Accepted Manuscript

British Journal of General Practice

Predictors for inappropriate proton pump inhibitor use: observational study in primary care

Koggel, Lieke; Lantinga, Marten; Büchner, Frederike; Drenth, Joost; Frankema, Jacqueline; Heeregrave, Edwin; Heringa, Mette; Numans, Mattijs; Siersema, Peter

DOI: https://doi.org/10.3399/BJGP.2022.0178

To access the most recent version of this article, please click the DOI URL in the line above.

Received 31-March-2022
Revised 27-May-2022
Accepted 20-June-2022

Predictors for inappropriate proton pump inhibitor use: observational study in primary care

Authors

Lieke Maria Koggel[1], Marten Alexander Lantinga[1,2], Frederike Leonie Büchner[3], Joost Paulus Hubertus Drenth[1], Jacqueline Sarah Frankema[4], Edwin Johannes Heeregrave[4], Mette Heringa[5], Mattijs Everard Numans[3], Peter Derk Siersema[1]

Author's affiliations

[1] Department of Gastroenterology and Hepatology, Radboud Institute for Health Sciences, Radboud university medical centre, Postbus 9101, 6500 HB Nijmegen, The Netherlands

[2] Department of Gastroenterology and Hepatology, Amsterdam Gastroenterology and Metabolism, University Medical Centres Amsterdam, Postbus 22660, 1100 DD Amsterdam, The Netherlands

[3] Department of Public Health and Primary Care, Leiden University Medical Centre, Postbus 9600, 2300 RC Leiden, The Netherlands

[4] The Dutch National Health Care Institute, Postbus 320, 1110 AH Diemen, The Netherlands

[5] SIR Institute for Pharmacy Practice and Policy, Theda Mansholtstraat 5B, 2331 JE Leiden, The Netherlands

Author information

Lieke Maria Koggel, MSc

PhD candidate at Department of Gastroenterology and Hepatology, Radboud university medical centre, Nijmegen

Marten Alexander Lantinga, MD, PhD

Senior Researcher at Department of Gastroenterology and Hepatology, Radboud university medical centre, Nijmegen. Gastroenterologist at Department of Gastroenterology and Hepatology, University Medical Centres Amsterdam, Amsterdam.

Frederike Leonie Büchner, MD, PhD

Senior Researcher at Department of Public Health and Primary Care, Leiden University Medical Centre, Leiden.

Joost Paulus Hubertus Drenth, MD, PhD

Professor of Gastroenterology and Hepatology at Radboud university medical centre, Nijmegen. Head Department of Gastroenterology and Hepatology, Radboud university medical centre, Nijmegen.

Jacqueline Sarah Frankema, MD, PhD

Medical Advisor Appropriate care project of The Dutch National Health Care Institute, Diemen.

Edwin Johannes Heeregrave, MD, PhD

Project Manager Appropriate care project of The Dutch National Health Care Institute, Diemen.

Mette Heringa, PharmD, PhD

Pharmacist and Senior Researcher, SIR Institute for Pharmacy Practice and Policy, Leiden.

Mattijs Everard Numans, MD, PhD

Professor of General Practice at Department of Public Health and Primary Care, Leiden University Medical Center, Leiden. Head Department of Public Health and Primary Care, Leiden University Medical Centre, Leiden.

Peter Derk Siersema, MD, PhD

Professor of Endoscopic Gastrointestinal Oncology Radboud university medical centre, Nijmegen. Head Endoscopy Centre, Radboud university medical centre, Nijmegen.

ORCHID iDs

Lieke M. Koggel: 0000-0001-9826-0676, Marten A. Lantinga: 0000-0003-3137-901X, Frederike L. Büchner: 0000-0001-8977-5344, Joost P.H. Drenth: 0000-0001-8027-3073, Mette Heringa: 0000-0001-8316-8148, Mattijs E. Numans: 0000-0002-0368-5426, Peter D. Siersema: 0000-0002-6940-8499

Corresponding author

L.M. Koggel, Department of Gastroenterology and Hepatology, Radboud university medical centre, Postbus 9101, 6500 HB Nijmegen, The Netherlands, E-mail: lieke.koggel@radboudumc.nl, Phone: +31 24 3619190

Authorship Statement

LK, ML, FB, JD, MH, MN and PS designed the study. LK collected the data and performed the analysis. All authors discussed the results and contributed to the final manuscript. All authors approved the final version of the manuscript, including the authorship list.

ABSTRACT

Background: Proton pump inhibitor (PPI) indications are limited to gastrointestinal disorders and ulcer prophylaxis. Still, PPIs are among the most frequently prescribed drugs.

Aim: To evaluate the appropriateness of PPI prescriptions and identify predictive factors for inappropriate PPI use.

Design and Setting: Observational study using a Dutch primary care database with all new PPI prescriptions between 2016 and 2018.

Methods: Individual patient data and details on PPI use were collected. Appropriateness of initiation and continuation of PPI prescriptions was evaluated using the applicable guidelines.

Results: We evaluated 148,926 patients (≥ 18 years) from 27 general practices. A total of 23,601 (16%) patients started PPI therapy (mean age 57 ± 17 years, 59% female). Valid PPI indications at initiation were seen in 10,466 PPI users (44%). Predictors for inappropriately initiated PPI use were older age (OR 1.03, 95%CI 1.03-1.03), and use of non-selective NSAIDs (OR 5.15, 95%CI 4.70-5.65), ADP receptor inhibitors (OR 5.07, 95%CI 3.46-7.41), coxibs (OR 3.93, 95%CI 2.92-5.28) and low-dose aspirin (OR 3.83, 95%CI 3.07-4.77). Despite an initial valid indication, PPI use was inaccurately continued in 32% of patients on short-course therapy for dyspepsia and in 11% of patients on ulcer prophylaxis.

Conclusion: More than half of PPI users in primary care seem to have an inappropriate indication with unnecessary ulcer prophylaxis related to drug use being one of the leading causes. Future initiatives to reduce PPI use for unnecessary ulcer prophylaxis and timely deprescription if PPI is no longer indicated, are needed.

KEYWORDS

Anti-Ulcer Agents; Inappropriate prescribing; Primary Health Care; Proton Pump Inhibitors; Non-Steroidal Anti-Inflammatory Drugs; Dyspepsia

HOW THIS FITS IN

While overuse of proton pump inhibitors (PPI) is a common issue worldwide, predictors for this remain insufficiently known. This observational study using real-world primary care data identified older age and non-selective NSAID use as most predictive for inappropriate PPI use. The study also showed that unnecessarily

continued PPI therapy is common in patients using PPI therapy for dyspepsia or as ulcer prophylaxis. Future initiatives on reducing inappropriate PPI use should target these patient groups.

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most prescribed drugs worldwide and are the cornerstone for treating and preventing acid-related disorders[1-4]. Its use has a major impact as it accounts for at least 37 million euros spent on health care annually in the Netherlands alone[5].

PPI therapy is frequently prescribed in the absence of an appropriate indication[6]. Examples of inappropriate PPI use are ulcer prophylaxis in patient without risk factors (for example steroid therapy alone) and overtreatment of functional dyspepsia[6]. Inappropriate PPI use may potentially harm patients through adverse drug reactions (ADR) or drug-drug interactions. Increasing evidence shows that long-term PPI use is associated with severe ADRs, such as *Clostridium difficile* colitis, malabsorption of magnesium, osteoporosis, and kidney disease[7-10].

Prior studies have identified unnecessary PPI use as ulcer prophylaxis (i.e., in patients without risk factors) as an important factor associated with inappropriate PPI therapy[11,12]. However, use of certain drugs or clinical conditions that are most predictive for inappropriate PPI use in clinical practice remain largely unknown which hampers targeted interventions to reduce PPI use. This study aimed to evaluate the appropriateness of PPI therapy in a large primary care setting in the Netherlands and to determine predictors for inappropriate PPI use.

METHODS

This study uses real-world, pseudonymised, routine primary care data covering the Leiden/The Hague region in the Netherlands. Continuous updated electronic medical record data from all patients (≥ 18 years) from general practitioner (GP) centres in the Extramural LUMC Academic Network (ELAN) were accessible. A total of 27 general practice centres associated with ELAN (each with 2-6 practising GPs) could be approached for this study, covering 148,926 patients. All practice centres associated with ELAN use an 'informed opt-out' procedure, so electronic medical record data of the patients enlisted with these practices can be used for research purposes. No more than 5% of all patients chose informed opt-out. The general practice centres can be characterized as representative for the average Dutch population, randomly spread over rural, suburban and highly urbanized areas. According to the Dutch healthcare system, all residents primarily contact their GP in case of a health problem. GPs can deal with routine health issues, including upper gastrointestinal disorders. If indicated, GPs can refer their patient to a specialist. Formal medical ethical review was waived for this study (METC region Arnhem-Nijmegen, reference 2020-6394).

Data collection

The database used International Classification of Primary Care (ICPC) codes for medical conditions and Anatomic Therapeutic Chemical (ATC) codes for drug use. Available data included patient characteristics, medical history, drug prescriptions, and GP consultations. Drug prescriptions were linked to the pharmacist's database in which all pharmacy data from participating GP practices is stored. Therefore, drug prescriptions included all drugs prescribed by GPs and non-prescription medicine in case this was registered by pharmacies. All patients with PPI prescriptions and upper gastrointestinal symptoms or conditions were identified using ATC and ICPC codes (**Supplementary Table 1 and 2**). The accuracy of ICPC code registration in Dutch GP practices is around 90%[13]. Data between 2015 and 2018 were available. New PPI usage periods were identified over the years 2016-2018. The data in 2015 was used to confirm that PPI prescriptions were initiated between 2016-2018, defined as no PPI use during at least three months before the start of the new PPI prescription.

Drug prescription variables

We calculated drug usage periods by merging repeat (refill) prescriptions. The usage periods of drugs that are known for chronic use or as a treatment during a predefined period of time (corticosteroids, anticoagulants,

antidepressants, and spironolactone) were defined as the start date of the first prescription until the end date of the last prescription. For drugs that are potentially used for short-term (PPIs, H2-blockers, antacids, *H. pylori* eradication therapy, and non-steroidal anti-inflammatory drugs), a unique usage period was created if the interval between two prescriptions exceeded three months. For example, if the interval between the end date of prescription 1 and the start date of prescription 2 was more than three months, the end date of prescription 1 was considered the end date of the first usage period and the start date of prescription 2 as the start date of the second usage period.

End dates of a drug prescription were calculated using the start date, dosage, and usage frequency. To categorize drug prescriptions that did not specify an exact frequency, the lowest possible usage frequency was selected (for example: 'one to three times daily' was transformed into 'one time daily'). Furthermore, on-demand use was converted to one-third of the time used (for example: 'one time daily, on demand' was transformed to 'one time daily, every three days'). If the prescribed frequency was not provided, it was replaced by once daily. Finally, if no dosage was available, prescriptions were considered to end after three months.

Chronic PPI use was defined as >180 Defined Daily Doses (DDDs)/year, a technical unit measuring drug consumption, as a proxy of >6 months PPI use[14,15]. Non-steroidal anti-inflammatory drug (NSAID) prescriptions were recorded as high-dose if the DDD was exceeded. Lastly, *H. pylori* eradication therapy was defined as either a fixed-dose combination or the prescription of a PPI with at least two types of antibiotics initiated simultaneously.

Appropriateness of PPI therapy

Appropriateness of PPI therapy was assessed for all patients receiving a new PPI prescription between 2016-2018. In case of multiple PPI usage periods in a single patient, appropriateness of PPI use was categorized based on the earliest PPI usage period and scored according to the Dutch College of General Practitioners guideline 'upper gastrointestinal symptoms' (version 2013) and clinical decision rules[16-18]. PPI therapy was deemed appropriate if used for: (a) confirmed gastroesophageal reflux disease, (b) peptic ulcer disease (PUD) (if registered <3 months before start of PPI), (c) short-course therapy for dyspepsia (if registered <6 months before start of PPI), (d) alarm symptoms (e.g. hematemesis) (if registered <1 month before start of PPI), and (e) as part of the eradication therapy for *H. pylori*[18]. Furthermore, PPI use was determined appropriate for ulcer prophylaxis in high-risk patients when using NSAIDs, low-dose aspirin, or in patients with a history of PUD. To assess if a

patient was at high risk of developing gastroduodenal ulcers, we evaluated age, comorbidities, and concomitant drug use at the time of PPI prescription. Chronic use of PPIs is only indicated for severe reflux esophagitis, Barrett's esophagus, Zollinger–Ellison syndrome, and chronic ulcer prophylaxis[19,20]. Indications were evaluated based on registered ICPC- and ATC-codes. ICPC codes of medical conditions such as reflux esophagitis are only used if confirmed by additional examination such as a gastroscopy. In case a medical condition is not confirmed, symptom ICPC codes such as pyrosis were used. **Supplementary Table 2** shows all valid PPI indications, including corresponding ICPC and ATC codes.

Appropriate duration of PPI therapy

The accepted duration of PPI use for a temporary indication to treat upper gastrointestinal disorders was limited to three months. These include short-course PPI therapy for dyspepsia, treatment of PUD, alarm features such as hematemesis, and *H. pylori* eradication. If a PPI was started as ulcer prophylaxis, it had to be stopped within three months after cessation of the drug that initiated PPI use.

Predictors for inappropriate PPI use

To identify predictive factors for inappropriate PPI use, we compared PPI users with non-PPI users who had consulted the GP for upper gastrointestinal conditions as a control group. Factors in the regression model included patient characteristics (e.g. age, gender, BMI), comorbidities (e.g. diabetes mellitus and heart failure), antireflux medication used before the start of PPI and concomitant drug use associated with PPI indications. To allow comparison between inappropriate PPI users and non-PPI users, concomitant drug use in the inappropriate PPI user group was not restricted to a specific time interval between 2016-2018. This means that all concomitant drug use in the period of 2016-2018 was included regardless the duration of use or, for the inappropriate PPI users group, interval between PPI use and concomitant drug use.

Statistical analysis

Normally distributed data were presented as mean ± standard deviation and non-normally distributed data as median and interquartile range. Chi-square testing was performed to compare categorical variables. Patients were clustered within practices and therefore, a mixed model logistic regression was used to determine predictive factors for inappropriate PPI use. We performed a random intercept model with the other factors

fixed. Variables with a p-value <0.2 in the univariate analysis were included in the multivariate analysis. A backwards model was used to stepwise eliminate the variables with the highest p-value until all variables in the model had a p-value <0.05. Two-sided testing with a p-value of <0.05 was considered significant. SPSS statistics version 25.0 (IBM Corp., Armonk, New York, USA) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria), packages *haven*, *funnelR*, and *ggplot2*, were used to process and analyse the data[21-23].

RESULTS

PPI prescriptions and patient characteristics

We identified 339,816 new PPI prescriptions between 2016 and 2018 in 23,601 patients (16%). Merging consecutive (refill) prescriptions resulted in 32,401 PPI usage periods (**Figure 1**). The prescribed frequency and dosage were not provided in 3,190 (1%) and 36 (0.01%) of PPI prescriptions, respectively. The number of new PPI usage periods was relatively stable throughout 2016-2018 (11,235 in 2016, 10,955 in 2017, and 10,211 in 2018, respectively). **Figure 2** shows the age and gender distribution of all patients with PPI usage periods in 2016-2018. Mean age at initiation of PPI prescription was 57 years (SD 17 years), of whom 59% were female (**Table 1**). A total of 2,823 (12%) patients were registered as active smokers and 3,106 (13%) as active alcohol users. Mean BMI was 28 kg/m^2 (SD 6), and diabetes mellitus was registered in 2,536 (11%) patients and heart failure in 446 (2%) patients. At the time of PPI prescription, 9,281 (39%) patients used non-selective NSAIDs and 3,048 (13%) patients low-dose aspirin. Antacids were prescribed prior to the start of PPI in 884 (4%) and H2-blockers in 801 (3%) patients. In 16,328 (69%) patients, PPIs were prescribed for less than three months. A total of 6,794 (29%) PPI users fulfilled the criteria for chronic PPI use.

Appropriateness at start of PPI therapy

A total of 10,466 (44%) patients had an appropriate indication for PPI use at the start of PPI therapy. The indication for PPI use was equally distributed between treatment for upper gastrointestinal conditions (n=4,749, 20%) and ulcer prophylaxis (n=5,382, 23%). **Table 2** and **Figure 3** show the indications for appropriately prescribed PPIs. Dyspepsia was the leading upper gastrointestinal symptom in patients with a PPI (n=3,260, accounting for 69% of PPIs started as treatment of upper gastrointestinal disorders). Use of non-selective NSAIDs and low-dose aspirin use were responsible for 78% (n=4,191) and 17% (n=935) of ulcer prophylaxis indications, respectively.

An inappropriate PPI indication was identified in 13,135 (56%) patients. In this group, 8,493 patients (65%) used drugs associated with an indication as ulcer prophylaxis at the time of PPI prescription. These drugs primarily included non-selective NSAIDs (34%), low-dose aspirin (10%), and systemic corticosteroids (9%) (**Table 1**).

Appropriateness of PPI therapy ranged from 47% to 67% between general practices (p<0.001, **Supplementary Table 3 and Supplementary Figure 4**).

Appropriate duration of PPI therapy

Of patients receiving a short-course of PPI for dyspepsia, 1,042 (32%) did not stop PPI treatment within three months. In 3,944 PPI users (69%) with an appropriate indication for PPI as ulcer prophylaxis, the drug that initiated PPI treatment was stopped during follow-up. Despite stopping, 445 (11%) patients continued PPI use for more than three months. This included 311 (10%) patients that used a PPI as ulcer prophylaxis for non-selective NSAIDs use, 118 (17%) for low-dose aspirin use, 5 (9%) for coxib use, and 11 (35%) patients with a history of PUD combined with comedication use that is associated with a higher bleeding risk.

Predictors for inappropriate PPI therapy

A total of 13,135 inappropriate PPI users were compared with 3,155 non-PPI users (**Supplementary Table 5**). Variables with substantial missings (BMI), not fully registered data (smoking, alcohol use, antacid and H2-blocker use), small numbers (rheumatoid arthritis, PUD, and spironolactone), or a direct association with an appropriate PPI indication (reflux esophagitis) were excluded.

Predictors for inappropriate PPI use were age (OR 1.03 increment per year, 95% CI 1.03-1.03) and drug use associated with PPI indications (**Table 3**). Non-selective NSAID use (OR 5.15, 95% CI 4.70-5.65) and ADP receptor inhibitor use (OR 5.07, 95% CI 3.46-7.41) had the strongest association with inappropriate PPI use, followed by coxib use (OR 3.93, 95% CI 2.92-5.28) and low-dose aspirin use (OR 3.83, 95% CI 3.07-4.77).

DISCUSSION

Summary

In this study we found that more than half of PPIs prescribed in primary care are not adequately indicated at the time of analysis. Most important predictors for inappropriate PPI therapy were age and use of drugs for which ulcer prophylaxis is only indicated in high-risk patients such as non-selective NSAIDs. One-third of PPIs started as short-course therapy for dyspepsia and one-tenth of PPIs started as ulcer prophylaxis were continued after the indication was no longer valid.

Strengths and limitations

The data used was obtained directly from electronic medical records without a pre-known research purpose. Using real-world data allows accurate investigation of current clinical practice. Moreover, a strength of this study is the large size which allowed a detailed assessment of PPI appropriateness. Also, as most PPIs are prescribed in a primary care setting in the Netherlands, this population is representative for assessing the appropriateness of PPI use[18].

This study is however limited by its retrospective design. We used patient characteristics, registered comorbidity and comedication prescriptions as a proxy to determine appropriateness of PPI use. Some assumptions were needed for comorbidity stages and duration of comedication use; however, appropriateness of PPI therapy was always given the benefit of the doubt. Secondly, not all antireflux medication use was known as non-prescription drug registration was incomplete. However, apart from including drugs prescribed by GPs, we also included non-prescription drug use registered by pharmacists. Moreover, as a proxy for general non-PPI users, non-PPI users that consulted the GP for upper gastrointestinal conditions were used as a control group for the logistic regression analysis. Nonetheless, we compared two groups without valid PPI indication to determine possible predictors for inappropriate PPI use. Furthermore, some variables, such as BMI and alcohol use, could not be included in the logistic regression analysis due to missing data. Lastly, total duration of PPI use and number of chronic users may have been underestimated as we only had access to data up to 2018.

Comparison with existing literature

The high percentage of inappropriately initiated PPI prescriptions (56%) corresponds with an earlier Dutch study[24]. In contrast to our study, these authors had no access to electronic primary care patient records which potentially may overestimate the number of inappropriate PPI users. Another study from Denmark had similar access to primary care source data and showed that 25% of patients had an invalid PPI indication[25]. However, appropriateness could have been overestimated in this study as all patients using NSAIDs or aspirin were considered as appropriate PPI users. Moreover, bias could have been introduced as the prescribing physicians collected the data themselves, which was prevented in our study as we extracted real-world data and had no role in prescribing PPI therapy.

Patients using non-selective NSAIDs were identified as having the highest odds for inappropriate PPI use. This finding is in line with previous studies[11,12,24]. A questionnaire study showed that inappropriate PPI therapy as ulcer prophylaxis was recommended by 35% of GPs and internists when starting NSAIDs in low-risk patients[26]. When also taking the large-scale use into account, non-selective NSAID use in low-risk patients is likely one of the leading causes of inappropriate PPI use[27].

Moreover, patient age was found to be predictive for inappropriate PPI therapy. This could be related to the increasing number of drugs patients use when age increases[28]. A previous study showed that the number of drugs used was a predictor of inappropriate PPI therapy in elderly[29]. A possible explanation could be that physicians tend to prescribe more often ulcer prophylaxis in frail elderly regardless of a valid indication[30].

Another important risk factor for inappropriate PPI use is unjustified continuation of temporary indicated PPIs in patients with dyspepsia or as ulcer prophylaxis, as already suggested by prior studies[31,32]. Not explicitly informing patients that PPI treatment is of limited duration and lack of physician follow-up may lead to unjustified continuation of PPI therapy. Furthermore, rebound symptoms may complicate discontinuation of PPI use and, in case of dyspepsia, suggesting an alternative therapy such as lifestyle measures to patients can be challenging[33,34].

Implications for research and/or practice

By identifying predictors for PPI overuse, we provide possible targets for future interventions to reduce inappropriate PPI use. Previous studies have shown different interventions that successfully reduce inappropriate PPI use, such as prescriber and patient education, PPI use evaluation and self-management plans[24,35,36]. However, sustainable and time-efficient strategies are lacking. One potential strategy is a close

collaboration between GPs and pharmacists to double-check PPI indications and to stress on discontinuing inappropriate PPI therapy. Furthermore, GPs could also play a role when they notice that PPIs are inappropriately prescribed by medical specialists in secondary care.

NOTES

Funding

This study was funded in full by the Dutch National Health Care Institute, grant number 2019027556.

Ethical approval

Formal medical ethical review was waived for this study (METC region Arnhem-Nijmegen, reference 2020-6394).

Competing interests

JF and EH are employees of the Dutch National Health Care Institute and were involved in the process of allocating funding for this study.

JD has received research funding from Gilead & Abbvie, is a participant on the COIN-B data safety monitoring board and is Chair of the Dutch Society of Hepatology.

MN has received research funding from the Dutch Stomach, Liver and Bowel Foundation and is member of the Dutch College of General Practitioners guideline committees 'upper gastrointestinal tract' and 'liver'.

PS has received research funding from Pentax, The E-Nose company, Lucid Diagnostics, Micro-Tech, Motus GI, Magentiq Eye and has served as an advisor for Motus GI.

LK, ML, FB, and MH have no conflicts of interests.

Acknowledgements

We would like to thank the Dutch National Health Care Institute[37] initiative of reducing PPIs, reference number 2019027556, and are grateful to R.P. Akkermans for assisting in the statistical analysis of this study.

REFERENCES

1. Lanza FL, Chan FK, Quigley EM, Practice Parameters Committee of the American College of G. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol.* 2009;104(3):728-738.
2. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2013;108(3):308-328; quiz 329.
3. Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and Treatment of Peptic Ulcer Disease. *Am J Med.* 2019;132(4):447-456.
4. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *JAMA.* 2015;314(17):1818-1831.
5. Reimbursement 2016-2020 for ATC subgroup A02B : Drugs for peptic ulcers and gastroesophageal reflux. https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=B_01-basis&tabel_h_00-totaal=B_01-basis&geg=vg&spec=&item=A02B. Accessed 18-01-2021.
6. Savarino V, Marabotto E, Zentilin P, et al. Proton pump inhibitors: use and misuse in the clinical setting. *Expert Rev Clin Pharmacol.* 2018;11(11):1123-1134.
7. Furuya-Kanamori L, Stone JC, Clark J, et al. Comorbidities, Exposure to Medications, and the Risk of Community-Acquired Clostridium difficile Infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol.* 2015;36(2):132-141.
8. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *Jama.* 2013;310(22):2435-2442.
9. Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. *Gastroenterology.* 2017;152(4):706-715.
10. Islam MM, Poly TN, Walther BA, et al. Adverse outcomes of long-term use of proton pump inhibitors: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2018;30(12):1395-1405.
11. Parente F, Cucino C, Gallus S, et al. Hospital use of acid-suppressive medications and its fall-out on prescribing in general practice: a 1-month survey. *Aliment Pharmacol Ther.* 2003;17(12):1503-1506.
12. Sattayalertyanyong O, Thitilertdecha P, Auesomwang C. The inappropriate use of proton pump inhibitors during admission and after discharge: a prospective cross-sectional study. *Int J Clin Pharm.* 2020;42(1):174-183.
13. Jabaaij L, Njoo K, Visscher S, Hoogen H, Levelink H, Verheij R. Verbeter uw verslaglegging, gebruik de EPD-scan-h. *Huisarts en Wetenschap.* 2009;52:240-246.
14. ATC/DDD Index. https://www.whocc.no/atc_ddd_index/, 2021.
15. Haastrup PF, Jarbøl DE, Thompson W, Hansen JM, Søndergaard J, Rasmussen S. When does proton pump inhibitor treatment become long term? A scoping review. *BMJ Open Gastroenterol.* 2021;8(1).
16. Base TRDPAaH. Medisch Farmaceutische Beslisregel (MFB): Maagbescherming bij NSAID-gebruik. In:2013.
17. Base TRDPAaH. Medisch Farmaceutische Beslisregel (MFB): Maagbescherming bij salicylaat-/coxibgebruik. In:2014.
18. Numans ME dWN, Dirven J, Heemstra-Borst C, Hurenkamp G, Scheele M, Burger J, Geijer R, de Jongh E. NHG-Standaard Maagklachten. 2013:26-35.
19. Shaheen NJ, Falk GW, Iyer PG, Gerson LB, American College of G. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. *Am J Gastroenterol.* 2016;111(1):30-50; quiz 51.
20. Ito T, Igarashi H, Uehara H, Jensen RT. Pharmacotherapy of Zollinger-Ellison syndrome. *Expert Opin Pharmacother.* 2013;14(3):307-321.

21. haven: Import and Export 'SPSS', 'Stata' and 'SAS' Files. 2019. https://CRAN.R-project.org/package=haven.
22. funnelR: Funnel Plots for Proportion Data. 2018. https://CRAN.R-project.org/package=funnelR.
23. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York; 2016. https://ggplot2.tidyverse.org.
24. van Vliet EP, Steyerberg EW, Otten HJ, et al. The effects of guideline implementation for proton pump inhibitor prescription on two pulmonary medicine wards. *Aliment Pharmacol Ther.* 2009;29(2):213-221.
25. Jarbol DE, Lykkegaard J, Hansen JM, Munck A, Haastrup PF. Prescribing of proton-pump inhibitors: auditing the management and reasons for prescribing in Danish general practice. *Fam Pract.* 2019;36(6):758-764.
26. Murthy SK, Kauldher S, Targownik LE. Physicians' approaches to the use of gastroprotective strategies in low-risk non-steroidal anti-inflammatory drug users. *Aliment Pharmacol Ther.* 2006;23(9):1365-1372.
27. Jones R. Nonsteroidal anti-inflammatory drug prescribing: past, present, and future. *Am J Med.* 2001;110(1A):4S-7S.
28. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA.* 2008;300(24):2867-2878.
29. Voukelatou P, Vrettos I, Emmanouilidou G, et al. Predictors of Inappropriate Proton Pump Inhibitors Use in Elderly Patients. *Curr Gerontol Geriatr Res.* 2019;2019:7591045.
30. Laine L, Bombardier C, Hawkey CJ, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology.* 2002;123(4):1006-1012.
31. Van Soest EM, Siersema PD, Dieleman JP, Sturkenboom MC, Kuipers EJ. Persistence and adherence to proton pump inhibitors in daily clinical practice. *Aliment Pharmacol Ther.* 2006;24(2):377-385.
32. Chau SH, Sluiter RL, Hugtenburg JG, Wensing M, Kievit W, Teichert M. Cost-Utility and Budget Impact Analysis for Stopping the Inappropriate Use of Proton Pump Inhibitors After Cessation of NSAID or Low-Dose Acetylsalicylic Acid Treatment. *Drugs Aging.* 2020;37(1):67-74.
33. Reimer C, Sondergaard B, Hilsted L, Bytzer P. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology.* 2009;137(1):80-87, 87 e81.
34. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med.* 2006;166(9):965-971.
35. Lin D, Eke C, Cai C, Thrift AP, Shukla R. Decreasing Overall and Inappropriate Proton Pump Inhibitor Use: Perspective From a Large Safety-Net Healthcare System. *Clin Gastroenterol Hepatol.* 2020;18(4):763-766.e762.
36. Murie J, Allen J, Simmonds R, de Wet C. Glad you brought it up: a patient-centred programme to reduce proton-pump inhibitor prescribing in general medical practice. *Qual Prim Care.* 2012;20(2):141-148.
37. Dutch National Health Care Institute. In. https://english.zorginstituutnederland.nl/.

TABLES

Table 1. Patient characteristics, based on first PPI usage period per patient

	All PPI users (n=23,601)	**Appropriate PPI users (n=10,466)**	**Inappropriate PPI users (n=13,135)**
Female, n (%)	13,916 (59)	6,237 (60)	7,679 (59)
Age in years, mean ± SD	57 ± 17	61 ± 18	54 ± 16
BMI in kg/m^2 mean ± SD†	28 ± 6	28 ± 5	28 ± 6
Current smoker, n (%)	2,823 (12)	1,222 (12)	1,601 (12)
Use of alcohol, n (%)	3,106 (13)	1,678 (16)	1,428 (11)
Diabetes mellitus, n (%)	2,536 (11)	1,346 (13)	1,190 (9)
Heart failure, n (%)	446 (2)	206 (2)	240 (2)
Rheumatoid arthritis, n (%)	125 (1)	59 (1)	66 (1)
Peptic ulcer disease, n (%)	596 (3)	483 (5)	113 (1)
Reflux esophagitis, n (%)	523 (2)	523 (5)	0 (0)
Antacid, n (%)	884 (4)	440 (4)	444 (3)
H2RA, n (%)	801 (3)	527 (5)	274 (2)
Non-selective NSAID, n (%)	9,281 (39)	4,790 (46)	4,491 (34)
Coxib, n (%)	560 (2)	165 (2)	395 (3)
Low-dose aspirin, n (%)	3,048 (13)	1,699 (16)	1,349 (10)
Vitamin K antagonist, n (%)	926 (4)	403 (4)	523 (4)
ADP receptor inhibitor, n (%)	1,030 (4)	393 (4)	637 (5)
DOAC, n (%)	513 (2)	201 (2)	312 (2)
LMWH, n (%)	845 (4)	436 (4)	409 (3)
Systemic corticosteroid, n (%)	1,943 (8)	825 (8)	1,118 (9)
SSRI, n (%)	1,565 (7)	804 (8)	761 (6)
Trazadone, n (%)	43 (<1)	23 (<1)	20 (<1)
Venlafaxine, n (%)	279 (1)	151 (1)	128 (1)
Duloxetine, n (%)	54 (<1)	20 (<1)	34 (<1)
Spironolactone, n (%)	285 (1)	106 (1)	179 (1)

†n=14,764 missings, ADP; adenosine diphosphate, BMI; Body Mass Index, DOAC; direct acting oral anticoagulant, H2RA; H2 receptor antagonist, LMWH; low molecular weight heparin, PPI; proton pump inhibitor, SSRI; selective serotonin reuptake inhibitor.

Table 2. Proton pump inhibitor indications

		PPI users (n=23,601)
TREATMENT OF UPPER GASTROINTESTINAL DISORDERS, n (%)		**4,749 (20)**
Temporary indication	Dyspepsia	3,260 (14)
	Peptic ulcer disease	40 (<1)
	Alarm features (f.e. haematemesis)	106 (<1)
	Eradication of *H. pylori*	73 (<1)
Chronic indication	Esophageal disease (f.e. Barrett's esophagus)	458 (2)
	Reflux esophagitis	347 (1)
Multiple PPI indications as treatment of upper gastrointestinal disorders		465 (2)
ULCER PROPHYLAXIS, n (%)		**5,382 (23)**
Non-selective NSAID		4,191 (18)
Low-dose aspirin		935 (4)
Coxib		82 (<1)
Peptic ulcer disease in medical history†		71 (<1)
- and usage of coumarins		10 (<1)
- and usage of DOAC		6 (<1)
- and usage of LMWH		2 (<1)
- and usage of ADP receptor inhibitor		13 (<1)
- and usage of thrombolytics		0 (0)
- and usage of systemic corticosteroid		15 (<1)
- and usage of SSRI		8 (<1)
- and usage of venlafaxine		0 (0)
- and usage of duloxetine		0 (0)
- and usage of trazodone		0 (0)
- and usage of spironolactone		3 (<1)
- overlay in comedication use		14 (<1)
Multiple PPI indications as ulcer prophylaxis		103 (<1)
BOTH TREATMENT OF UPPER GASTROINTESTINAL DISORDERS AND ULCER PROPHYLAXIS, n (%)		**335 (1)**
NO ACCEPTED INDICATION, n (%)		**13,135 (56)**

†If not already in combination with NSAID or low-dose aspirin usage, ADP; adenosine diphosphate, DOAC; direct acting oral anticoagulant, LMWH; low molecular weight heparin, NSAID; non-steroidal anti-inflammatory drug, PPI; proton pump inhibitor, SSRI; selective serotonin reuptake inhibitor.

Table 3. Mixed model multivariate logistic regression analysis for inappropriate PPI use.

	Univariate logistic regression		Multivariate logistic regression	
	OR	**95% CI**	**OR**	**95% CI**
Gender, male	1.13	1.04 - 1.23		
Age, increment per year	1.03	1.03 – 1.03	1.03	1.03 – 1.03
Diabetes mellitus	1.58	1.35 - 1.84		
Heart failure	1.37	1.08 - 1.75		
Non-selective NSAID	3.44	3.16 - 3.74	5.15	4.70 – 5.65
Coxib	4.92	3.70 - 6.54	3.93	2.92 – 5.28
Low-dose aspirin	5.31	4.32 - 6.52	3.83	3.07 – 4.77
Vitamin K antagonist	1.97	1.57 - 2.49		
ADP receptor inhibitor	8.57	5.94 - 12.35	5.07	3.46 – 7.41
DOAC	3.55	2.56 - 4.92	2.54	1.80 – 3.57
LMWH	4.58	3.50 – 5.99	2.91	2.20 – 3.85
Systemic corticosteroids	3.08	2.69 - 3.53	2.37	2.05 – 2.74
SSRI	1.66	1.41 – 1.96	1.77	1.49 - 2.11
SNRI	2.37	1.66 - 3.38	2.18	1.49 – 3.19

ADP; adenosine diphosphate, DOAC; directy acting oral anticoagulant, LMWH; low molecular weight heparin, NSAID; non-steroidal anti-inflammatory drug, PPI; proton pump inhibitor, SNRI; serotonin and norepinephrine reuptake inhibitor, SSRI; selective serotonin reuptake inhibitor.

FIGURES

Figure 1. Selection of proton pump inhibitor (PPI) usage periods in 2016-2018

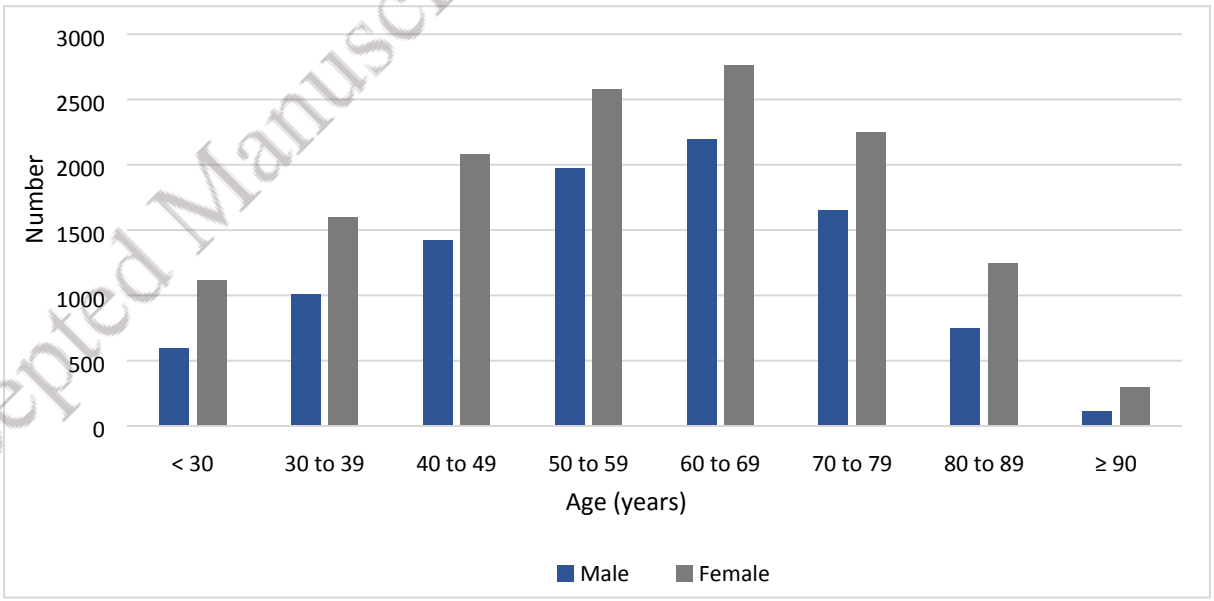

Figure 2. Age and gender of patients with a proton pump inhibitor usage period in 2016-2019

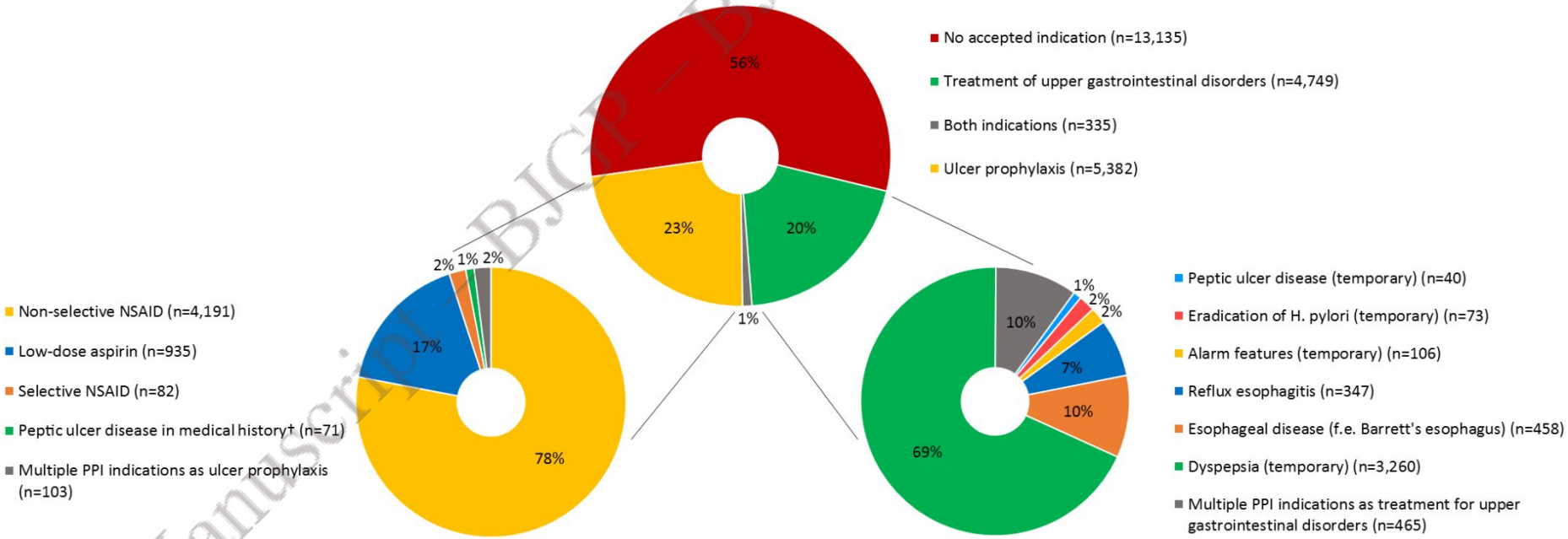

Figure 3. Proton pump inhibitor indications. †If not already in combination with NSAID or low-dose aspirin usage, NSAID; non-steroidal anti-inflammatory drug, PPI; proton pump inhibitor.