Annals of Gastroenterology (2021) **34,** 781-787

An educational intervention to optimize use of proton pump inhibitors in a Greek university hospital

Lazaros-Dimitrios Lazaridis, Evripidis Rizos, Lamprini Bounou, Anna Theodorou-Kanakari, Sotirios Kalousios, Electra-Antonia Mavroeidi, Maria Roma, Alexandros Chatzidakis, Georgia Vlachonicolou, Konstantinos Miltiadou, Paraskevas Gkolfakis, Georgios Tziatzios, Konstantinos Triantafyllou

Medical School, National and Kapodistrian University of Athens, "Attikon" University General Hospital, Athens, Greece

Abstract

Background Misuse of proton pump inhibitors (PPIs) is an alarming issue for patients and healthcare systems.

Methods We conducted a 3-phase interventional, prospective study in a Greek university hospital. During Phase I, we collected data from patients' records to evaluate the appropriate use of PPIs. During Phase II, educational seminars about the proper use of PPIs were offered to the medical staff. In Phase III we collected data from the records of patients admitted to the hospital department with the highest rate of inappropriate PPI administration during Phase I, to evaluate the efficacy of the intervention. Inappropriate use was defined as either PPI administration without indication, or lack of use despite adequate indication. Appropriateness of PPI use was measured at admission, during hospitalization and at discharge.

Results The rate of inappropriate PPI use was higher (51.7% and 48.6%) during hospitalization than at admission (34.9% and 21.9%), but at discharge was similar to pre-hospitalization levels (26.9% and 23.6%), in Phases I and III, respectively. At discharge during Phase I, the inappropriate use of PPIs was significantly higher (odds ratio 3.79, 95% confidence interval 1.98-7.19) for internal medicine patients than for surgical patients. The educational intervention failed to reduce the inappropriate use of PPIs during hospitalization (51.7% vs. 48.6%, P=0.478) or at discharge (26.9% vs. 23.6%, P=0.391) in the internal medicine patients.

Conclusions The rate of inappropriate PPI use is almost double during hospitalization compared to the rates at admission and at discharge. Implementation of an educational intervention failed to reduce the inappropriate use of PPIs in internal medicine patients.

Keywords Proton pump inhibitor, intervention, inappropriate use, misuse, education

Ann Gastroenterol 2021; 34 (6): 781-787

Hepatogastroenterology Unit, Second Department of Internal Propaedeutic Medicine-, Medical School, National and Kapodistrian University of Athens, "Attikon" University General Hospital, Athens, Greece

Conflict of Interest: None

Correspondence to: Konstantinos Triantafyllou, Professor of Gastroenterology, Hepatogastroenterology Unit, Second Department of Internal Propaedeutic-Medicine-, Medical School, National and Kapodistrian University of Athens, "Attikon" University General Hospital, 1, Rimini Street, 124 62 Athens, Greece, e-mail: ktriant@med.uoa.gr

Received 8 February 2021; accepted 20 April 2021; published online 2 July 2021

DOI: https://doi.org/10.20524/aog.2021.0654

Introduction

Proton pump inhibitors (PPIs) are among the most frequently prescribed classes of drugs worldwide [1] and this trend has increased over the last decade [2]. Although their use is guided by well-defined indications [3], inappropriate PPIs prescription has been observed in primary care [4] and the hospital setting [5].

Long-term use of PPIs has been associated with serious adverse effects, such as *Clostridium difficile* infection, community-acquired pneumonia, bone fractures, dementia, chronic kidney disease, and micronutrient deficiencies [6], and it imposes a significant burden on the healthcare costs of developed countries [7]. In hospitalized patients, uncritical continuation

of medications at admission can prolong unneeded PPI use during hospital stay and after discharge [8]. Furthermore, unnecessary PPI use is often initiated in hospitalized patients because of poor compliance with guidelines and liberal interpretation of indications in favor of a minimal expected beneficial effect on the clinical outcome [9]. Hence, strategies for PPIs discontinuation have been proposed to limit their inappropriate use [10]. Conversely, underutilization of PPIs is also a significant aspect of PPI misuse, since patients with a valid treatment indication are prone to serious complications and worse clinical outcomes [11].

In this context, hospitalization status may become a critical checkpoint to control the proper prescription of PPIs, and educational initiatives to inform physicians about correct PPI use are of the utmost importance [12]. We therefore conducted a study aiming to document inappropriate prescription of PPIs in a Greek university general hospital and to evaluate the impact of an educational intervention on limiting PPI misuse.

Patients and methods

Study design

This was a prospective, 3-phase, cross-sectional, prescription-indication drug-utilization, chart-review study in hospitalized patients, in a tertiary 600-bed hospital in Athens, Greece, conducted between March 2017 and July 2019. Study Phase I was an internal audit, not requiring Ethics Committee approval. However, the study protocol for the intervention and follow up (Phase III) was approved by Hospital Ethics Committee (protocol number: 2188/9-3-2017).

We collected data from the charts of consecutive adult patients admitted to the different hospital wards during the study periods. Patients admitted to the intensive care unit, psychiatric, pediatric and obstetrics departments, as well as those admitted to the one-day clinic, were excluded.

The following demographic and clinical data were retrieved from the patients' hospital medical records and charts files: i) demographics: age, sex, reason for admission, admission clinic, length of hospital stay and outcome (death, deterioration, stable status, improvement, complete healing) at discharge; ii) PPI use before admission, during hospitalization and at discharge (formulation, dosage, route of administration, indication); and iii) inappropriate use of PPIs: at admission, during hospitalization and at discharge. Data collection was anonymous, and patients' personal data were protected.

Study phases

During Phase I of the study, data of patients admitted in 3 consecutive hospital on-call days were collected and the inappropriate use of PPIs was measured. In addition, hospital departments with the highest risk for PPI misuse were identified, using the administration of PPIs in gastroenterology patients as reference. We also estimated the annual cost of PPI overuse during hospitalization, as well as the number of patients exposed to the risk of upper gastrointestinal (GI) complications due to PPI underuse at discharge.

After the analysis of data collected during Phase I, a multifaceted educational intervention was conducted (Phase II). A lecture was organized in the hospital amphitheater, with the participation of approximately 30% of the medical staff, to present the results of the first phase of the study and to highlight the need for proper use of PPIs. Posters with the indications for PPIs were posted in the Emergency Department and in doctors' offices in every department/clinic of the hospital.

Specific educational sessions by the Hepatogastroenterology Unit staff were held for all departments/clinics, to highlight in detail, overall and specifically per department, the Phase I data, and to present the indications and the risks of inappropriate use of gastroprotective medications. Sessions were held twice (2-6 months apart) for the departments/clinics with the highest risk of PPI misuse detected during Phase I, to further raise awareness of the problem.

Phase III of the study aimed to measure the effectiveness of the educational intervention. During 4 consecutive hospital call days, we assessed data from admitted patients' medical records and chart files in the departments that had been categorized as high-risk for inappropriate PPIs during study Phase I. The medical staff of the hospital were unaware of the study's conduction during this final Phase.

Definitions

Inappropriate use

Inappropriate use of PPIs was defined either as overuse (administration of the medication without indication) or as underuse (omission of administration despite adequate indication). According to the Greek National Organization of Medicines Formulary, legitimate indications for PPI prescription include gastroesophageal reflux disease, peptic ulcer, Zollinger-Ellison syndrome, and gastric protection when using nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin in the concomitant presence of one of the following risk factors: a) age ≥70 years; b) history or complications of peptic ulcer; c) untreated *Helicobacter pylori* infection; d) history of bleeding or perforation; e) or coadministration of antiplatelets or anticoagulants [13].

Estimations

Annual cost of PPI overuse during hospitalization

We estimated the annual cost of PPI overuse by assuming that Phase I results could be applied to the 90 on-call days of the hospital per year. We measured the total number of *per os* and intravenous (iv) doses of PPIs administered without indication during Phase I and we multiplied these excess doses by the average cost of PPIs administered in the hospital at this time.

Number of patients exposed to the risk of upper GI complications due to PPI underuse at discharge

We estimated the annual number of patients exposed to the risk of upper GI complications by PPI underuse at discharge, assuming that Phase I results could be applied to the 90 on-call days of the hospital per year.

Study endpoints

Primary endpoint

To measure the rate of inappropriate use of PPIs (overall, overuse, underutilization) in patients admitted to the "Attikon" University General Hospital and to identify the departments at highest risk for inappropriate PPI administration.

Secondary endpoints

1. To assess the impact of the educational intervention on optimizing PPI administration during hospitalization and at discharge.
2. To estimate the annual costs of PPI overuse during hospitalization, and the number of subjects exposed to the risk of upper GI complications because of PPI underuse at discharge.

Statistical analysis

We used the Population Proportion-Sample Size calculator (https://select-statistics.co.uk/calculators/sample-size-calculator-population-proportion/) to determine the appropriate sample size for estimating the proportion of a population at risk of inappropriate PPI use, with a 5% margin of error and 90% confidence level. A total of 270 subjects were required to be enrolled from a population larger than 100,000, with a likelihood of sample size proportion set at 50% due to uncertainty. Categorical data were expressed as number (%) and quantitative data were expressed as mean ± standard deviation (SD). We performed per protocol analysis: chi-square or Fischer exact tests were used to compare categorical data between the different groups, and the odds ratios (OR) and their 95% confidence intervals (CIs) were calculated. Comparisons between groups for quantitative data were made using the Mann-Whitney *U* test. P-values <0.05 were considered significant.

Results

The study phases are shown in Fig. 1 and the patients' clinical and demographic characteristics retrieved from their records and charts in Phases I and III of the study are shown in Table 1.

Primary endpoint

Phase I of the study was conducted in March 2017. Overall, files from 470 patients admitted in 3 consecutive on-call days were assessed (Table 1). Among admitted patients, 32.5%, 65.6% and 33.2% received PPIs before admission, during hospitalization and at discharge, respectively. The

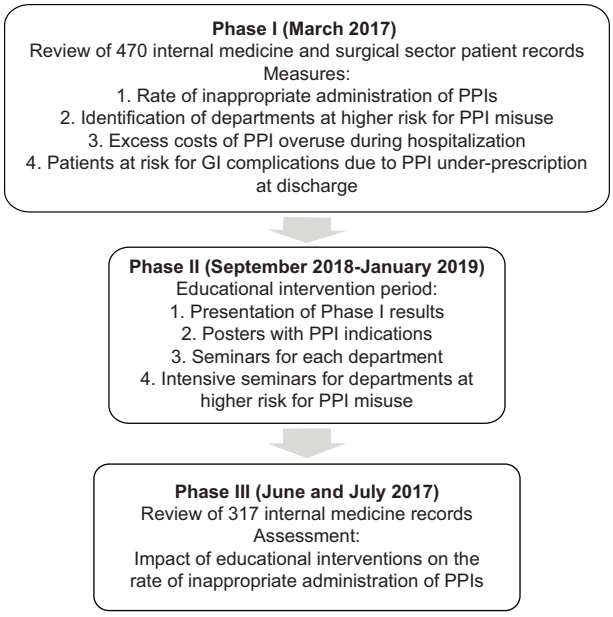

Figure 1 Flow diagram of the study
PPI, proton pump inhibitor; GI, gastrointestinal

Table 1 Characteristics of patients receiving PPIs

Characteristics	Study phase	
	Phase I (n=470)	Phase III (n=317)
Sex, n (%)		
Male	237 (50.4)	166 (52.4)
Female	233 (49.6)	151 (47.6)
Mean age, years ± SD	66.97±18.58	69.08±18.40
Sector of admission, n (%)		
Internal medicine	331 (70.4)	317 (100)
Surgical	139 (29.6)	
Duration of hospitalization, days ± SD	9.72±11.84	8.73±9.95
Route of PPI administration during hospitalization, n (%)		
Oral	63 (13.4)	52 (16.4)
Intravenous	241 (51.3)	149 (47)
Intravenous drip	6 (1.3)	1 (0.3)
Patients' outcomes, n (%)		
Complete healing	7 (1.5)	0 (0)
Improvement	391 (83.2)	252 (81.8)
Stable status	37 (7.9)	27 (8.8)
Deterioration	4 (0.9)	0
Death	31 (6.6)	29 (9.4)

PPI, proton pump inhibitor; SD, standard deviation

rates of inappropriate PPI administration were 25.9%, 49.2% and 21.4%, respectively. More specifically, PPI overuse was documented in 15.7% of patients before admission, in 41.1% of those hospitalized and in 12.4% of the discharged patients, while the respective percentages for PPI underuse were 10.2%, 8.1% and 9%. The duration of hospitalization (10.03±11.86 vs. 9.41±11.84 days, P=0.257) and patients' outcomes (complete healing and improvement: 50.5% vs. 49.5%, P=0.205) were not related to inappropriate PPI use.

Table 2 summarizes the risk for inappropriate PPI use during hospitalization in the departments of the hospital as compared to the Gastroenterology unit. The patients in the internal medicine department were more likely to be exposed to inappropriate use of PPIs than patients in other departments. As shown in Table 3, patients discharged from the internal medicine sector of the hospital were at a significantly increased risk of inappropriate PPI use compared to patients discharged from the surgery sector (OR 3.79, 95%CI 1.98-7.19; P<0.001), with this difference being significant for both PPI overuse and underuse (OR 3.37, 95%CI 1.48-7.69; P=0.002 and 3.33, 95%CI 1.27-8.67; P=0.011). Moreover, significant PPI underuse during hospitalization was detected among patients admitted to the internal medicine sector compared to those admitted to the surgery sector of the hospital (OR 5.35, 95%CI 1.62-17.86; P= 0.001).

Secondary endpoints

Phase II of the study was conducted between September 2018 and January 2019. Based on the results of Phase I, the medical staff of the internal medicine sector, where the inappropriate use of PPIs was more frequent, underwent—apart from the information campaign for all medical staff of the Hospital—2 additional intensive educational seminars on the appropriate use of PPIs, as described in the Patients and methods section.

Table 2 Inappropriate use of PPIs during hospitalization during Phase I, by department

Department	Patients (n=470) with PPIs inappropriate use (during hospitalization)		OR (95%CI)
	Yes	No	
Gastroenterology	3	9	1
Internal Medicine	102	73	4.2 (1.1-16.0)
Internal Medicine, others*	27	27	3.0 (0.7-12.3)
Cardiology	39	51	2.3 (0.6-9.0)
General Surgery	12	18	2.0 (0.4-8.9)
Surgical, others**	48	61	2.4 (0.6-9.2)

*Neurology, Pulmonary Medicine, Dermatology, Nephrology, Hematology and Oncology departments

**Otorhinolaryngology, Ophthalmology, Thoracic Surgery, Vascular Surgery, Cardiothoracic Surgery, Oral and maxillofacial surgery, Neurosurgery, Orthopedic, Obstetrics and Gynecology departments

PPI, proton pump inhibitor; OR odds ratio; CI, confidence interval

Therefore, Phase III of the study (June and July 2019) focused on the internal medicine departments. Overall, the records and charts of 317 patients admitted in 4 consecutive on-call days were assessed during Phase III. Among them, PPIs were prescribed in 21.9%, 64.5% and 29.7% before admission, during hospitalization and at discharge, respectively. Inappropriate use of PPIs was documented in 22.3%, 48.6% and 23.6% at the same time points.

As shown in Table 4, the rates of inappropriate use of PPIs were not significantly different during hospitalization (51.7% vs. 48.6%, P=0.478) and at discharge (26.9% vs. 23.6%, P=0.391) between Phases I and III. However, we observed a 3-fold decrease in PPI underuse during Phase III compared to the initial assessment. Hospitalization duration was longer in patients with inappropriate PPI use (9.62±9.50 vs. 7.78±10.28 days, P=0.03), while patients' outcomes (complete healing and improvement: 46% vs. 54%, P=0.297) were not related to inappropriate PPI use during Phase III of the study.

During study Phase I, the average cost of PPIs (omeprazole, lansoprazole, pantoprazole, esomeprazole) administered in our hospital was 3.435 euro and 0.235 euro for the iv and the *per os* dose, respectively. During the same period, we detected that 1850 iv and 430 *per os* doses of PPIs were administered in 193 patients without indication during the 10 (mean value) days of their hospitalization. Of these patients, 80% received the medications iv (80% q.d. and 20% b.i.d.) and the rest orally (90% q.d. and 10% b.i.d.). Assuming that these numbers and rates of inappropriate PPI use could be applied to all 90 on-call days of the hospital per year, the annual expenses of the hospital due to PPI overuse was calculated at 193,674 euros. Using the same model, we estimated that 1200 patients (40 patients every 3 hospital on-call days) would be at risk of GI complications annually, due to under-prescribing of PPIs at discharge from the hospital.

Discussion

Following a worldwide trend, PPI overuse is a concern for the Greek healthcare system. Ntaios *et al* retrospectively studied the discharge letters of 1693 adult patients, revealing that 81.4% of PPI prescriptions had an improper indication [14], and Voukelatou *et al* showed that 84% of PPIs were prescribed inappropriately among 758 admitted elderly patients [15]. Our findings indicate a lower PPI misuse rate in Greece compared to previously published studies. However, we estimated that the annual cost of the inappropriate prescription of PPIs in a Greek tertiary hospital exceeds the cost of purchasing one modern, fully equipped endoscopy system, and that 1200 patients would be at risk of developing GI complications due to under-prescribing of PPIs at their discharge. We also detected that the patients discharged from the internal medicine sector clinics/departments were at a higher risk of PPI misuse compared to those discharged from the surgical sector. This finding contrasts with the results of 2 studies where a larger proportion of surgical patients were found to receive PPIs inappropriately and in higher doses compared to the internal medicine patients [5,12].

Table 3 Administration of PPIs in internal medicine and surgical sectors during Phase I of the study

Point of PPI administration	PPI	Internal Medicine Sector, n/N (%)	Surgical Sector, n/N (%)	P-value	OR	95%CIs
At admission*	use	113/324 (34.9)	36/136 (26.5)	0.082	1.49	0.95-2.32
	inappropriate use	93/324 (28.7)	26/136 (19.1)	0.036	1.70	1.04-1.70
	overuse	54/324 (16.7)	18/136 (13.2)	0.401	1.31	0.74-2.33
	underutilization	39/324 (12.0)	8/136 (5.9)	0.062	2.19	0.95-4.81
In hospital	use	212/331 (64.0)	96/139 (69.1)	0.339	0.80	0.52-1.22
	inappropriate use	37/331 (51.7)	60/139 (43.2)	0.106	1.41	0.94-2.10
	overuse	136/331 (41.1)	57/139 (41.0)	1.000	1.00	0.67-1.50
	underutilization	35/331 (10.6)	3/139 (2.2)	0.001	5.34	1.62-17.85
At discharge**	use	119/308 (38.6)	28/135 (20.7)	<0.001	2.40	1.50-3.88
	inappropriate use	83/308 (26.9)	12/135 (8.9)	<0.001	3.79	1.98-7.19
	overuse	48/308 (15.6)	7/135 (5.2)	0.002	3.37	1.49-7.69
	underutilization	35/308 (11.4)	5/135 (3.7)	0.011	3.33	1.28-8.70

*Missing data from 7 internal medicine and 3 surgery patients

**Missing data from 23 internal medicine and 4 surgery patients

PPI, proton pump inhibitor; OR odds ratio; CI, confidence interval

Table 4 Administration of PPIs in internal medicine sector during study Phases I and III

Point of PPI administration	PPI	Phase I, n/N (%)	Phase III, n/N (%)	P-value
At admission*	use	113/324 (34.9)	66/301 (21.9)	<0.001
	inappropriate use	93/324 (28.7)	67/301 (22.3)	0.067
	overuse	54/324 (16.7)	39/301 (13)	0.216
	underutilization	39/324 (12.0)	28/301 (9.3)	0.302
In hospital**	use	212/331 (64.0)	202/313 (64.5)	0.934
	inappropriate use	177/331 (51.7)	152/313 (48.6)	0.478
	overuse	136/331 (41.1)	143/313 (45.7)	0.265
	underutilization	35/331 (10.6)	9/313 (2.9)	<0.001
At discharge***	use	119/308 (38.6)	82/276 (29.7)	0.029
	inappropriate use	83/308 (26.9)	65/276 (23.6)	0.391
	overuse	48/308 (15.6)	43/276 (15.6)	1.000
	underutilization	35/308 (11.4)	22/276 (8.0)	0.209

*Missing data from 10 Phase I and 16 Phase III patients

**Missing data from 4 Phase III patients

***Missing data from 27 Phase I patients and 41 Phase III patients

PPI, proton pump inhibitor

During the second phase of the study, we implemented an educational campaign to present the study Phase I results and to highlight the indications and potential harms of PPI misuse. Finally, we examined the effects of the intervention in the third phase of the study only in the internal medicine sector, where we detected the larger deviation from the correct PPI administration. Phase III was conducted long after Phase I, when the medical stuff were unaware of being monitored.

Our educational intervention failed to reduce the inappropriate use of PPIs. We may speculate that the lack of a close feedback program in our comprehensive educational intervention was one of the contributing factors for this failure. Similar educational interventions accompanied by visual stimulation throughout various hospital sites were also inconclusive, yet implied a reduction in inappropriate PPI use elsewhere [16,17]. Moreover, interventions which included continuous and regular review and benchmarking, apart from educational sessions, were more effective in reducing PPI overuse during hospitalization and after discharge [18,19]. Unfortunately, these studies lacked a long follow up, for

clinicians' prescription habits and for patients' clinical outcomes. However, it seems that a combination of educational sessions, along with a close feedback program engaging and motivating clinicians to prescribe appropriately, might be more effective. Measures such as clearly written and easily applicable local clinical guidelines, in both printed and electronic form, frequent reminders such as email newsletters, as well as live or web platforms where physicians can view current data and address questions and concerns, could be important steps in this direction [12,20].

On the other hand, our intervention showed for the first time the effectiveness of an educational intervention in reducing the underutilization of PPIs in a hospital setting. PPI underutilization is an underappreciated but concerning issue, mainly reported in patients under NSAID treatment [21]. The burden of potential upper GI complications in high-risk hospitalized patients (NSAIDs, antiplatelet or anticoagulant treatment users, critically ill patients in need of stress ulcer prophylaxis) as well as their greater risk of death and length of hospitalization are well established [22]. However, our observation is limited by the fact we found no difference regarding patients' outcomes according to the appropriateness of PPI use.

Surprisingly, we observed that the rate of PPI misuse doubled during hospitalization compared to the pre-admission rate, but it returned to pre-hospitalization levels at discharge. This motif was observed in both phases I and III of the study, showing from a different perspective that our intervention had no impact on physicians' PPI prescription habits. Moreover, any explanation of this motif is difficult and highly speculative. Uncertainty about patients' outcomes, ignorance of PPIs' indications and risks, inadequate long-term monitoring of the medications administered, and reliance on the correctness of the pre-hospitalization treatment might, at least partially, explain why the opportunity of correcting long-term PPI misuse was lost during hospitalization [12]. Routine prophylaxis for stress ulcer, gastroprotection for NSAID, antiplatelet, anticoagulant or corticosteroid therapy without other bleeding risk factors, and uncritical PPI use in cirrhosis, cancer or pancreatic diseases, are some well-defined and widespread wrong indications for PPI use in hospitalized patients [21].

Our study is the first to evaluate the effect of an educational intervention on the administration of PPIs in Greece and one of the very few worldwide. The multifaceted character of the intervention and the large number of patients that were included in the study strengthens the reliability of our results. The fact that the exact dates of the phases of the study were unknown to the hospital staff limited the potential bias of the hospital physicians to act as if under review. On the other hand, our study was a cross-sectional data recording, preventing the estimation of a potential relationship between clinical or demographic factors and PPI prescribing and the follow up of PPI administration after the patients' discharge from hospital. Evaluation of the effect of the educational intervention only on the internal medicine sector can also be considered a study limitation.

In conclusion, inappropriate PPI prescription in the hospital setting is a worrisome issue, and Greece is no exception. Since hospitalization provides an opportunity for a thorough medical assessment, intervention programs training hospital physicians to prescribe PPIs properly should be conducted. The failure of our intervention to control PPIs prescribing might, at least, be explained by the lack of close monitoring, feedback and benchmarking to further motivate medical staff to improve PPI use in clinical practice.

Summary Box

What is already known:

- Inappropriate use of proton pump inhibitors (PPIs) may expose patients to unjustified risks
- PPI overuse imposes a significant financial burden on healthcare systems worldwide
- Hospitalization might become a critical checkpoint to control PPI prescription with educational initiatives to inform physicians about correct PPI use

What the new findings are:

- Our study revealed an unexplained greater rate of PPI misuse during hospitalization, which returned to the pre-admission level at discharge
- The risk of PPI misuse is higher among patients in the internal medicine sector
- A comprehensive, educational intervention involving the medical stuff of the wards at highest risk for PPI misuse failed to optimize the administration of these medications one year after the intervention

References

1. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008;**336**:2-3.
2. Haastrup P, Paulsen MS, Zwisler JE, et al. Rapidly increasing prescribing of proton pump inhibitors in primary care despite interventions: a nationwide observational study. *Eur J Gen Pract* 2014;**20**:290-293.
3. Savarino V, Dulbecco P, de Bortoli N, Ottonello A, Savarino E. The appropriate use of proton pump inhibitors (PPIs): Need for a reappraisal. *Eur J Intern Med* 2017;**37**:19-24.
4. Sánchez-Cuén JA, Irineo-Cabrales AB, Bernal-Magaña G, Peraza-Garay Fde J. Inadequate prescription of chronic consumption of proton pump inhibitors in a hospital in Mexico. Cross-sectional study. *Rev Esp Enferm Dig* 2013;**105**:131-136.
5. Kelly OB, Dillane C, Patchett SE, Harewood GC, Murray FE. The inappropriate prescription of oral proton pump inhibitors in the hospital setting: a prospective cross-sectional study. *Dig Dis Sci* 2015;**60**:2280-2286.
6. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology* 2017;**153**:35-48.
7. Ladd AM, Panagopoulos G, Cohen J, Mar N, Graham R. Potential costs of inappropriate use of proton pump inhibitors. *Am J Med Sci* 2014;**347**:446-451.

8. Grant K, Al-Adhami N, Tordoff J, Livesey J, Barbezat G, Reith D. Continuation of proton pump inhibitors from hospital to community. *Pharm World Sci* 2006;**28**:189-193.
9. Singh A, Bodukam V, Saigal K, et al. Identifying risk factors associated with inappropriate use of acid suppressive therapy at a community hospital. *Gastroenterol Res Pract* 2016;**2016**:1973086.
10. Haastrup P, Paulsen MS, Begtrup LM, Hansen JM, Jarbøl DE. Strategies for discontinuation of proton pump inhibitors: a systematic review. *Fam Pract* 2014;**31**:625-630.
11. Targownik LE, Metge CJ, Leung S. Underutilization of gastroprotective strategies in aspirin users at increased risk of upper gastrointestinal complications. *Aliment Pharmacol Ther* 2008;**28**:88-96.
12. Del Giorno R, Ceschi A, Pironi M, Zasa A, Greco A, Gabutti L. Multifaceted intervention to curb in-hospital over-prescription of proton pump inhibitors: A longitudinal multicenter quasi-experimental before-and-after study. *Eur J Intern Med* 2018;**50**:52-59.
13. National Organization for Medicines. National prescription drug database, 17 Jan. 2021. Available from: http://www.eof.gr/web/guest/gnf [Accessed 6 June 2021]. In Greek.
14. Ntaios G, Chatzinikolaou A, Kaiafa G, Savopoulos C, Hatzitolios A, Karamitsos D. Evaluation of use of proton pump inhibitors in Greece. *Eur J Intern Med* 2009;**20**:171-173.
15. 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.
16. Atkins R, Smith L. Impact of pharmacy intervention on the use of proton-pump inhibitors in the hospital setting. *Consult Pharm* 2013;**28**:786-792.
17. Hamzat H, Sun H, Ford JC, Macleod J, Soiza RL, Mangoni AA. Inappropriate prescribing of proton pump inhibitors in older patients: effects of an educational strategy. *Drugs Aging* 2012;**29**:681-690.
18. Urfer M, Elzi L, Dell-Kuster S, Bassetti S. Intervention to improve appropriate prescribing and reduce polypharmacy in elderly patients admitted to an internal medicine unit. *PLoS One* 2016;**11**:e0166359.
19. Wehling M, Burkhardt H, Kuhn-Thiel A, et al. VALFORTA: a randomised trial to validate the FORTA (Fit fOR The Aged) classification. *Age Ageing* 2016;**45**:262-267.
20. Wilsdon TD, Hendrix I, Thynne TR, Mangoni AA. Effectiveness of interventions to deprescribe inappropriate proton pump inhibitors in older adults. *Drugs Aging* 2017;**34**:265-287.
21. Scarpignato C, Gatta L, Zullo A, Blandizzi C; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. *BMC Med* 2016;**14**:179.
22. Cook D, Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. *N Engl J Med* 2018;**378**:2506-2516.