Digestive and Liver Disease 55 (2023) 485–489

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Using an algorithm to assess the rate and trend over time of inappropriate proton pump inhibitors prescription upon hospital discharge

Orly Sneh-Arbib[a,f,*], Shir Ben-Shitrit[b,f], Yaara Leibovici Weisman[b,f], Shiri Koshnir[c,f], Zohar Levi[b,d,f], Bronya Calivarysky[e,f]

[a] Division of Gastroenterology and liver disease, Talpiot, Clalit Health Services, Jerusalem, Israel
[b] Sackler School of Medicine, Tel-Aviv University, Israel
[c] Clalit Research Institute, Tel-Aviv, Israel
[d] Division of Gastroenterology, Rabin Medical Center, Petach-Tikva, Israel
[e] Department of Pharmacy, Rabin Medical Center, Petach-Tikva, Israel
[f] School of Pharmacy, the faculty of medicine, Hebrew University, Jerusalem, Israel

ARTICLE INFO

Article history:
Received 7 August 2022
Accepted 19 October 2022
Available online 15 November 2022

Keywords:
Accepted clinical indications
"Choosing wisely" principles
Inadequate use
Proton pump inhibitors

ABSTRACT

Background: There is an increasing interest in inappropriate proton pump inhibitors prescription (InPPIp), as defined by the National Institute for Clinical Excellence (NICE) guidelines.
Aims: To evaluate the rate, trend over time and factors associated with InPPIp upon discharge from internal medicine departments.
Methods: We evaluated patients discharged from internal medicine departments with a PPI prescription in 2014 and 2017 at an academic referral center according to a developed algorithm.
Results: A total of 3,982 patients were included (50.8% women, 74% ≥ 65 years). The rate of InPPIp was 44.3% (95% CI 42.8–45.9) for the entire cohort; 68.1% for subjects aged < 65 years and 36.0% for those aged ≥ 65 years ($p<0.001$); 43.2% in 2014 and 45.6% in 2017 ($p = 0.130$). In a decision-tree analysis, after the exclusion of 448 patients with gastrointestinal indications, 89.4% (1,580/1,766) of all InPPIp cases were of patients without dual antiplatelet treatment (DAPT) and 8.6% (151/1,766) were of patients younger than 65 years, who were taking aspirin.
Conclusions: The rate of InPPIp is high, especially among patients not receiving DAPT and young patients taking aspirin. Time trend analysis showed no improvement over time. Our algorithm may serve as an automated quality measuring tool to reduce InPPIp.
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1. Introduction

The inappropriate use of proton pump inhibitors (PPIs) represents a global healthcare problem, leading to significant adverse events in patients and to economic consequences worldwide [1–5]. Proper indications for long-term PPI use are few and well defined: prior upper gastrointestinal (GI) bleeding [6], maintenance treatment after healing of erosive esophagitis (Los Angeles classification C, D) [6,7], Barrett's esophagus [8], use of nonsteroidal anti-inflammatory drugs (NSAIDs) or antiplatelet agents in patients with increased bleeding risk [9], pathological hypersecretory conditions and maintenance therapy for symptoms control in patients with gastroesophageal reflux disease (GERD) [7,9–12]. As part of the general efforts to reduce the overuse of medical tests and treatments, several organizations are trying to reduce the inappropriate use of PPIs [6,8,9,13–19]. Unwarranted initiation of PPIs during hospitalization, and the recommendation to continue such therapy after discharge, are substantial causes for the widespread and inadequate use of PPIs [2,20–23]. Since indications for long-term PPIs use are based on multiple factors, including complex drug combinations and medical history (past and current), the appropriateness of PPIs is complex. Clalit Health Services is a well-known health maintenance organization (HMO) with primary, secondary, and tertiary health resources, and a comprehensive database which includes chronic diagnoses, drugs issued at the primary care level and in-hospital data [24]. In this study, we aimed to measure the rate of inappropriate long term PPIs prescription upon discharge from internal medicine departments. We also aimed to evaluate a trend over time, using an algorithm based on the electronic database of the *Clalit Health Services*.

* Corresponding author at: Jabotinsky 39, Petach-Tikva Israel, POB 49100.
E-mail address: orlys2@clalit.org.il (O. Sneh-Arbib).

https://doi.org/10.1016/j.dld.2022.10.018
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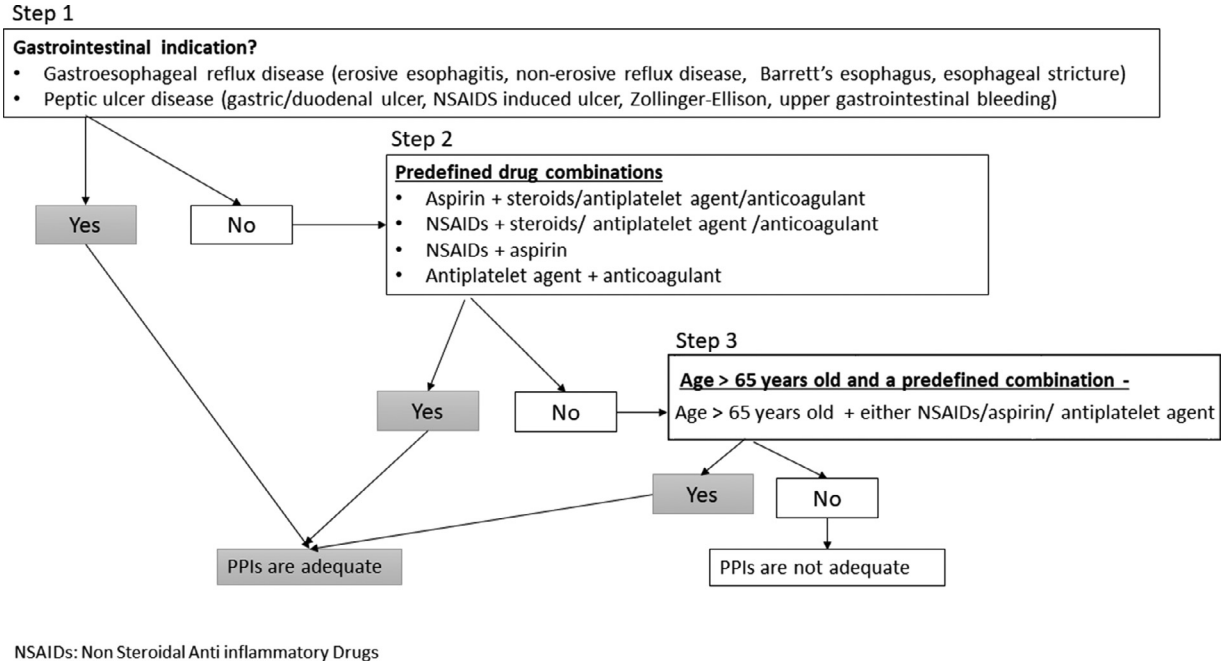

Fig. 1. The process of defining an inadequate PPIs prescription.

2. Material and methods

2.1. Study population

We performed a retrospective analysis of adults admitted to internal medicine or geriatric departments at *Rabin Medical Center* (a tertiary hospital affiliated to *the Clalit Health Services*) in 2014 and 2017 (the first six months of each year). We included patients insured by *Clalit Health Services* who were prescribed PPIs upon discharge, with a recommendation for long-term use. We excluded patients who died in the hospital or were transferred between departments during hospitalization. We also excluded those with a hospitalization length that exceeded three months. If such existed, only the first of several admissions during the researched time period were included in our analysis.

2.2. Data source

We first extracted data for all included patients from the hospital's computerized database. This information included age, gender, current and past diagnoses, and medications upon arrival to the hospital and release. We recorded the relevant gastrointestinal diagnoses: ulcer (gastric, duodenal), Barrett's esophagus, reflux, gastroesophageal bleeding, and melena. We screened the database for the following medications: PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole), aspirin, antiplatelet agents (clopidogrel, prasugrel, ticagrelor), anticoagulants (warfarin, apixaban, dabigatran, rivaroxaban), oral or parenteral steroids (prednisone, dexamethasone, hydrocortisone) and NSAIDs (naproxen, ibuprofen, diclofenac).

Data regarding ethnicity, socioeconomic status (SES), Charlson comorbidity index (CCI), previous diagnosis of ulcer (gastric, duodenal), Barrett's esophagus, reflux, gastrointestinal bleeding, melena or PPIs usage prior to hospitalization (at least one month long) were extracted from the *Clalit* data warehouse. The data warehouse uses a single, universally adopted electronic health record system throughout the organization.

2.3. Developing the algorithm

Based on published guidelines, the "choosing wisely" principles, and expert opinions, we defined scenarios in which there clearly is

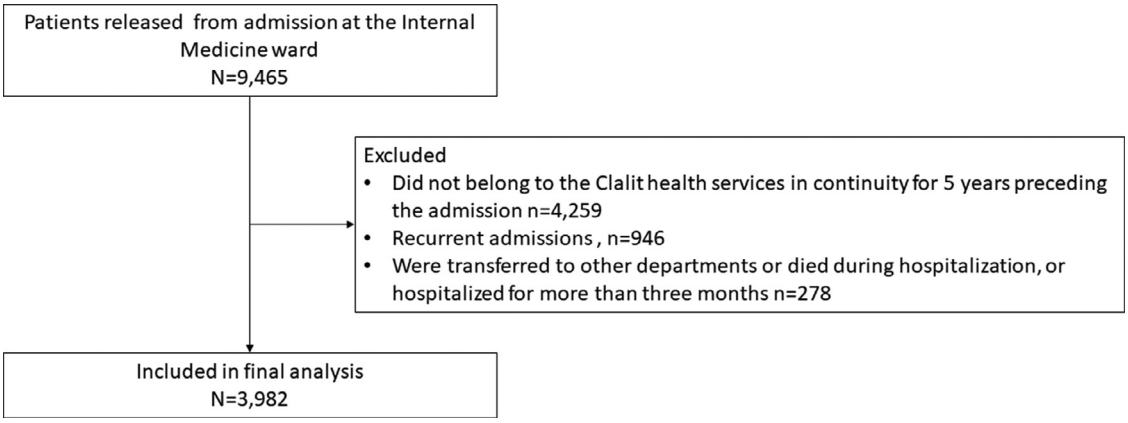

Fig. 2. Study flowchart.

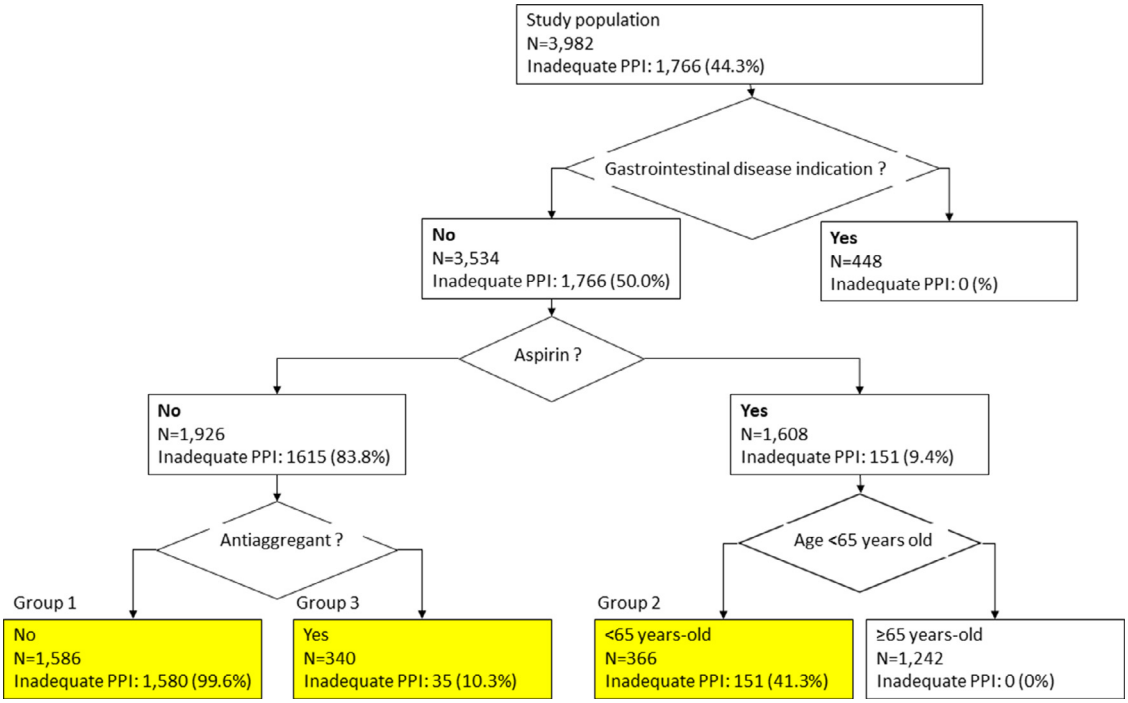

Fig. 3. Decision-tree analysis for inadequate PPI use.

no indication for long-term PPI use [6,8,9,13–18], Fig. 1, Appendix 1. We manually validated a hundred health records in which the algorithm found inadequate PPIs prescription. The validation entailed thoroughly examining the records and searching for a justified reason for PPI. We randomly selected 100 files with equal representation of year, gender, and age (age<65 vs. ≥65). Of the 100 records reviewed, eight prescriptions were found justified after our review (three hospitalizations in 2014 and five in 2017). In the remaining 92 files, we found no justification for PPI. Furthermore, 100 files that were classified as justified by the algorithm were reviewed, and all were indeed explained, yielding an accuracy of 96%.

2.4. Statistical analysis

A production of inadequate prescription rate was performed in a simple descriptive method, followed by a trend test between two time periods (2014 and 2017), which was performed using χ^2 test. To identify risk factors for inadequate PPIs use, we performed a multivariable logistic regression of the model, which included the factors described above. Decision-tree analysis was performed to predict values of a dependent variable based on values of independent variables, which provides a validation tool for exploratory and confirmatory classification analysis. Statistical analysis was performed using SPSS software. We used SPSS version 24.0 (IBM SPSS Statistics for Windows, version 24.0. Armonk, NY. IBM Corporation).

3. Results

3.1. Study population

The initial cohort included 9465 records. After all exclusions (4259 patients were not insured by *Clalit Health Services* for five consecutive years before admission; 946 were recurrent admissions, and 278 patients were transferred to other departments or hospitalized for more than three months), a total of 3982 patients remained (50.8% women, 74% ≥ 65 years old) (See Fig. 2 for study flowchart). Most patients were already on chronic PPI use at least one month before hospital admission (92.4%), Table 1.

Table 1
Patients' characteristics.

		N (%)
All		3982 (100)
By age group	Age < 65 years	1036 (26.0)
	Age ≥ 65 years	2946 (74.0)
Sex	Male	1958 (49.2)
	Female	2024 (50.8)
Ethnicity	Jewish	3662 (92.0)
	Arabic	320 (8.0)
Socioeconomic status	High	1205 (30.3)
	Medium	1696 (42.6)
	Low	1048 (26.3)
Charlson Comorbidity Index points	0 (no burden)	344 (8.6)
	1–2 (mild burden)	980 (24.6)
	3–5 (moderate burden)	1441 (36.2)
	≥ 6 (severe burden)	1172 (29.4)
PPIs first prescribed	Before admission	3678 (92.4)
	Upon admission	304 (7.6)
Admission year	2014	2130 (53.5)
	2017	1852 (46.5)

PPIs: proton pump inhibitors.

3.2. Rate of inappropriate PPIs use and associated factors

The overall rate of inappropriate PPI use was 44.3% (95% CI 42.8–45.9) for the entire cohort; 68.1% for subjects aged < 65 years vs. 36.0% for subjects aged ≥ 65 years ($p<0.001$). By time periods, inappropriate use was 43.2% in 2014 and 45.6% in 2017 ($p = 0.130$). In multivariate analysis, age under 65 years old, female gender, low SES, and no prior PPIs prescription were all significantly associated with inappropriate prescription, Table 2.

In a decision-tree analysis for inadequate PPIs use, after excluding patients with clear GI indications ($n = 448$), 1766 patients with inadequate PPI use remained. We identified three major groups of patients: Group I included patients who weren't taking

Table 2
Rate and factors associated with inadequate PPIs prescription.

		Adequacy of PPIs prescription				Univariate analysis				Multivariate analysis			
		Adequate		Inadequate		OR	95%CI		P	AdjOR	95%CI		P
		N	%	N	%								
All		2216	55.7%	1766	44.3%								
Age, years	≥ 65	1885	64.0%	1061	36.0%	1.00				1.00			
	< 65	331	31.9%	705	68.1%	3.78	3.26	4.40	<0.001	3.59	3.05	4.22	<0.001
Gender	Male	1154	58.9%	804	41.1%	1.00				1.00			
	Female	1062	52.5%	962	47.5%	1.30	1.15	1.47	<0.001	1.53	1.34	1.76	<0.001
Ethnicity	Jewish	2072	56.6%	1590	43.4%	1.00				1.00			
	Arabic	144	45.0%	176	55.0%	1.59	1.27	2.00	<0.001	1.10	0.84	1.44	0.498
Socioeconomic status	High	719	59.7%	486	40.3%	1.00				1.00			
	Medium	925	54.5%	771	45.5%	1.23	1.06	1.43	0.006	1.14	0.97	1.33	0.111
	Low	557	53.1%	491	46.9%	1.30	1.10	1.54	0.002	1.03	0.85	1.25	0.775
								total	0.003			total	0.235
Charlson comorbidity Index points	0	129	37.5%	215	62.5%	1.00				1.00			
	1–2	489	49.9%	491	50.1%	0.60	0.47	0.78	<0.001	0.77	0.59	1.00	0.052
	3–5	856	59.4%	585	40.6%	0.41	0.32	0.52	<0.001	0.61	0.47	0.80	<0.001
	> 6	723	61.7%	449	38.3%	0.37	0.29	0.48	<0.001	0.59	0.45	0.77	<0.001
								total	<0.001			total	<0.001
PPI first prescribed	Before admission	2092	56.9%	1586	43.1%	1.00							
	Upon admission	124	40.8%	180	59.2%	1.92	1.51	2.43	<0.001	1.44	1.11	1.87	0.006
Admission year	2014	1209	56.8%	921	43.2%	1.00							
	2017	107	11.2%	845	88.8%	1.10	0.97	1.25	0.131				

Adjusted for age, gender, ethnicity, SES, CCI, and first PPI prescribed.
PPIs: proton pump inhibitors.

dual antiplatelet treatment (DAPT): 89.4% (1580/1766); Group II included patients younger than 65 that were taking aspirin only, 8.6% (151/1766)]; Group III included patients who received a single antiplatelet agent other than aspirin, 1.9% (35/1776), Fig. 3.

Out of all subjects classified as inappropriate PPI use, 42.4% (748/1766) were not using either aspirin, NSAIDS, antiplatelet, antiaggregant, anticoagulant or steroid; 26.3% (464/1766) were using steroids; 24.6% (435/1766) were using anticoagulants; 8.6% (151/1766) were using aspirin; 2.0% (35/1766) were using antiaggregant; 0.9% (16/1766) were using NSAIDS.

4. Discussion

This study aimed to evaluate the rate of inadequate PPIs prescription upon discharge from internal medicine wards, according to an algorithm developed by us based on the National Institute for Clinical Excellence (NICE) guidelines. We report that the rate of inadequate PPIs prescription is about 45% of all prescriptions at discharge. We also report that most of the patients classified by our algorithm as receiving inadequate PPIs prescriptions were either patients who were not taking DAPT or patients younger than 65 who were taking only aspirin. Finally, we report no trend of improvement in the rate of inadequate PPIs prescription over time. Previous studies, as well as a recent Australian review article of international studies investigating inappropriate PPIs use, reported that the rate ranged from 11 to 84%, with high variation even within the same country, and concluded that, on average, almost half of PPIs prescriptions might be inappropriate, a proportion similar to our current results [25–27]. And yet, no single methodology is a consensus in determining inappropriate PPI use.

As stated above, we report no improvement over time in the rate of inappropriate PPIs prescription. This finding is surprising since more and more publications regarding PPIs‘ harmful side effects are being published. Furthermore, the "choosing wisely" campaign has been attempting to reduce inappropriate usage [15,22]. And yet, our findings are consistent with the recent report by Naunton et al. [25]

Most of our study population already received PPIs before admission (92.3%), prescribed by their general practitioner or during a previous hospitalization. This raises a concern regarding the unneeded continuation of these drugs; In both settings (hospital and general practice), the clinicians might rely on a previous recommendation by a colleague without reviewing the indications themselves, believing that discontinuing the PPI might be detrimental rather than helpful [23,28]. In addition, several studies have shown that general physicians tend not to review and document indications for PPI after discharge from the hospital. This fact often results in their long-term or even indefinite continuation [5]. Our findings indicate that when discharging a patient, reviewing the indications for PPIs prescription is essential. We assume that the high rates of inappropriate prescription during admission are driven by management of acute and complicated patients, by non-evidenced based prescription of PPIs and by prophylaxis therapy against complications caused by steroids or antiplatelet agents [2].

Interestingly, we report that about 40% of the subjects classified as receiving inappropriate PPI prescriptions were not using any of the drugs evaluated, probably representing subjects with functional dyspepsia. Also, about 26% were using steroids alone, and 25% were using anticoagulants, reflecting the tendency of the physicians to prescribe PPI drugs, irrespective of the clinical guidelines.

We also report that female gender, low SES, higher comorbidity score, and initiation of PPIs during hospital admission were all significantly associated with inappropriate PPIs prescription. These findings are consistent with previous reports [21,23,26]. The main limitation of our study is its retrospective nature.

After reviewing updated guidelines and literature, we found it difficult to define clear indications for PPIs use. In fact, except for the FDA-approved GI indications, there are no well-defined guidelines for other potentially needed indications for PPIs. Those non-GI indications are considered experts' opinions. We suggest that healthcare policymakers adopt an algorithm, such as ours, to standardize the routine evaluation of PPI's appropriateness.

In conclusion, although limited by the retrospective nature of our study, our findings indicate that the number of PPI prescriptions is unacceptably high, especially for patients who are not receiving DAPT and for young patients who are treated with aspirin alone. We also report that the time trend analysis showed no improvement over time. Undoubtedly, more action is needed to raise physicians' knowledge and attention to the subject while providing automated and standardized technology-based tools to reduce inappropriate PPIs use using an acceptable algorithm.

Conflict of interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.10.018.

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