036.2000.00768.x

Lazarus, B., Chen, Y., Wilson, F. P., Sang, Y., Chang, A. R., Coresh, J., & Grams, M. E. (2016). Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med*, *176*(2), 238-246. https://doi.org/10.1001/jamainternmed.2015.7193

McCaffrey, D. F., Griffin, B. A., Almirall, D., Slaughter, M. E., Ramchand, R., & Burgette, L. F. (2013). A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med*, *32*(19), 3388-3414. https://doi.org/10.1002/sim.5753

MHRA. (2017). *MHRA reclassifies Viagra Connect tablets to a Pharmacy medicine*. Retrieved 5 March 2024 from https://www.gov.uk/government/news/mhra-reclassifies-viagra-connect-tablets-to-a-pharmacy-medicine

Nolde, M., Bahls, M., Friedrich, N., Dorr, M., Dreischulte, T., Felix, S. B., Ruckert-Eheberg, I. M., Ahn, N., Amann, U., Schwedhelm, E., Volzke, H., Lerch, M. M., Linseisen, J., Meisinger, C., & Baumeister, S. E. (2021). Association of proton pump inhibitor use with endothelial function and metabolites of the nitric oxide pathway: A cross-sectional study. *Pharmacotherapy*, *41*(2), 198-204. https://doi.org/10.1002/phar.2504

Pinheiro, L. C., Oliveira-Paula, G. H., Portella, R. L., Guimaraes, D. A., de Angelis, C. D., & Tanus-Santos, J. E. (2016). Omeprazole impairs vascular redox biology and causes xanthine oxidoreductase-mediated endothelial dysfunction. *Redox Biol*, *9*, 134-143. https://doi.org/10.1016/j.redox.2016.08.001

Razdan, S., Greer, A. B., Patel, A., Alameddine, M., Jue, J. S., & Ramasamy, R. (2018). Effect of prescription medications on erectile dysfunction. *Postgrad Med J*, *94*(1109), 171-178. https://doi.org/10.1136/postgradmedj-2017-135233

Romano, L., Granata, L., Fusco, F., Napolitano, L., Cerbone, R., Priadko, K., Sciorio, C., Mirone, V., & Romano, M. (2022). Sexual Dysfunction in Patients With Chronic Gastrointestinal and Liver Diseases: A neglected Issue. *Sex Med Rev*, *10*(4), 620-631. https://doi.org/10.1016/j.sxmr.2021.02.002

Rosen, R. C., Fisher, W. A., Eardley, I., Niederberger, C., Nadel, A., Sand, M., Men's Attitudes to Life, E., & Sexuality, S. (2004). The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. *Curr Med Res Opin*, *20*(5), 607-617. https://doi.org/10.1185/030079904125003467

Rothmore, J. (2020). Antidepressant-induced sexual dysfunction. *Med J Aust*, *212*(7), 329-334. https://doi.org/10.5694/mja2.50522

Shamloul, R., & Ghanem, H. (2013). Erectile dysfunction. *Lancet*, *381*(9861), 153-165. https://doi.org/10.1016/S0140-6736(12)60520-0

Shen, S. (2019). Chronic Disease Burden, Sexual Frequency, and Sexual Dysfunction in Partnered Older Adults. *J Sex Marital Ther*, *45*(8), 706-720. https://doi.org/10.1080/0092623X.2019.1610127

Stringer, J. D. (2016). Gender and Sexual Health: Sexual Dysfunction. *FP Essent*, *449*, 18-26. https://www.ncbi.nlm.nih.gov/pubmed/27731968

Trinchieri, M., Trinchieri, M., Perletti, G., Magri, V., Stamatiou, K., Cai, T., Montanari, E., & Trinchieri, A. (2021). Erectile and Ejaculatory Dysfunction Associated with Use of Psychotropic Drugs: A Systematic Review. *J Sex Med*, *18*(8), 1354-1363. https://doi.org/10.1016/j.jsxm.2021.05.016

Valeiro, C., Matos, C., Scholl, J., & van Hunsel, F. (2022). Drug-Induced Sexual Dysfunction: An Analysis of Reports to a National Pharmacovigilance Database. *Drug Saf*, *45*(6), 639-650. https://doi.org/10.1007/s40264-022-01174-3

Yepuri, G., Sukhovershin, R., Nazari-Shafti, T. Z., Petrascheck, M., Ghebre, Y. T., & Cooke, J. P. (2016). Proton Pump Inhibitors Accelerate Endothelial Senescence. *Circ Res*, *118*(12), e36-42. https://doi.org/10.1161/CIRCRESAHA.116.308807

Yogarajah, M., & Mula, M. (2017). Sexual Dysfunction in Epilepsy and the Role of Anti-Epileptic Drugs. *Curr Pharm Des*, *23*(37), 5649-5661. https://doi.org/10.2174/1381612823666171004115230

Yoshida, K., Solomon, D. H., & Kim, S. C. (2015). Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol*, *11*(7), 437-441. https://doi.org/10.1038/nrrheum.2015.30

Annexes

Annex 1 - Information on Databases and Healthcare systems included

IQVIA™ Disease Analyzer (DA) Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included, which covers all patients consulting a practice. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2,500 practices and 3,100 physicians (13 speciality groups) representing over 15,000,000 patients. This database used to be named IMS® Disease Analyzer Germany and some use of this terminology may persist.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results in order to enable reliable analysis.

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK, as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

Annex 2 - Codelists

EXPOSURES: PPIs AND H2RAs

- **IQVIA™ Disease Analyzer Germany**

PPIs

INN	EPHMRA ATC Code	EPHMRA ATC Text
ACETYLSALICYLIC ACID + ESOMEPRAZOLE	B01C5	Platelet aggregation inhibitors, combinations
AMOXICILLIN + OMEPRAZOLE + CLARITHROMYCIN	A02B2	Proton pump inhibitors
DICLOFENAC + OMEPRAZOLE	M01A1	Anti-rheumatics, non-steroidal plain
ESOMEPRAZOLE	A02B2	Proton pump inhibitors
LANSOPRAZOLE	A02B2	Proton pump inhibitors
NAPROXEN + ESOMEPRAZOLE	M01A1	Anti-rheumatics, non-steroidal plain
OMEPRAZOLE	A02B2	Proton pump inhibitors
PANTOPRAZOLE	A02B2	Proton pump inhibitors

H2ARs

INN	EPHMRA ATC Code	EPHMRA ATC Text
CIMETIDINE	A02B1	H2 antagonist
FAMOTIDINE	A02B1	H2 antagonist
NIZATIDINE	A02B1	H2 antagonist
RANITIDINE	A02B1	H2 antagonist

- **IQVIA™ Medical Research Data (IMRD) UK**

PPIs

Generic Drug Name
ESOMEPRAZOLE
LANSOPRAZOLE
OMEPRAZOLE
PANTOPRAZOLE
RABEPRAZOLE
KETOPROFEN/OMEPRAZOLE
NAPROXEN/ESOMEPRAZOLE
AMOXICILLIN/CLARITHROMYCIN/LANSOPRAZOLE
METRONIDAZOLE/CLARITHROMYCIN/LANSOPRAZOLE

H2ARs

Generic Drug Name
CIMETIDINE
FAMOTIDINE
NIZATIDINE
RANITIDINE
RANITIDINE BISMUTH CITRATE
CIMETIDINE/ALGINIC ACID
FAMOTIDINE/CALCIUM/MAGNESIUM

OUTCOME: SEXUAL DYSFUNCTION

- **IQVIA™ Disease Analyzer Germany**

WHO ICD10 code	WHO ICD10 Text
F52.0	Lack or loss of sexual desire
F52.1	Sexual aversion and lack of sexual enjoyment
F52.2	Failure of genital response
F52.3	Orgasmic dysfunction
F52.6	Nonorganic dyspareunia
F52.8	Other sexual dysfunction, not caused by organic disorder or disease
F52.9	Unspecified sexual dysfunction, not caused by organic disorder or disease
N48.4	Impotence of organic origin
N94.1	Dyspareunia
N48.3	Priapism -- Painful erection

- **IQVIA™ Medical Research Data (IMRD) UK**

Read code	Term
E2275	Inhibited male orgasm
67IA	Advice about impotence
7A6G0	Revascularisation for impotence
7A6G5	Ligation of penile veins for impotence
Eu521	Sexual aversion disorder
K27y1	Impotence of organic origin
1ABG	Sexual intercourse difficult
1ABB	Cannot get an erection
1ABC	Cannot sustain an erection
ZV417	Abnormal sexual function
15D	Pain on sexual intercourse
E2273	Impotence
E2273-1	Erectile dysfunction

Read code	Term
Eu520-3	[X] Lack of libido
Eu521-1	[X]Anhedonia sexual
7C25E	Management of erectile dysfunction
Eu522	Failure of genital response
Eu520-2	[X]Hypoactive sexual desire disorder
Eu523-1	[X]Inhibited orgasm
Eu520	Lack or loss of sexual desire
Eu522-2	[X]Male erectile disorder
Eu523	Orgasmic dysfunction
Eu52y	[X]Oth sex dysfunction, not caused by organic disordr/dsease
Eu523-2	Anorgasmia
Eu522-3	Psychogenic impotence
Eu52	Non-organic sexual dysfunction
Eu52z	[X]Unspec sex dysfunction not caused by organic disordr/dis
K28y7	Dyspareunia due to non psychogenic cause in the male
E2272	Frigidity
E227-99	Frigidity and impotence
K580-99	Dyspareunia - non psychogenic
K27y1-99	Erectile dysfunction organic
EMISCDY1	Dyspareunia
EMISCPA6	Pain during or after sexual intercourse
EMISCIM4	Impotency
1D1B	C/O erectile dysfunction
EMISNQRE309	Reduced libido
EMISNQPR146	Problem getting an erection
EMISICD10|F5211	Lack of sexual enjoyment
K27y7	Erectile dysfunction due to diabetes mellitus
^ESCTLO263343	Low libido
^ESCTPS316073	Psychologic dyspareunia
^ESCTPA332307	Painful ejaculation
^ESCTOR351791	Orgasm incapacity
^ESCTPO357750	Poor erection
^ESCTDY366015	Dyspareunia
^ESCTOR384422	Orgasm disorder
^ESCTDO392066	Does not enjoy having sex
^ESCTIM451123	Impotence education
^ESCTDY479108	Dyspareunia due to non-psychogenic cause in the male
^ESCTDE494548	Decreased sexual function
^ESCTDR509827	Drug-induced impotence
^ESCTEN509828	Endocrine impotence
^ESCTCO509899	Coital failure
^ESCTSU524375	Superficial pain on intercourse
^ESCTDE524377	Deep pain on intercourse

Read code	Term
^ESCTDE524378	Deep dyspareunia
^ESCTSE524379	Sexual function painful
^ESCTDE526179	Delayed erection
^ESCTER526208	Erection without orgasm
^ESCTWE526211	Weak orgasm
^ESCTHY551800	Hypoactive sexual desire disorder
^ESCTPA562100	Pain on penetration
^ESCTDY572132	Dyspareunia - non-psychogenic
^ESCTER655321	Erectile dysfunction appliance
^ESCTSE748154	Secondary erectile dysfunction
^ESCTCO748662	Complaining of erectile dysfunction
^ESCT1395247	Erectile dysfunction
^ESCT1395249	Male erectile disorder
^ESCT1395253	Erectile dysfunction due to psychophysiologic disorder
^ESCT1409249	Erectile dysfunction due to diabetes mellitus
^ESCT1450429	Non-psychogenic dyspareunia

FREQUENCY OF RECORDING OF SUBSTANCES AND CLINICAL CONDITIONS IN DATABASES

Data on frequency of recording of the abovementioned substances and diagnosis in the databases are provided upon request.

Annex 3 – Supplementary results

Table A1. Number of SD events within 1-year follow-up by ICD10 codes in IQVIA™ Disease Analyzer Germany, including only treatment cohorts (esomeprazole, omeprazole, lansoprazole and H2RAs)

ITT				PP			
ICD10 code	ICD10 Term	N	%	ICD10 code	ICD10 Term	N	%
F522	FAILURE GENITAL RESPONSE	2,665	89.61	F522	FAILURE GENITAL RESPONSE	2,560	89.73
N484	IMPOTENCE ORGANIC ORIGIN	123	4.14	N484	IMPOTENCE ORGANIC ORIGIN	119	4.17
F529	UNSP SEX DYSF N/ORG DIS	76	2.56	F529	UNSP SEX DYSF N/ORG DIS	72	2.52
F520	LACK/LOSS SEXUAL DESIRE	55	1.85	F520	LACK/LOSS SEXUAL DESIRE	52	1.82
F528	O/SEX DYSFUNC N/ORG DIS	34	1.14	F528	O/SEX DYSFUNC N/ORG DIS	31	1.09
F523	ORGASMIC DYSFUNCTION	9	0.30	F523	ORGASMIC DYSFUNCTION	8	0.28
N483	PRIAPISM	6	0.20	N483	PRIAPISM	6	0.21
N941	DYSPAREUNIA	<6	<0.20	N941	DYSPAREUNIA	<6	<0.21
F521	SEXUAL AVERSION	<6	<0.20	F521	SEXUAL AVERSION	<6	<0.21
TOTAL		**2,974**	**100.00**	**TOTAL**		**2,853**	**100.00**

ITT: intention-to-treat analytical approach; PP: per-protocol analytical approach.

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

Table A2. Number of SD events within 1-y follow-up by Read codes during the study period in IQVIA™ Medical Research Data (IMRD), including only treatment cohorts (esomeprazole, omeprazole, lansoprazole and H2RAs)

		ITT				PP	
Read code	Read term	N	%	Read code	Read term	N	%
E2273-1	Erectile dysfunction	2,694	66.98	E2273-1	Erectile dysfunction	2,512	66.68
E2273	Impotence	613	15.24	E2273	Impotence	565	15.00
1D1B	C/O erectile dysfunction	470	11.69	1D1B	C/O erectile dysfunction	454	12.05
67IA	Advice about impotence	68	1.69	67IA	Advice about impotence	66	1.75
Eu522-2	[X]Male erectile disorder	35	0.87	Eu522-2	[X]Male erectile disorder	34	0.90
^ESCT1395247	Erectile dysfunction	24	0.60	^ESCT1395247	Erectile dysfunction	23	0.61
1ABC	Cannot sustain an erection	19	0.47	1ABC	Cannot sustain an erection	19	0.50
1ABB	Cannot get an erection	15	0.37	1ABB	Cannot get an erection	15	0.40
K27y1	Impotence of organic origin	12	0.30	K27y1	Impotence of organic origin	11	0.29
ZV417	Abnormal sexual function	10	0.25	ZV417	Abnormal sexual function	10	0.27
Eu520	Lack or loss of sexual desire	9	0.22	7C25E	Management of erectile dysfunction	8	0.21
7C25E	Management of erectile dysfunction	9	0.22	Eu520	Lack or loss of sexual desire	7	0.19
EMISNQRE309	Reduced libido	7	0.17	EMISNQRE309	Reduced libido	7	0.19
Eu522	Failure of genital response	7	0.17	Eu522	Failure of genital response	7	0.19
^ESCTPO357750	Poor erection	6	0.15	15D	Pain on sexual intercourse	6	0.16
15D	Pain on sexual intercourse	6	0.15	^ESCTPO357750	Poor erection	<6	<0.16
Eu520-3	[X] Lack of libido	<6	<0.15	Eu520-3	[X] Lack of libido	<6	<0.16
Eu523	Orgasmic dysfunction	<6	<0.15	Eu523	Orgasmic dysfunction	<6	<0.16
E2275	Inhibited male orgasm	<6	<0.15	E2275	Inhibited male orgasm	<6	<0.16
Eu522-3	Psychogenic impotence	<6	<0.15	Eu522-3	Psychogenic impotence	<6	<0.16
EMISNQPR146	Problem getting an erection	<6	<0.15	EMISNQPR146	Problem getting an erection	<6	<0.16
Eu52	Non-organic sexual dysfunction	<6	<0.15	Eu52	Non-organic sexual dysfunction	<6	<0.16
K27y7	Erectile dysfunction due to diabetes mellitus	<6	<0.15	K27y7	Erectile dysfunction due to diabetes mellitus	<6	<0.16
EMISCPA6	Pain during or after sexual intercourse	<6	<0.15	EMISCPA6	Pain during or after sexual intercourse	<6	<0.16
Eu521-1	[X]Anhedonia sexual	<6	<0.15	Eu521-1	[X]Anhedonia sexual	<6	<0.16
TOTAL		**4,022**	**100.00**	**TOTAL**		**3,767**	**100.00**

ITT: intention-to-treat analytical approach; PP: per-protocol analytical approach.

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

Table A3. Number of SD events within 1-year follow-up by ICD10 codes in IQVIA™ Disease Analyzer Germany, including treatment cohorts (esomeprazole, omeprazole, lansoprazole and H2RAs) and non-initiator of treatment cohort

		ITT				PP	
ICD10 code	ICD10 Term	N	%	ICD10 code	ICD10 Term	N	%
F522	FAILURE GENITAL RESPONSE	2,342	89.80	F522	FAILURE GENITAL RESPONSE	2,244	90.16
N484	IMPOTENCE ORGANIC ORIGIN	122	4.68	N484	IMPOTENCE ORGANIC ORIGIN	114	4.58
F529	UNSP SEX DYSF N/ORG DIS	61	2.34	F529	UNSP SEX DYSF N/ORG DIS	54	2.17
F520	LACK/LOSS SEXUAL DESIRE	39	1.50	F520	LACK/LOSS SEXUAL DESIRE	38	1.53
F528	O/SEX DYSFUNC N/ORG DIS	25	0.96	F528	O/SEX DYSFUNC N/ORG DIS	22	0.88
F523	ORGASMIC DYSFUNCTION	7	0.27	N483	PRIAPISM	7	0.28
N483	PRIAPISM	7	0.27	F523	ORGASMIC DYSFUNCTION	6	0.24
N941	DYSPAREUNIA	<6	<0.24	N941	DYSPAREUNIA	<6	<0.24
F521	SEXUAL AVERSION	<6	<0.24	F521	SEXUAL AVERSION	<6	<0.24
TOTAL		**2,608**	**100.00**	**TOTAL**		**2,489**	**100.00**

ITT: intention-to-treat analytical approach; PP: per-protocol analytical approach.

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

Table A4. Number of SD events within 1-year follow-up by Read codes in IQVIA™ Medical Research Data (IMRD), including treatment cohorts (esomeprazole, omeprazole, lansoprazole and H2RAs) and non-initiator of treatment cohort

		ITT				PP	
Read code	**Read term**	**N**	**%**	**Read code**	**Read term**	**N**	**%**
E2273-1	Erectile dysfunction	2,479	62.04	E2273-1	Erectile dysfunction	2,327	61.90
1D1B	C/O erectile dysfunction	639	15.99	1D1B	C/O erectile dysfunction	610	16.23
E2273	Impotence	612	15.32	E2273	Impotence	570	15.16
67IA	Advice about impotence	106	2.65	67IA	Advice about impotence	100	2.66
^ESCT1395247	Erectile dysfunction	27	0.68	^ESCT1395247	Erectile dysfunction	24	0.64
Eu522-2	[X]Male erectile disorder	22	0.55	Eu522-2	[X]Male erectile disorder	21	0.56
K27y1	Impotence of organic origin	20	0.50	K27y1	Impotence of organic origin	20	0.53
1ABB	Cannot get an erection	18	0.45	1ABB	Cannot get an erection	17	0.45
1ABC	Cannot sustain an erection	17	0.43	1ABC	Cannot sustain an erection	16	0.43
ZV417	Abnormal sexual function	12	0.30	ZV417	Abnormal sexual function	12	0.32
EMISNQRE309	Reduced libido	7	0.18	Eu520	Lack or loss of sexual desire	6	0.16
Eu520	Lack or loss of sexual desire	6	0.15	EMISNQRE309	Reduced libido	6	0.16
7C25E	Management of erectile dysfunction	<6	<0.15	7C25E	Management of erectile dysfunction	<6	<0.16
^ESCTPO357750	Poor erection	<6	<0.15	^ESCTPO357750	Poor erection	<6	<0.16
EMISNQPR146	Problem getting an erection	<6	<0.15	EMISNQPR146	Problem getting an erection	<6	<0.16
Eu522	Failure of genital response	<6	<0.15	Eu522	Failure of genital response	<6	<0.16
Eu523	Orgasmic dysfunction	<6	<0.15	Eu522-3	Psychogenic impotence	<6	<0.16
Eu522-3	Psychogenic impotence	<6	<0.15	E2275	Inhibited male orgasm	<6	<0.16
E2275	Inhibited male orgasm	<6	<0.15	Eu523	Orgasmic dysfunction	<6	<0.16
Eu521-1	[X]Anhedonia sexual	<6	<0.15	Eu521-1	[X]Anhedonia sexual	<6	<0.16
Eu520-3	[X] Lack of libido	<6	<0.15	Eu520-3	[X] Lack of libido	<6	<0.16
Eu52	Non-organic sexual dysfunction	<6	<0.15	Eu52	Non-organic sexual dysfunction	<6	<0.16
^ESCTDY366015	Dyspareunia	<6	<0.15	^ESCTDY366015	Dyspareunia	<6	<0.16
15D	Pain on sexual intercourse	<6	<0.15	15D	Pain on sexual intercourse	<6	<0.16
K27y7	Erectile dysfunction due to diabetes mellitus	<6	<0.15	K27y7	Erectile dysfunction due to diabetes mellitus	<6	<0.16
TOTAL		**3,996**	**100.00**	**TOTAL**		**3,759**	**100.00**

ITT: intention-to-treat analytical approach; PP: per-protocol analytical approach.

Note: In accordance with database rules on the management of low cell counts, cells with low numbers (<6) have been removed prior to publication of this report.

A3.1 Main analysis: Comparison between esomeprazole/omeprazole and active treatment cohorts

Figure A1. Absolute standardized differences between treatment arms for each baseline covariate **before** stabilized inverse probability of treatment weighting (IPTW) in IQVIA™ DA Germany. Control refers to the non-initiator of treatment cohort. The vertical lines indicate an absolute difference at 0, 10 and 20. Of note, absolute differences presented here were multiplied by a factor of 100.

Figure A2. Absolute standardized differences between treatment arms for each baseline covariate **after** stabilized inverse probability of treatment weighting (IPTW) in IQVIA™ DA Germany. Control refers to the non-initiator of treatment cohort. The vertical lines indicate an absolute difference at 0, 10 and 20. Of note, absolute differences presented here are multiplied by a factor of 100. Treatment weights at the 1st and 99th percentiles of the non-truncated distribution were truncated. Observations with weights above or below the truncation limits (1st and 99th percentiles) took the weight of the corresponding truncation limit.

Figure A3. Absolute standardized differences between treatment arms for each baseline covariate **before** stabilized inverse probability of treatment weighting (IPTW) in IMRD UK. Control refers to the non-initiator of treatment cohort. The vertical lines indicate an absolute difference at 0, 10 and 20. Of note, absolute differences presented here were multiplied by a factor of 100.

Figure A4. Absolute standardized differences between treatment arms for each baseline covariate **after** stabilized inverse probability of treatment weighting (IPTW) in IMRD UK. Control refers to the non-initiator of treatment cohort. The vertical lines indicate an absolute difference at 0, 10 and 20. Of note, absolute differences presented here are multiplied by a factor of 100. Treatment weights at the 1st and 99th percentiles of the non-truncated distribution were truncated. Observations with weights above or below the truncation limits (1st and 99th percentiles) took the weight of the corresponding truncation limit.

A3.1.1 Supplementary analysis: Comparison between esomeprazole/omeprazole and active comparator cohorts using PP

Table A5. Unadjusted and adjusted incidence rates per 100 person-years of sexual dysfunction by treatment arm and database using PP analytical approach

	Treatment arm	N	N index-dates	Follow-up (person-years)	n events	Unadjusted			Stabilized IPTW adjusted		
						IR	95% CI		IR	95% CI	
IQVIA™ DA Germany	H2RAs	14038	16496	13979.53	78	**0.56**	0.45	0.70	**0.58**	0.43	0.78
	Esomeprazole	28702	33469	28852.92	144	**0.50**	0.42	0.59	**0.50**	0.42	0.60
	Omeprazole	109553	138943	123748.70	672	**0.54**	0.50	0.59	**0.51**	0.46	0.55
	Pantoprazole	332811	429075	392471.60	1959	**0.50**	0.48	0.52	**0.51**	0.49	0.54
IMRD UK	H2RAs	16432	17952	14372.98	207	**1.44**	1.26	1.65	**1.48**	1.27	1.73
	Esomeprazole	2553	2748	2339.05	24	**1.03**	0.69	1.53	**0.93**	0.60	1.43
	Omeprazole	172555	228505	208659.60	2485	**1.19**	1.15	1.24	**1.21**	1.17	1.26
	Lansoprazole	81310	99726	88549.97	1051	**1.19**	1.12	1.26	**1.15**	1.08	1.22

PP: Per-protocol analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

Table A6. Unadjusted and adjusted hazard ratios of sexual dysfunction by treatment arm and database using PP analytical approach

		Target arm: Esomeprazole						Target arm: Omeprazole					
		Unadjusted			Stabilized IPTW adjusted			Unadjusted			Stabilized IPTW adjusted		
	Treatment arm	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
IQVIA™ DA Germany	H2RAs	**1.12**	0.85	1.47	**1.15**	0.81	1.63	**1.03**	0.81	1.30	**1.14**	0.84	1.56
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.92**	0.77	1.10	**1.00**	0.82	1.22
	Omeprazole	**1.09**	0.91	1.30	**1.00**	0.82	1.23	**1.00**	[Reference]		**1.00**	[Reference]	
	Pantoprazole	**1.00**	0.84	1.18	**1.02**	0.85	1.23	**0.92**	0.84	1.00	**1.01**	0.92	1.12
IMRD UK	H2RAs	**1.40**	0.92	2.14	**1.60**	1.01	2.54	**1.21**	1.05	1.40	**1.22**	1.04	1.44
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.86**	0.58	1.29	**0.76**	0.49	1.18
	Omeprazole	**1.16**	0.78	1.73	**1.31**	0.85	2.03	**1.00**	[Reference]		**1.00**	[Reference]	
	Lansoprazole	**1.16**	0.77	1.73	**1.24**	0.80	1.92	**1.00**	0.93	1.07	**0.94**	0.88	1.02

PP: Per-protocol analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

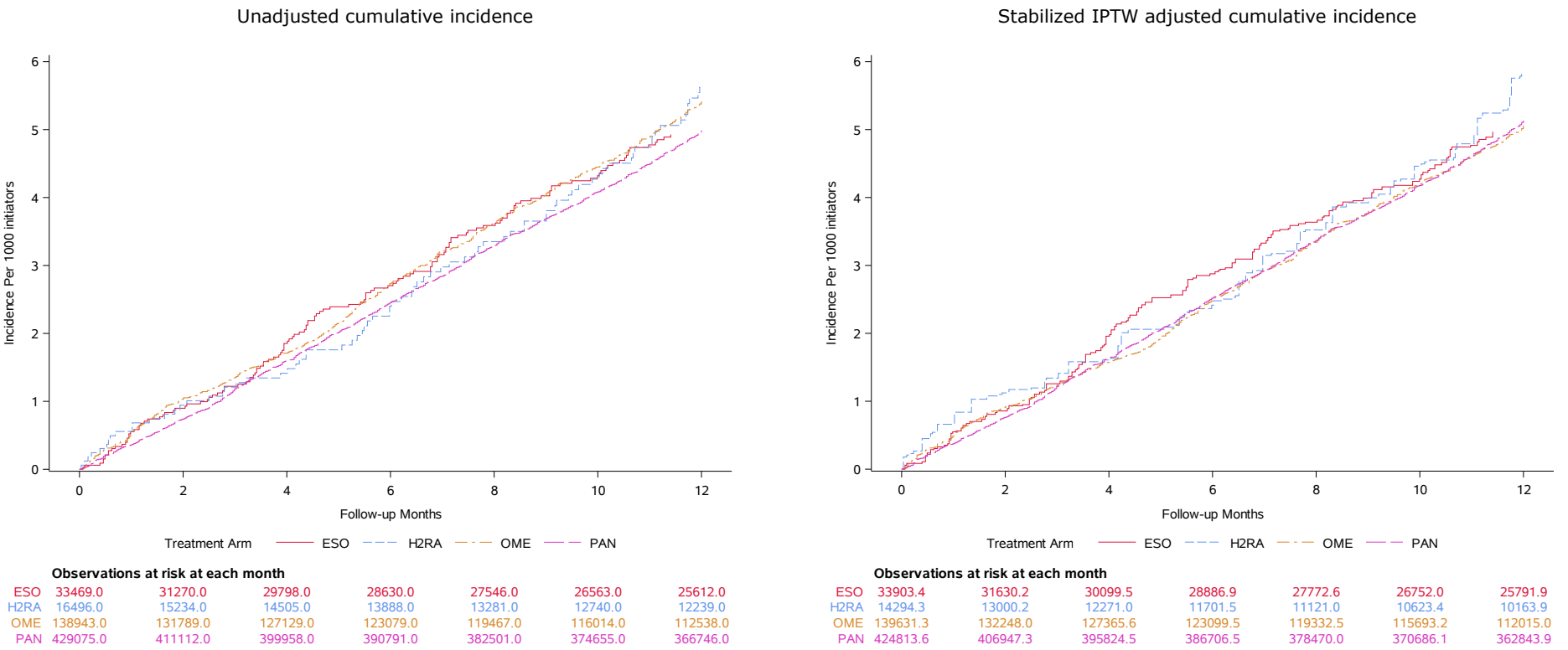

Figure A5. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IQVIA™ DA Germany using PP analytical approach

ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; PAN: Pantoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-to-treat analysis.

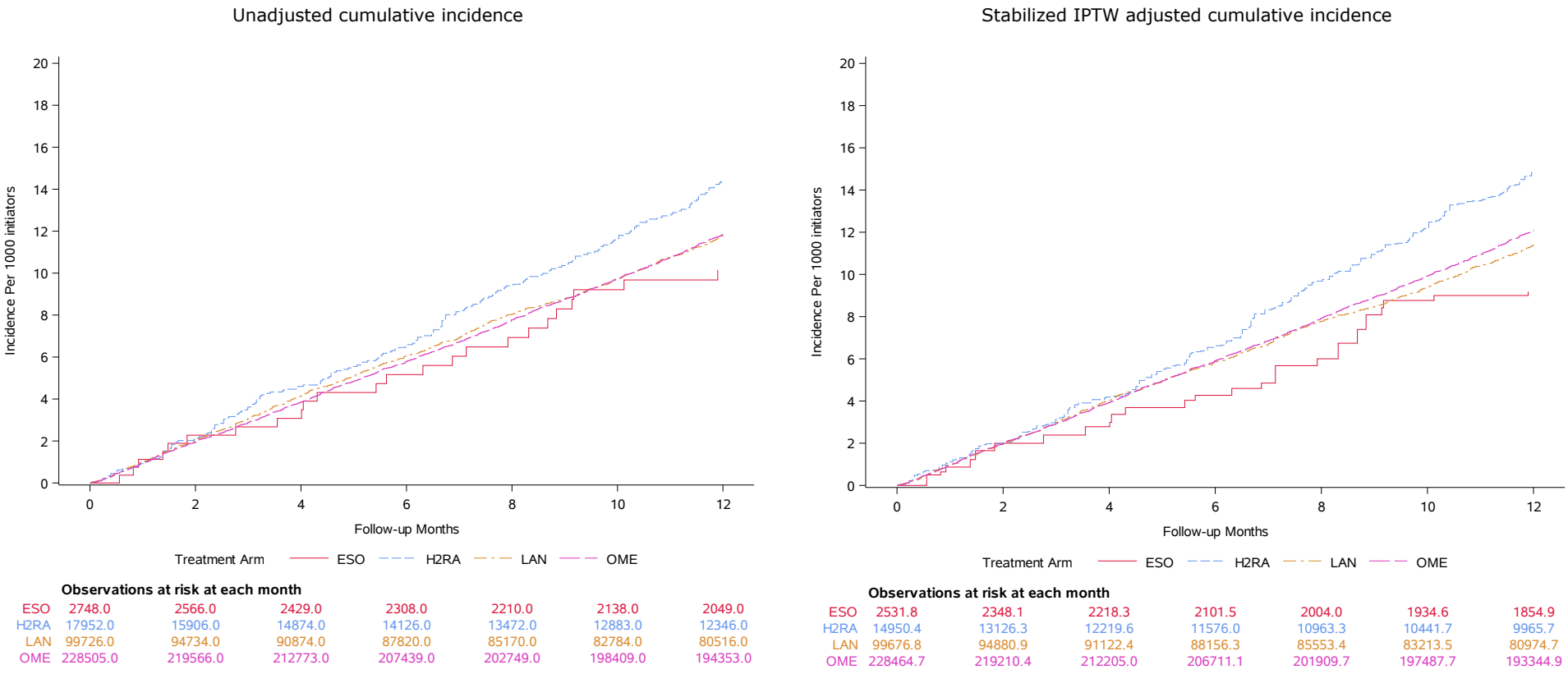

Figure A6. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IMRD UK using PP analytical approach

ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; LAN: Lansoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-to-treat analysis.

A3.2 Main analysis: Comparison between esomeprazole/omeprazole and non-initiator of treatment cohort

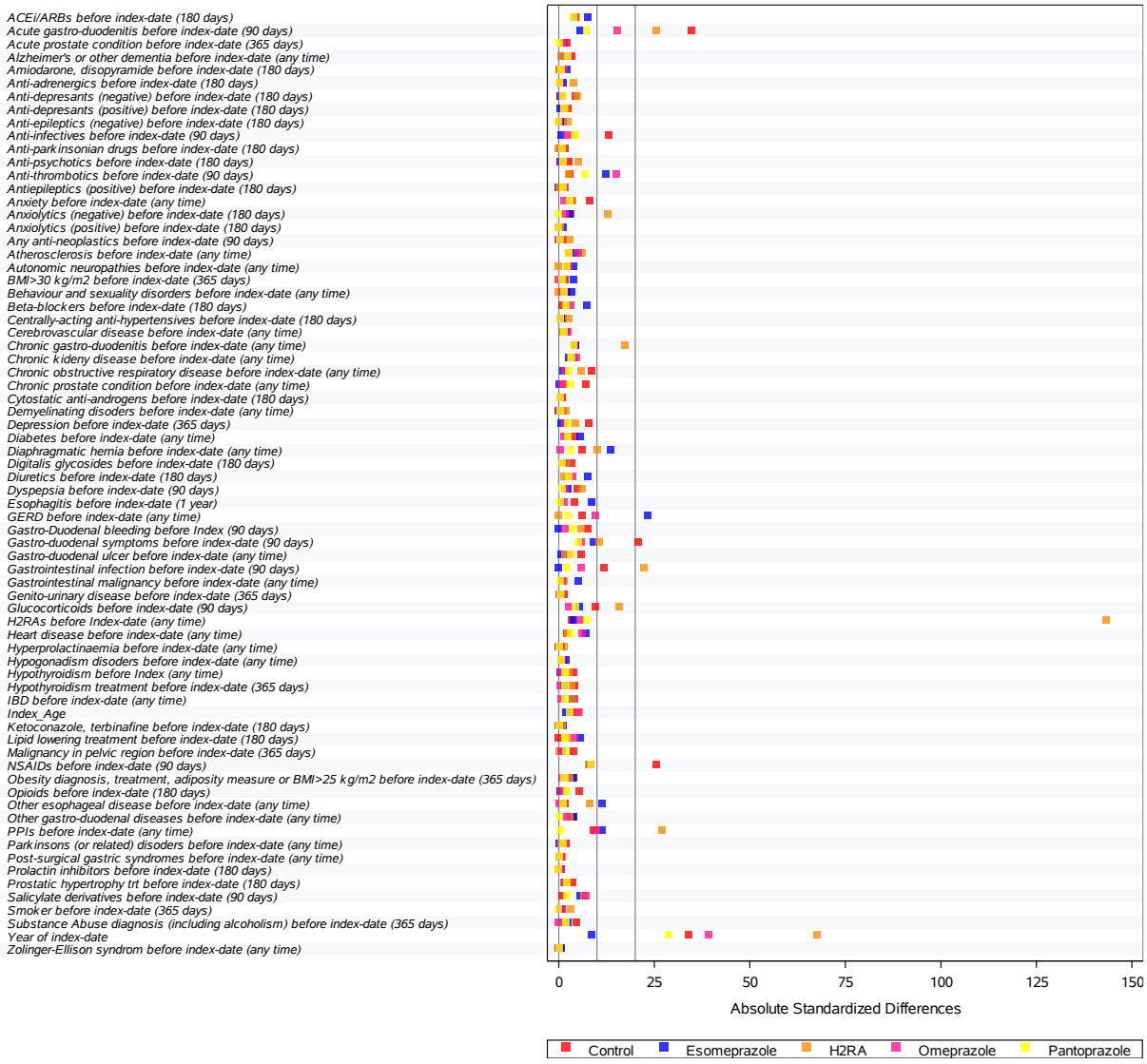

Figure A7. Absolute standardized differences between treatment arms for each baseline covariate **before** stabilized inverse probability of treatment weighting (IPTW) in IQVIA™ DA Germany. Control refers to the non-initiator of treatment cohort. The vertical lines indicate an absolute difference at 0, 10 and 20. Of note, absolute differences presented here are multiplied by a factor of 100.

Figure A8. Absolute standardized differences between treatment arms for each baseline covariate **after** stabilized inverse probability of treatment weighting (IPTW) in IQVIA™ DA Germany. Control refers to the non-initiator of treatment cohort. The vertical lines indicate absolute differences at 0, 10 and 20. Of note, absolute differences presented here are multiplied by a factor of 100. Treatment weights at the 1st and 99th percentiles of the non-truncated distribution were truncated. Observations with weights above or below the truncation limits (1st and 99th percentiles) took the weight of the corresponding truncation limit.

Figure A9. Absolute standardized differences between treatment arms for each baseline covariate **before** stabilized inverse probability of treatment weighting (IPTW) in IMRD UK. Control refers to the non-initiator of treatment cohort. The vertical lines indicate an absolute difference at 0, 10 and 20. Of note, absolute differences presented here are multiplied by a factor of 100.

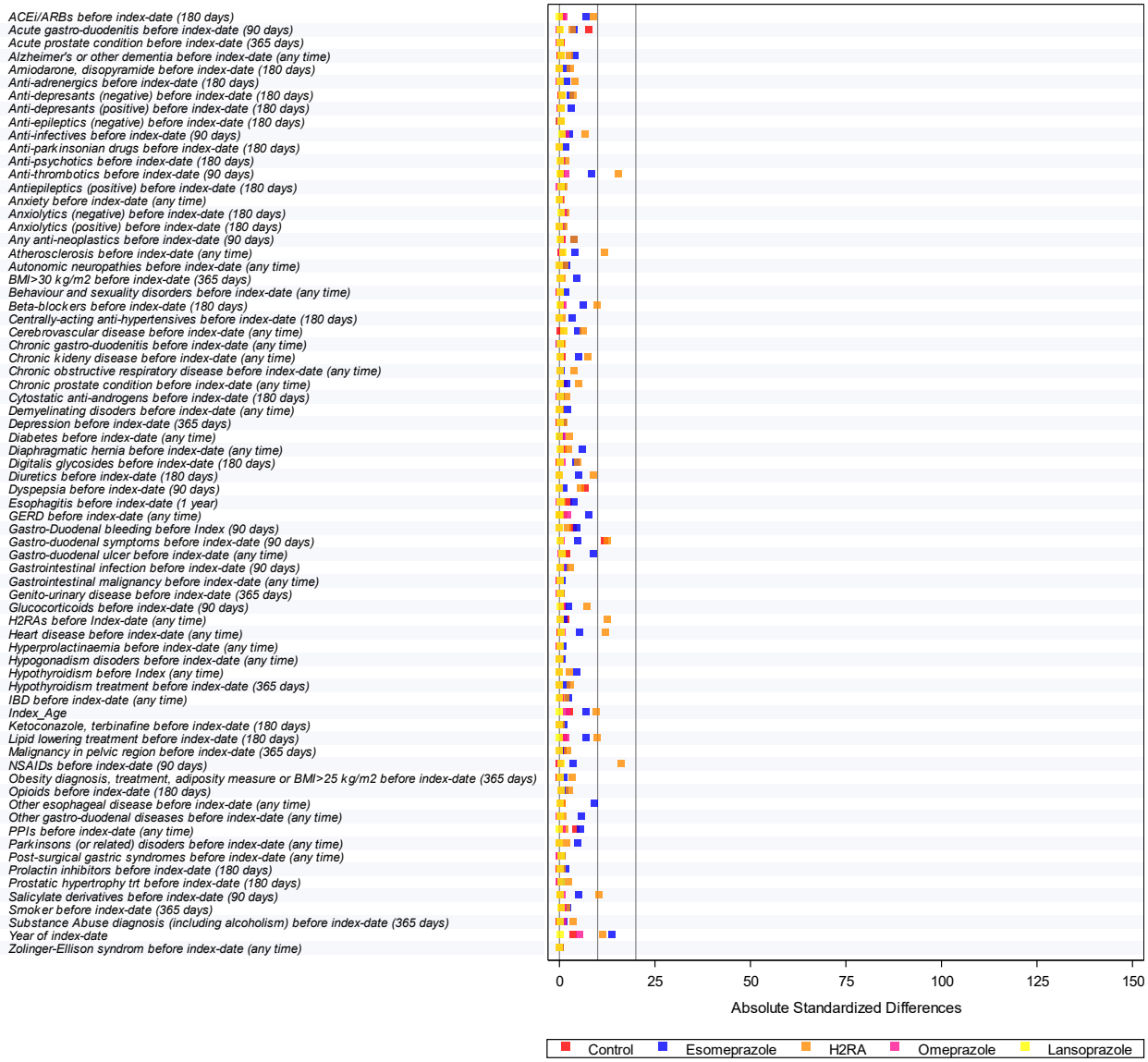

Figure A10. Absolute standardized differences between treatment arms for each baseline covariate **after** stabilized inverse probability of treatment weighting (IPTW) in IMRD UK. Control refers to the non-initiator of treatment cohort. The vertical lines indicate absolute differences at 0, 10 and 20. Of note, absolute differences presented here are multiplied by a factor of 100. Treatment weights at the 1st and 99th percentiles of the non-truncated distribution were truncated. Observations with weights above or below the truncation limits (1st and 99th percentiles) took the weight of the corresponding truncation limit.

A3.2.1 Supplementary analysis: Comparison between esomeprazole/omeprazole and non-initiator of treatment cohort using PP

Table A7. Unadjusted and adjusted incidence rates per 100 person-years of sexual dysfunction by treatment arm and database using PP analytical approach

	Treatment arm	N	N index-dates	Follow-up (person-years)	n events	Unadjusted			Stabilized IPTW adjusted		
						IR	95% CI		IR	95% CI	
IQVIA™ DA Germany	H2RAs	8201	9596	8064.74	53	**0.66**	0.50	0.86	**0.69**	0.48	1.00
	Esomeprazole	20406	23660	20375.18	106	**0.52**	0.43	0.63	**0.52**	0.43	0.64
	Omeprazole	73513	92596	82695.87	480	**0.58**	0.53	0.63	**0.53**	0.48	0.59
	Pantoprazole	232637	293874	269454.50	1409	**0.52**	0.50	0.55	**0.53**	0.50	0.56
	Non-initiators	96060	116253	105457.30	441	**0.42**	0.38	0.46	**0.42**	0.38	0.48
IMRD UK	H2RAs	7940	8561	6919.18	115	**1.66**	1.38	2.00	**1.70**	1.36	2.13
	Esomeprazole	1601	1706	1473.15	17	**1.15**	0.72	1.86	**1.26**	0.73	2.17
	Omeprazole	103502	129761	118785.40	1554	**1.31**	1.24	1.37	**1.37**	1.29	1.45
	Lansoprazole	46311	54519	48293.96	666	**1.38**	1.28	1.49	**1.34**	1.24	1.46
	Non-initiators	84607	131468	119372.7	1407	**1.18**	1.11	1.25	**1.17**	1.09	1.25

PP: Per-protocol analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

Table A8. Unadjusted and adjusted hazard ratios of sexual dysfunction by treatment arm and database using PP analytical approach

	Treatment arm	Target arm: Esomeprazole						Target arm: Omeprazole					
		Unadjusted			Stabilized IPTW adjusted			Unadjusted			Stabilized IPTW adjusted		
		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
IQVIA™ DA Germany	H2RAs	**1.26**	0.91	1.76	**1.32**	0.87	2.02	**1.13**	0.85	1.50	**1.29**	0.88	1.90
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.90**	0.73	1.11	**0.98**	0.78	1.23
	Omeprazole	**1.12**	0.90	1.38	**1.02**	0.81	1.29	**1.00**	[Reference]		**1.00**	[Reference]	
	Pantoprazole	**1.01**	0.83	1.22	**1.01**	0.82	1.26	**0.90**	0.81	1.00	**0.99**	0.88	1.11
	Non-initiators	**0.80**	0.65	1.00	**0.81**	0.64	1.03	**0.72**	0.63	0.82	**0.79**	0.68	0.92
IMRD UK	H2RAs	**1.44**	0.87	2.40	**1.35**	0.75	2.43	**1.27**	1.05	1.54	**1.25**	0.99	1.57
	Esomeprazole	**1.00**	[Reference]		**1.00**	[Reference]		**0.88**	0.55	1.42	**0.92**	0.54	1.60
	Omeprazole	**1.13**	0.70	1.83	**1.08**	0.63	1.87	**1.00**	[Reference]		**1.00**	[Reference]	
	Lansoprazole	**1.20**	0.74	1.94	**1.06**	0.61	1.84	**1.05**	0.96	1.15	**0.98**	0.89	1.09
	Non-initiators	**1.02**	0.63	1.65	**0.93**	0.54	1.60	**0.90**	0.84	0.97	**0.86**	0.78	0.93

PP: Per-protocol analysis; IPTW: Inverse probability of treatment weighting; H2RA: Histamine type 2 receptor antagonists.

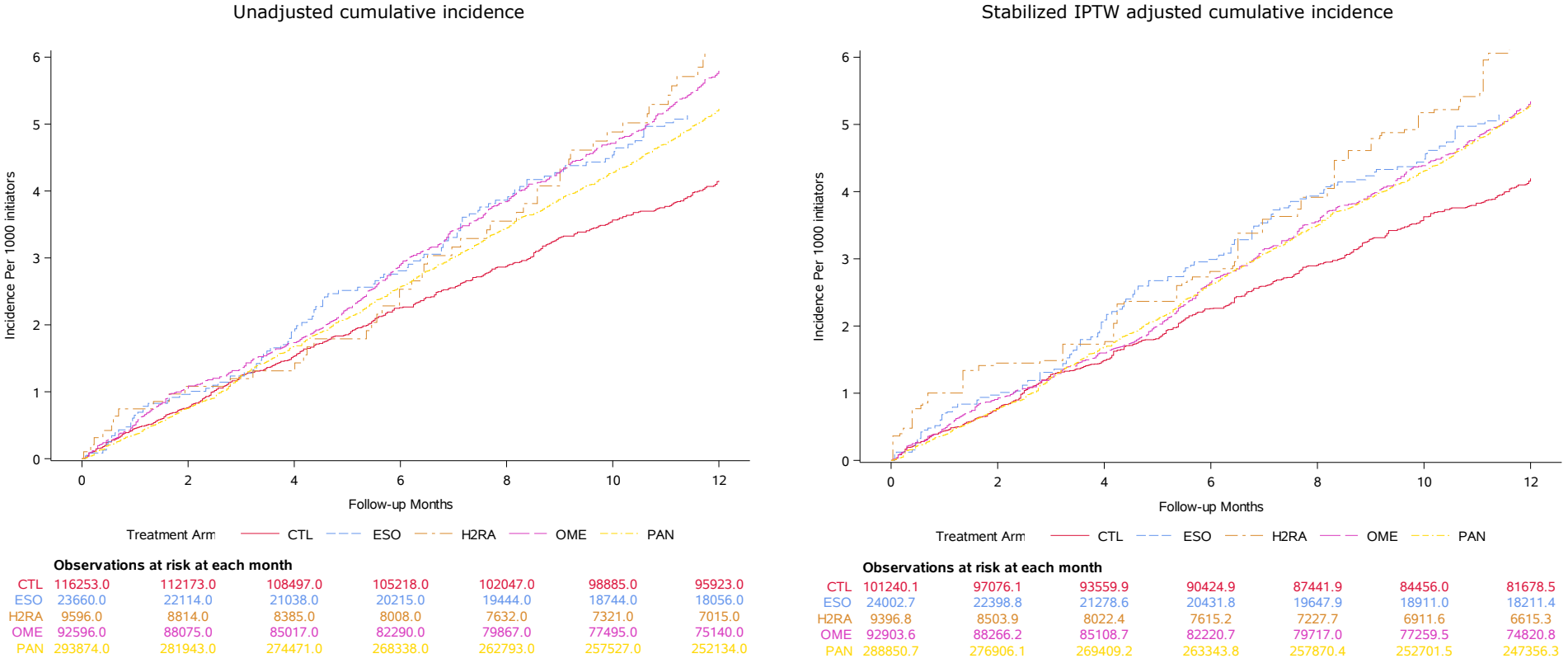

Figure A11. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IQVIA™ DA Germany using PP analytical approach

CTL: Non-initiator of treatment cohort; ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; PAN: Pantoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-to-treat analysis.

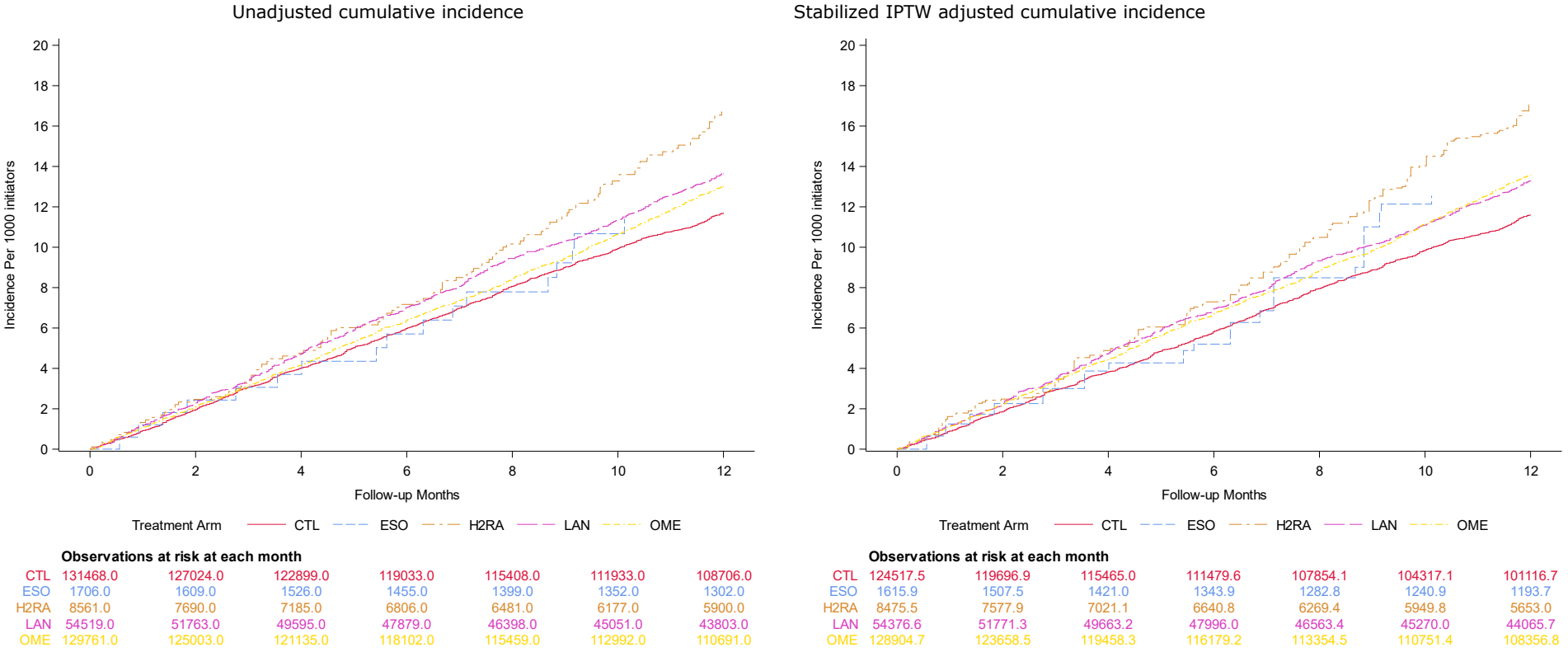

Figure A12. Unadjusted (left) and stabilized IPTW adjusted (right) cumulative incidence (%) of sexual dysfunction in IMRD UK using PP analytical approach

CTL: Non-initiator of treatment cohort; ESO: Esomeprazole; H2RA: Histamine type 2 receptor antagonists; OME: Omeprazole; PAN: Pantoprazole; IPTW: Inverse probability of treatment weighting; ITT: intention-to-treat analysis.