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Trends in Proton-Pump Inhibitor Use Among Danish Adults: A Nationwide Drug Utilization Study 2015–2023

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ABSTRACT

The global increase in proton-pump inhibitor (PPI) use has raised concerns about their appropriate use, particularly due to potential overprescription and associated adverse effects. This study examines PPI utilization patterns among Danish adults from 2015 to 2023 using the Danish nationwide health registries. We estimated the annual incidence rate (users per 100 person-years) and monthly prevalence (proportion with a filled prescription or sufficient tablets). Treatment duration was assessed using the ‘proportion of patients covered’ and the Kaplan–Meier method. We also calculated the proportion of adults with concomitant use of ulcerogenic drugs over time. We identified 1 729 440 adults who filled at least one PPI prescription during 2015–2023. The prevalence increased from 7.0% in 2015 to 8.2% in 2023, while incidence rate remained stable at ~3 users per 100 person years. PPI use increased with age. Three years after initiation, 17% used PPIs, while 1.5% had remained on continuous treatment. In 2023, 50% of users had concomitant ulcerogenic drug use, a 3.2% increase since 2015. The prevalence of PPI use in Denmark has risen markedly reaching a high stable level, with a clear age-dependent trend. Increased attention to appropriate PPI use is necessary to ensure rational prescribing and prevent potential overuse.

1 | Introduction

Proton-pump inhibitors (PPIs) are widely used for the management of acid-related disorders due to them being highly effective and relatively well-tolerated in both short- and long-term treatment [1]. However, growing concerns have emerged regarding the risk associated with long-term PPI use, including an increased risk of gastrointestinal infections and other rare side effects such as microscopic colitis [2]. Ongoing research continues to uncover additional potential risks of prolonged PPI therapy [2, 3].

PPI use has increased significantly over the last decades [4–10]. This surge, combined with concerns about adverse effects, has

heightened the awareness of appropriate PPI use [11]. In response, various initiatives, including clinical guidelines on when and how to deprescribe PPIs, have been introduced to curb inappropriate use and ensure that PPIs are prescribed rationally [12–14].

Mapping drug utilization trends is an important tool for healthcare stakeholders, as it helps identify areas for improvement in prescribing practices and informs future healthcare decision-making [15]. The PPI use in Denmark has previously been described from 2002 to 2014 [5]. In this context, we aimed to provide a detailed description of PPI utilization among Danish adults from 2015 to 2023. Specifically, we examined user characteristics, temporal trends and the concomitant use of ulcerogenic drugs.

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Summary

- The use of stomach acid inhibitors, known as proton-pump inhibitors (PPIs), has increased worldwide, raising concerns about unnecessary prescriptions and potential side effects. This study looked at how Danish adults used PPIs between 2015 and 2023 based on national health data.
- The number of people starting PPI treatment stayed about the same during the study, but more people in total used them in 2023 compared with 2015, suggesting that more people were taking them for a longer time. These findings highlight the need for careful prescribing to prevent unnecessary long-term use.

2 | Method

This nationwide descriptive drug utilization study examined the use of PPIs among Danish adults from 2015 to 2023 using data from the Danish healthcare registries.

2.1 | Data Sources

We used three main data sources: The Danish National Prescription Registry contains individual-level data on all prescriptions filled at Danish pharmacies since 1995, including dispensing dates, drug types, strength and the quantity expressed in defined daily doses (DDD) [16]. We used the WHO definition of DDD as the assumed average maintenance dose per day for a drug used for its main indication [17]. The registry does not include in-hospital and over-the-counter drug use, and all drugs listed are classified according to the Anatomic Therapeutic Chemical (ATC) index [18].

The Danish National Patient Registry provides information on all nonpsychiatric hospital admissions and outpatient contacts since 1977, with psychiatric hospital contacts included from 1995 [19]. Diagnoses have been coded according to the 10th revision of the International Statistical Classification of Diseases (ICD-10) since 1994.

The Danish Civil Registration System contains data on vital status and migration, which were linked to the health registry data using a unique person-specific identifier [20].

2.2 | Study Population

The study population included all individuals aged 18 years or older living in Denmark who filled at least one prescription for a PPI between 1 January 2015 and 31 December 2023. During the study period, the adult population of Denmark grew from 4.5 million in 2015 to 4.8 million in 2023 [21].

2.3 | Study Drugs

We analysed the use of five PPIs available in Denmark: omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole. DDD was used to quantify prescriptions (in Table A1), and the

ATC index was used to classify drugs. We identified and categorized prescriptions for ulcerogenic drugs, such as acetylsalicylic acid, using the ATC index (in Table A2) to identify potential reasons for PPI use.

2.4 | Definitions of PPI Users

An individual was considered a current PPI user if they had filled a prescription with enough doses to cover a given date. We assumed one tablet per day and added 25% of the total number of tablets per prescription to account for irregular refills and noncompliance. A maximum of 180 days was allocated per prescription to prevent excessively long coverage from a single prescription.

An individual was considered an incident PPI user if they filled their first-ever prescription or filled a prescription after a 5-year run-in period since their last prescription. In a sensitivity analysis, we changed the definition of incidence to the first prescription within a 2-year period.

A prevalent user was defined as an individual who had enough tablets for at least 1 day in a given study month or year, depending on the analysis.

2.5 | Statistical Analysis

First, we described the temporal changes in PPI use from 2015 to 2023 by summing the DDDs of all filled PPI prescriptions into total annual PPI use. PPI use was categorized by type and for each study year.

Second, we calculated the annual incidence rate of PPI use as the number of incident users per 100 person-years. Observation time (person-years) was approximated by the total Danish adult population on 1 January of each year. Incidence was estimated using a 5-year run-in period to define incident use and a 2-year run-in period as a sensitivity analysis.

Third, we calculated the monthly prevalence proportion of PPI use as the number of individuals who filled a PPI prescription or had enough tablets to cover the last day of each month during the study period (including 31 December 2023). This allowed individuals to switch between being a current PPI user and a nonuser. We calculated the prevalence proportion by dividing the number of current PPI users by the total adult population on the last day of the month. We also calculated the annual age- and sex-specific prevalence proportions for 2015, 2019 and 2023.

Fourth, we described both prevalent and incident PPI users by sex, age and selected comorbidities for the years 2015, 2019 and 2023. We defined comorbidities based on ICD-10 codes in the Danish National Patient Registry, using data from 1994 onwards provided in Table A3.

Fifth, treatment persistence was assessed using the 'proportion of patients covered' method [22]. Incident PPI users were followed up for up to 3 years from their first prescription. The number of current users was divided by all incident PPI users each day, giving a proportion of incident PPI users who remained on

treatment. Users were excluded if they had insufficient tablets for a given day but could re-enter if they filled a new prescription. Users who died or migrated were excluded from the analysis. Subgroup analyses were conducted based on age, sex and year of first prescription.

Sixth, the Kaplan–Meier method was used to estimate the duration of continuous PPI treatment among incident users, following them from their first prescription for up to 3 years. Users were censored at their first treatment break. The number of users remaining on treatment at each time point was divided by the total number of incident users who were alive and had not migrated.

Finally, to examine potential reasons for PPI use, we calculated the proportion of adults with concomitant use of ulcerogenic drugs for each year [23, 24]. This analysis followed all current PPI users to assess whether they used any of the selected drugs concurrently or within 90 days before a PPI prescription.

2.6 | Ethics and Approvals

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [25].

All analyses were conducted using R (version 4.3.3) and RStudio. The study was registered at the University of Southern Denmark (RIO no. 11.279). According to Danish law, studies based solely on register data do not require approval from an ethics review board [26].

3 | Results

During the study period (2015–2023), a total of 17 829 565 PPI prescriptions were filled by 1 715 923 Danish adults. Of these, 569 345 (33%) filled only one prescription, 453 966 (26%) filled

two to four prescriptions and 692 612 (40%) filled five or more prescriptions. The median DDD per prescription was 60 (IQR 30–100).

We observed a 17% increase in PPI consumption during the study period, reaching 152 884 548 DDD in 2023 (Figure 1). Pantoprazole accounted for the majority of this use, followed by omeprazole, lansoprazole and esomeprazole, while rabeprazole use remained minimal, with a peak of 43 008 DDDs in 2015. During the study period, the annual consumption of omeprazole, lansoprazole and rabeprazole decreased by 24%, 17% and 30%, respectively, while consumption of pantoprazole and esomeprazole increased by 65% and 181% (Figure 1).

During the study period, we identified 1 184 459 new PPI users. The incidence rate remained stable, with 2.9 incident users per 100 person-years in 2015 and 2.8 incident users per 100 person-years in 2023 (Figure S1). In the sensitivity analysis using a 2-year run-in period, we observed the same trend, with approximately one additional incident user per 100 person-years throughout and an incidence rate of 3.9 in 2023 (Figure S2).

Additionally, the point prevalence proportions increased steadily throughout the study period, starting at 7.0% in 2015 and reaching 8.2% by the end of 2023 (Figure 2). Prevalence of PPI use increased with age across the study years (2015, 2019 and 2023) and women consistently showed a slightly higher prevalence than men across nearly all age groups (Figure 3, Figure S3).

As presented in Table 1, incident PPI users had a median age of 57 years (IQR 41–70) in 2023, while prevalent users were older, with a median age of 64 years (IQR 51–75). Among incident users in 2023, the three most common comorbidities were essential hypertension (38%), cancer (13%) and diabetes (11%). Among prevalent users, the same most common comorbidities were observed, with slight increases from 2015 to 2023: essential hypertension (53%–56%), diabetes (14%–18%) and cancer (13%–16%).

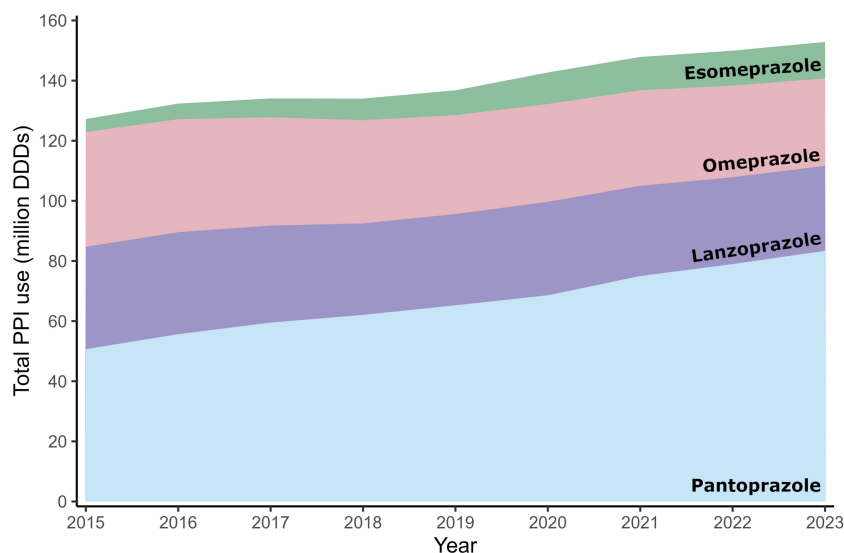


FIGURE 1 | Total amount of each proton-pump inhibitor used by the Danish adult population (≥ 18 years), measured in millions of defined daily dose (DDD). Rabeprazole is excluded from the figure due to its low usage, with the highest amount being 43 008 DDDs.



FIGURE 2 | Prevalence proportion of proton-pump inhibitor users among the Danish adult population (≥ 18 years) from 2015 to 2023.

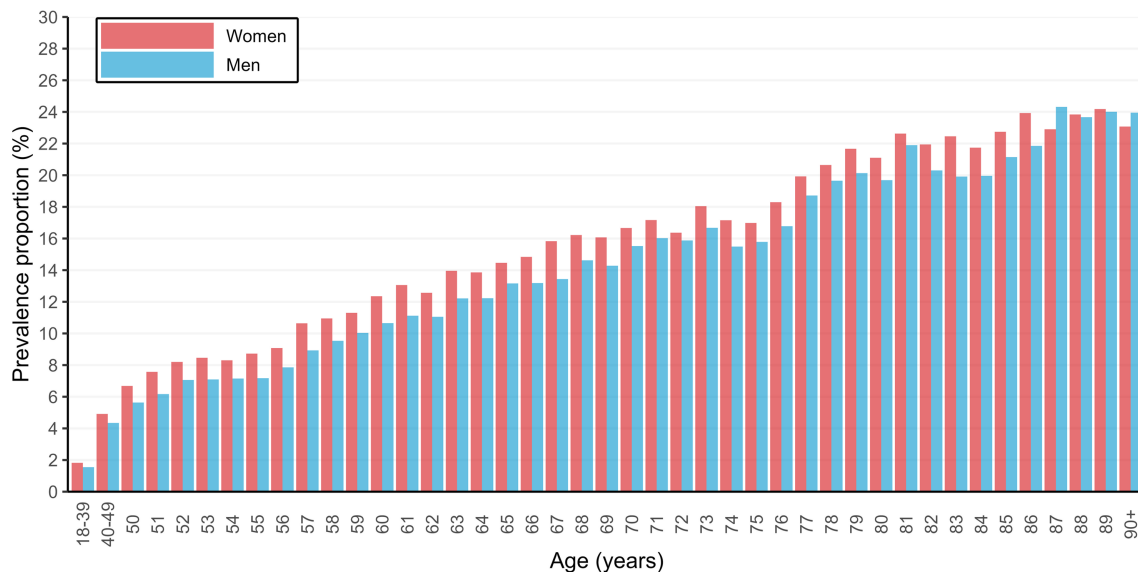


FIGURE 3 | Age- and sex-specific prevalence proportion of proton-pump inhibitor users among the Danish adult population (≥ 18 years) as of the end of 2023.

Other selected comorbidities remained relatively stable for both incident and prevalent users during the study period (Tables S1 and S2).

Figure 4 shows that 3 years after PPI initiation, only 1.5% of PPI users remained on continuous treatment (i.e., without a treatment break, using Kaplan Meier analysis), while 17% of patients were being treated 3 years after treatment initiation (using the ‘proportion of patients covered’ approach). After 1 year, these values were 6.1% and 18%, respectively. Treatment duration, when allowing for treatment breaks, was closely linked to age, with a higher proportion of users continuing treatment as age increased. Among those 80 years and older, 34% were still on treatment after 1 year, and 30% after 3 years. For those aged 18–39 years, 8.7% and 7.6% remained in treatment after 1 and 3 years, respectively (Figure 5). The three notable drops in treatment persistence correspond to PPI users who filled only one

prescription for a package containing approximately 30, 60 or 100 tablets. We found that neither sex nor the year of prescription initiation significantly impacted treatment duration (data not shown).

Concomitant use of ulcerogenic drugs was 50% in 2023, a 3.2% increase from 2015 (Figure 6). The use of acetylsalicylic acid and nonsteroidal anti-inflammatory drugs (NSAIDs) decreased by 28% and 4.5%, respectively, while concomitant use of oral anticoagulants and other platelet inhibitors increased by 49% and 3.0%, respectively.

4 | Discussion

We found a 17% relative increase in total PPI consumption among Danish adults between 2015 and 2023. This increase was

TABLE 1 | Characteristics of incident and prevalent proton-pump inhibitor users in 2023.

	Incident users	Prevalent users
	<i>n</i> = 135 243	<i>n</i> = 661 060
	<i>n</i> (%)	<i>n</i> (%)
Sex		
Male	61 979 (46)	293 577 (44)
Female	73 264 (54)	367 483 (56)
Age (median [IQR])	57 [41–70]	64 [51–75]
Age group		
18–39	31 191 (23)	77 817 (12)
40–59	43 977 (33)	190 180 (29)
60–79	47 581 (35)	297 980 (45)
≥ 80	12 494 (9.2)	95 083 (14)
Comorbidities		
Gastroesophageal reflux disease	4 549 (3.4)	86 159 (13)
Peptic ulcer disease	3 224 (2.4)	38 555 (5.8)
Ischaemic heart disease	10 683 (7.9)	98 925 (15)
Heart failure	3 339 (2.5)	28 357 (4.3)
Atrial fibrillation	7 872 (5.8)	57 511 (8.7)
Stroke	6 341 (4.7)	45 409 (6.9)
Essential hypertension	51 832 (38)	371 808 (56)
Diabetes mellitus	14 778 (11)	117 473 (18)
COPD	4 758 (3.5)	44 408 (6.7)
Cancer	18 008 (13)	106 594 (16)

Abbreviation: COPD = chronic obstructive pulmonary disease.

primarily driven by a rise in prevalent users, while the incidence rate remained stable throughout the study period. Concomitant use of ulcerogenic drugs remained stable, ruling it out as a major contributor to the increased consumption.

A main strength of this study is the use of the validated Danish National Prescription Registry to capture prescription data for the entire Danish population [16]. The use of the Danish Civil Registration System ensured that individuals were tracked throughout the entire study, minimizing the risks of selection bias, recall bias or loss to follow-up [20].

However, several limitations should be noted. First, while our data were comprehensive, we lacked information on the indications for PPI prescriptions, which limited our ability to assess whether the use adhered to clinical guidelines. We gathered comorbidity data from hospital admissions and hospital contacts, likely underestimating the prevalence of comorbidities, as many

diagnoses are managed by general practitioners. Second, over-the-counter PPIs were not included in our analysis. However, the proportion of PPI use attributable to over-the-counter sales, measured in DDD, accounted for only 2%–4% of total use during the study period, minimizing the potential impact of this exclusion [27]. Finally, we assumed that each individual took one tablet per day when calculating the duration of PPI treatment, but studies have shown that some patients with gastrointestinal reflux disease may take more than one tablet per day [28]. This suggests that we may have overestimated treatment duration, leading to an overestimation of prevalence, persistence and concomitant use if prescription coverage periods were artificially prolonged.

All PPIs are considered equally effective in terms of treatment outcomes, allowing for selection based on cost considerations [29]. Pantoprazole, in particular, is often preferred due to its lower risk of drug interactions compared with other PPIs, which may explain why it accounted for the largest share of total PPI use over the years [30, 31].

A previous Danish study showed a steep increase in PPI use compared with the present study, with a fourfold increase in the prevalence proportion from 2002 to 2014, reaching 7.4% [5]. A significant increase in prevalence was also found in other countries during the 2000s and 2010s [9, 32]. The slight increase in the prevalence proportion observed in this study aligns with trends reported in other countries in recent years [33, 34], suggesting that the rate of increase has slowed. The global slowdown in prevalence may be due to increased awareness of PPI overutilisation and potential adverse effects, leading to improved management and more frequent discontinuation of treatment [14, 35–37]. The increase in prevalence towards a stable point around 2021 alongside stable incidence is likely due to the accumulation of users over time, reaching a saturation point where discontinuations balance new initiations.

For the most common PPI indications, the recommended treatment duration is 4 to 8 weeks [29, 38, 39]. In our study, a large proportion of incident users discontinued treatment within 6 months, and only 6.1% remained on treatment after 1 year, when not allowing for treatment breaks. In 2023, 26% of PPI users also used NSAIDs, which could justify long-term PPI use for these individuals [40]. However, our analysis showed that more PPI users remained on treatment for up to 3 years when allowing for treatment breaks, suggesting that many patients may engage in on-demand use of PPIs rather than continuous, daily use. The increasing prevalence of some comorbidities among prevalent PPI users from 2015 to 2023, such as diabetes mellitus (14% to 18%) and cancer (13% to 16%), suggests a growing burden of chronic conditions among PPI users.

In conclusion, we found a modest increase in PPI consumption among Danish adults between 2015 and 2023, driven by a rise in prevalence, with a clear age-dependent trend. The stable incidence rate suggests that increased awareness of potential overutilisation has influenced usage patterns, underscoring the importance of continued efforts to optimize prescribing and de-prescribing practices.

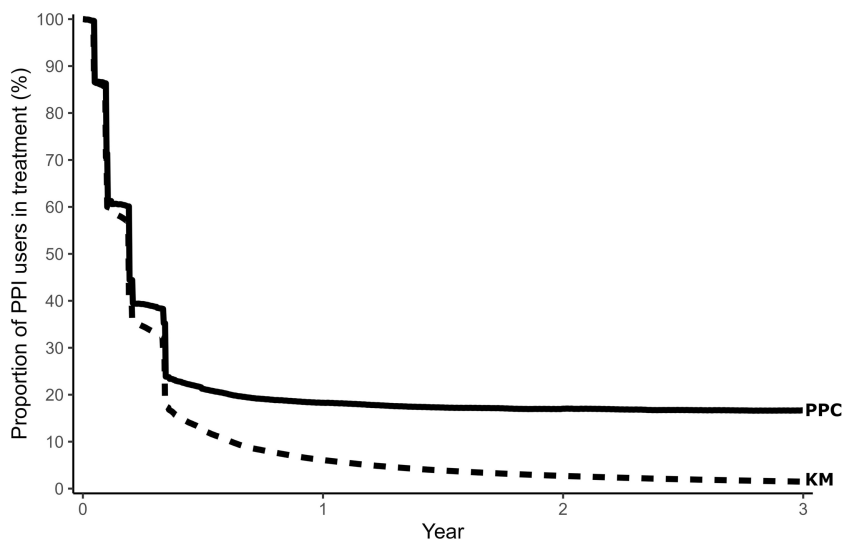


FIGURE 4 | Proportion of incident users who remained on proton-pump inhibitor (PPI) treatment for up to 3 years from their first prescription, measured using the 'proportion of patients covered' (PPC) and Kaplan–Meier (KM) method.

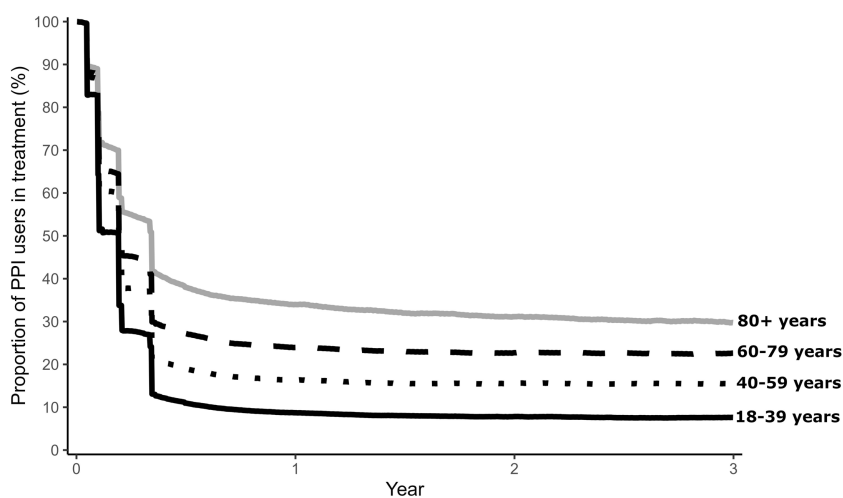


FIGURE 5 | Age-specific proportion of incident proton-pump inhibitor (PPI) users who remained on treatment for up to 3 years from their first prescription, as measured by the 'proportion of patients covered' method. This method covers users who were still in treatment on a given day.

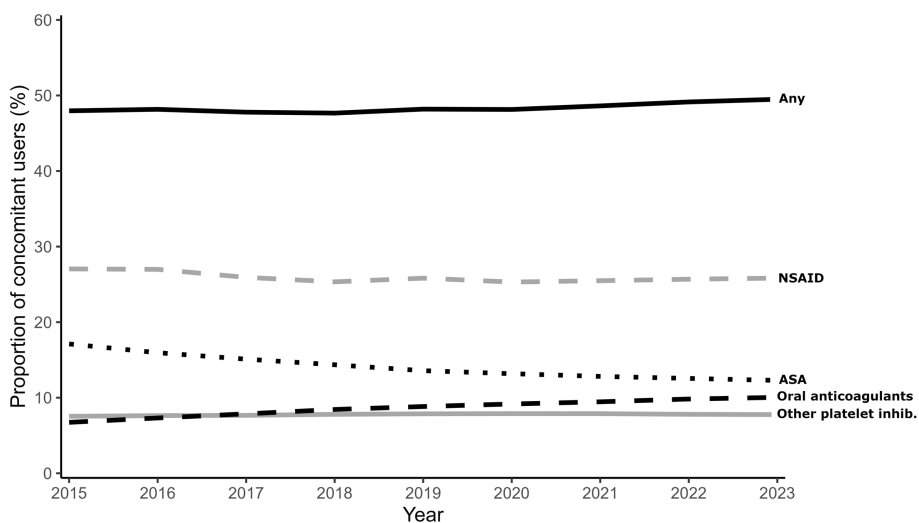


FIGURE 6 | Proportion of Danish proton-pump inhibitor users (≥ 18 years) with concomitant use of ulcerogenic drugs for each study year. ASA = acetylsalicylic acid; inhib = inhibitor; NSAID = nonsteroidal anti-inflammatory drugs.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from The Danish Health Data Authority. Restrictions apply to the availability of these data, which were used under license for this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Appendix

TABLE A1 | Characteristics of all proton-pump inhibitors authorized in Denmark.

Drug	ATC code	DDD (mg)	Strength disposable (mg)
Omeprazole	A02BC01	20	10, ^a 20 ^a and 40
Pantoprazole	A02BC02	40	20 ^a and 40
Lansoprazole	A02BC03	30	15 ^a and 30
Rabeprazole	A02BC04	20	10 and 20
Esomeprazole	A02BC05	30	10, 20 and 40

Abbreviations: ATC = anatomic therapeutic chemical; DDD = defined daily dose.
^aStrength is available as over-the-counter medicine at local pharmacies.

TABLE A2 | List of ulcerogenic drugs included in the analysis.

Drug	ATC code
Acetylsalicylic acid	B01AC06
	N02BA01
	B01AC30 ^a
NSAIDs	M01A ^b
Oral anticoagulants	B01AA
	B01AE
	B01AF
Other platelet inhibitors	B01AC07
	B01AC30 ^a
	B01AC04
	B01AC22
	B01AC24

Abbreviations: ATC = anatomic therapeutic chemical; NSAIDs = nonsteroidal anti-inflammatory drugs.

^aA combination of acetylsalicylic acid and dipyridamole.

^bExcl. M01AX.

TABLE A3 | ICD-10 and ATC codes used to define comorbidities in Table 1.

Diagnosis	ICD-10	ATC code
Gastroesophageal reflux disease	K21*	—
Peptic ulcer disease	K25*-K28*	—
Ischaemic heart disease	I20*-25*	—
Heart failure	I50*	—
Atrial fibrillation	I48*	—
Stroke	I60*-I64*	—
Essential hypertension	I10*	C09AA, C09CA, C08, C03AB
Diabetes mellitus	E10*-E14*	A10 (excluding weight loss medications, i.e., Wegovy and Saxenda)
COPD	J42*-44*	—
Cancer	C00*-C98* (excluding C44*)	—

Note: Comorbidities were defined as having at least one of the listed ICD-10 codes based on hospital diagnoses recorded in the Danish National Patient Registry at any time before the first proton-pump inhibitor (PPI) prescription date or a filled prescription for one of the listed ATC codes at any time before the first PPI prescription date.

Abbreviations: ATC = anatomic therapeutic chemical; COPD = Chronic obstructive pulmonary disease; ICD-10 = International Statistical Classification of Diseases, 10th revision.