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INAPPROPRIATE USE OF PROTON PUMP INHIBITORS IN ELDERLY PATIENTS DISCHARGED FROM ACUTE CARE HOSPITALS

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Abstract: *Background:* Proton-pump inhibitors (PPI) are extensively prescribed in older patients. However, little information is available on factors associated to PPI prescribing patterns among older patients discharged from hospital. *Objective:* To evaluate the appropriateness and clinical correlates of PPI prescription at discharge in a population of 1081 older patients discharged from acute care Italian hospitals. *Design:* We used data from the CRiteria to Assess Appropriate Medication Use among Elderly Complex Patients (CRIME) study, a multicenter observational study. The appropriateness of PPI prescriptions was defined according to the Italian Medicines Agency (AIFA) rules. Correlates of overprescribing (i.e prescribing without recognized AIFA indications) and underprescribing (i.e. not prescribing despite the presence of recognized AIFA indications) were investigated by logistic regression analysis. *Results:* Overprescribing was observed in 30% of patients receiving PPIs at discharge. Underprescribing was observed in 11% of patients not receiving PPIs at discharge. Overprescribing of PPIs at discharge was negatively associated with age (OR=0.88, 95%CI=0.85-0.91), depression (OR=0.58, 95%CI=0.35-0.96), use of aspirin (OR=0.03, 95%CI=0.02-0.06) and systemic corticosteroids (OR=0.02, 95%CI=0.01-0.04). The negative association with number of medications (OR=0.95, 95%CI=0.88-1.03) and overall comorbidities (OR=0.92, 95%CI=0.83-1.02) was nearly significant. Conversely, older age (OR=1.09, 95%CI=1.04-1.14), use of aspirin (OR=24.0, 95%CI=11.5-49.8) and systemic corticosteroids (OR=19.3, 95%CI=11.5-49.8) and overall comorbidities (OR=1.22, 95%CI=1.04-1.42) were independent correlates of underprescribing. *Conclusion:* Overprescribing of PPIs is more frequent in younger patients with lower burden of depression, whilst underprescribing is characterized by older age and greater burden of comorbidity and polypharmacy. Hospitalization should be considered as a clue to identify inappropriate use of PPIs and improve appropriateness of prescribing.

Key words: Proton pump inhibitors, inappropriate prescription, elderly, hospital.

Introduction

Proton pump inhibitors (PPIs) are widely prescribed to suppress gastric acid secretion in gastrointestinal disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease and upper gastrointestinal bleeding (1-3). In recent years, there has been a significant rise in the prescriptions for PPIs, especially in older populations (1), making these agents one of the most prescribed drugs worldwide (4, 5). Recent studies raised concerns about the potential risks associated with prolonged and potentially non-judicious use of PPIs, including mortality (6-8), functional decline (9), Clostridium difficile infections (10), fractures (11), cardiovascular events (12). Additionally, since PPIs are mainly metabolized by the cytochrome P450 system, interactions with other drugs also represent a relevant concern (13).

PPIs are often prescribed without a clear indication (14), thus contributing to increased expenditure for inappropriately prescribed medications (15). Nevertheless, only few studies have investigated the clinical correlates of inappropriate prescribing of PPIs in older population (16, 17). A better knowledge regarding additional PPI use is of paramount importance to identify effective strategies aimed at improving the quality of prescriptions. Therefore, the aim of the present study is to identify the clinical correlates of PPIs prescription and to evaluate the appropriateness of such prescriptions among older patients discharged from acute care hospitals in a large multicenter observational study.

Methods

Patients

This study uses data from the CRiteria to Assess Appropriate Medication Use among Elderly Complex Patients (CRIME) project, a multicenter prospective observational study aimed at collecting data about the patterns and quality of prescriptions among older patients admitted to seven geriatric and internal medicine acute care wards throughout Italy. The methods of the CRIME study have been extensively described elsewhere (18). Briefly, all patients consecutively admitted to

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participating wards between June 2010 and May 2011, were asked to participate in the study. Exclusion criteria included age<65 years and unwillingness to participate in the study. After obtaining a written informed consent, all participants were assessed within the first 24 hours from hospital admission and followed until discharge. Information was collected on demographic, socioeconomic, and clinical characteristics, with detailed data collection on pharmacological therapy and comprehensive geriatric assessment. After discharge, patients were reassessed at 3, 6, and 12 months. All Ethics Committees at participating institutions approved the study protocol.

This present study uses data collected during the hospitalization (time from hospital admission to discharge). Overall, 1123 patients were enrolled in the CRIME study. Patients who died during hospital stay (n=42, 3.7%) were excluded from this analysis, thus 1081 patients were included in this report.

Outcome

Drugs were coded using the Anatomical and Therapeutic Classification (ATC) (19). Participants taking PPIs at discharge were identified according to ATC code A02BC.

The appropriateness of the prescription of PPIs at discharge was evaluated according to indications released by the Italian Medicines Agency (AIFA) (20). Treatment with PPI was deemed appropriate in: i) patients on chronic treatment with systemic corticosteroids or low-dose ASA when one or more of the following risk factors is present: a. history of gastrointestinal bleeding or ulceration, b. treatment with anticoagulants or corticosteroids, c. age ≥75 years; ii) patients with peptic ulcer or GERD.

An analytical variable was created to compare patients receiving appropriate prescription of PPIs to those receiving PPIs without fulfilling any AIFA indications (overprescribing group). Similarly, we compared characteristics of patients fulfilling AIFA indications but not receiving PPIs (underprescribing group) with patients appropriately not receiving PPIs at discharge.

Variables

Variables included in the analysis were age, gender, cognitive impairment (age- and education-adjusted Mini Mental State Examination, MMSE score<24) (21), depression (Geriatric Depression Scale, GDS score>5) (22), dependency in basic activities of daily living (BADL) (23) , alcohol consumption(>2 wine glasses/day), nutritional status (Body Mass Index, BMI<20 kg/m^2, serum albumin<3.5 g/dl), number of drugs prescribed at discharge with the exclusion of PPIs, and history of adverse drug reaction (ADR) during hospital stay. Use of PPIs before hospital admission was considered as a potential confounder. Drugs potentially affecting the prescription of PPIs (i.e. aspirin and other antiplatelet agents, anticoagulants, NSAIDs, and systemic steroids) were also considered in the analysis. Selected conditions were considered as potential confounders, including: i) indications to the use of antiplatelet drugs (cardio- and cerebro-vascular diseases, peripheral artery disease, heart failure and diabetes mellitus) (24); ii) diseases for which the risk is increased by PPIs (infections and osteoporosis) (10, 25, 26); iii) potential side effects of PPIs (diarrhea and constipation). Anemia was defined as haemoglobin<1 g/dl for males and <12 g/dl for females, and was also considered among potential confounders. Finally, the overall number of comorbidities was calculated by excluding peptic ulcer (with or without haemorrhage) and GERD and included in the analysis.

Analytic approach

Patients were initially grouped on the basis of receiving or not receiving a prescription of PPIs at discharge. Therefore, patients receiving overprescribed PPIs at discharge were compared to patients receiving appropriate prescription of PPIs with regard to study variables. Similarly, patients in the underprescribing group were compared to those in which PPIs were appropriately not prescribed. The chi-square test or one way analysis of variance was used when appropriate.

Variables significantly distinguishing groups in preliminary analysis were entered into separate logistic regression models to investigate independent correlates of overprescription and underprescription at discharge. All analyses were performed using SPSS V10.0 Statistical Software Package for Windows.

Results

Participants included in the analysis had mean age of 81.2±7.4 years and 604 (55.9%) were women.

At discharge, overprescribed PPI patients were younger, had a lower number of comorbidities and were taking a lower number of drugs at discharge, including aspirin and systemic corticosteroids, when compared to patients with an appropriate PPI prescription.

In regards to comorbidities, overprescribed patients had a lower prevalence of depression, coronary artery disease, heart failure, and constipation (Table 1).

At discharge, underprescribed PPI patients, were older, had a significantly greater number of comorbidities, and were more frequently prescribed aspirin and systemic corticosteroids, received a greater number of drugs. In regards to specific comorbidities, these patients had a greater prevalence of peripheral artery disease and constipation compared to appropriately not prescribed patients. In addition, there was a greater prevalence of PPI use at the time of admission in the underprescribed PPI group compared to patients for which PPIs were appropriately not prescribed (Table 1).

After adjusting for potential confounders, the overprescription of PPIs at discharge was negatively associated with age, depression, use of aspirin and systemic corticosteroids. The negative association with number of medications and overall comorbidities was nearly significant

Table 1
Demographic and clinical characteristics of patients divided according to PPI prescription at discharge

	Patients with PPI prescription at discharge N=717			Patients without PPI prescription at dischange N=364		
	Appropriate N=394	Overprescription N=323	P	Appropriate N=247	Underprescription N=117	P
Age	83.0±6.5	80.2±8.1	0.001	79.4±7.5	81.9±6.1	0.002
Gender (F)	57.4	55.1	0.545	54.7	55.6	0.872
Current smokers	7.1	8.4	0.531	9.7	8.5	0.720
Alcohol consumption>2 wine glasses/day	1.8	2.5	0.515	2.8	3.4	0.761
BMI<20 kg/m^2	8.4	8.0	0.982	4.0	3.4	0.729
Hypoalbuminemia	41.1	38.1	0.408	32.8	31.6	0.845
Cognitive impairment	45.2	38.1	0.053	41.7	41.0	0.713
Depression	29.7	21.4	0.045	26.7	28.2	0.839
Dependency in at least 1 BADL at the admission	42.9	40.2	0.475	30.8	27.4	0.505
Any ADR during stay	6.3	7.7	0.466	5.3	7.7	0.364
Drugs prescribed at discharge						
Aspirin	61.7	17.6	0.001	12.1	60.7	0.001
Antiplatelet agents (excluding aspirin)	10.9	11.5	0.819	12.6	15.4	0.459
Anticoagulating agents	13.5	10.2	0.185	9.7	9.4	0.924
NSAIDs	1.3	2.2	0.351	2.0	0.9	0.413
Systemic steroids	29.4	2.5	0.001	2.4	16.2	0.001
No. of drugs* at discharge	7.2±2.6	6.4±2.8	0.001	6.0±2.8	7.5±2.7	0.001
PPIs before admission	45.9	44.6	0.716	29.1	40.2	0.036
Diagnoses						
Coronary artery disease	38.3	29.4	0.012	24.3	29.9	0.254
Peripheral artery disease	8.6	7.4	0.558	4.0	10.3	0.020
Heart failure	35.5	25.7	0.005	15.8	22.2	0.135
Stroke/TIA	23.4	21.4	0.526	17.8	17.9	0.975
Diabetes mellitus	27.7	32.8	0.134	27.1	33.3	0.223
Diarrhea	3.8	4.0	0.881	0.8	3.4	0.068
Constipation	17.3	10.8	0.015	7.7	17.9	0.003
Infections	11.9	9.9	0.390	7.7	9.4	0.580
Osteoporosis	15.0	14.6	0.874	19.0	17.1	0.657
Anemia	59.1	55.4	0.316	43.7	46.2	0.663
No. of diagnoses**	5.5±2.6	4.8±2.5	0.001	4.1±2.1	5.4±2.4	0.001

*Excluding PPIs; **Excluding peptic ulcer and GERD.

(Table 2). After excluding the use of aspirin and systemic steroids from the multivariable model, age (OR=0.94, 95%CI=0.92-0.96), depression (OR=0.66, 95%CI=0.45-0.97), and number of medications (OR=0.89, 95%CI=0.83-0.95) were significantly associated with overprescribing. Conversely, older age, use of aspirin, systemic corticosteroids and overall comorbidities were independent correlates of underprescription of PPI (Table 2). After excluding the use of aspirin and systemic steroids from the model, age (OR=1.09, 95%CI=1.05-1.14) and number of medications (OR=1.21, 95%CI=1.09-1.33) qualified as significant correlates of undeprescribing, while the association with overall comorbidity (OR=1.16, 95%CI=0.99-1.30) was nearly significant.

Discussion

This report confirms that overprescribing of PPIs is frequent among patients discharged from hospital. Though

less frequent, underprescribing at discharge can be observed in a not negligible proportion of patients. The overprescribing of PPIs has been previously reported and has been shown to range between 27% and 71% (16, 27, 28). More recently, an overprescribing of PPIs was found in 80% of 2686 patients discharged with a PPI prescription over a 4-year period (29). On the other hand, the few studies investigating the underprescribing of PPIs at discharge showed a prevalence ranging between 28% and 60% (30, 31).

Table 2
Summary logistic regression analysis of selected variables to overprescribing (upper panel) or underprescribing (lower panel) of PPIs at discharge

	OVERPRESCRIBING	
	OR	**95%CI**
Age	0.88	0.85-0.91
Gender (F)	0.87	0.57-1.34
Cognitive impairment	0.99	0.65-1.52
Depression	0.58	0.35-0.96
Drugs prescribed at discharge		
Aspirin	0.03	0.02-0.06
Systemic steroids	0.02	0.01-0.04
No. of drugs*	0.95	0.88-1.03
Diagnoses		
Coronary artery disease	0.94	0.59-1.52
Heart failure	0.72	0.43-1.20
Constipations	0.91	0.47-1.76
No. of diagnoses**	0.92	0.83-1.02
UNDERPRESCRIBING		
	OR	**95%CI**
Age	1.09	1.04-1.14
Gender (F)	1.71	0.90-3.25
Drugs prescribed at discharge		
Aspirin	24.0	11.5-49.8
Systemic steroids	19.3	5.9-62.7
No. of drugs*	1.06	0.95-1.20
PPIs at the admission	1.56	0.83-2.91
Diagnoses		
Peripheral vascular disease	1.31	0.37-4.62
Constipation	1.79	0.69- 4.64
Diarrhea	4.34	0.52-36.3
No. of diagnoses**	1.22	1.04-1.42

*Excluding PPIs; **Excluding peptic ulcer and GERD.

Compared to previous studies, we found that overprescribing was inversely associated with age, depression, number of diagnoses, aspirin, systemic steroids and the number of drugs prescribed at discharge. Ahrens et al. (32) demonstrated that the use of PPI before hospital admission was an independent determinant of overprescribing in multivariable analysis, as well as low dose aspirin, older age and hospitalization in a regional care center. Jarchow-MacDonald et al (17) found that institutionalization, polypharmacy and overall comorbidity were significantly associated with overprescribing of PPIs during hospitalization. A possible explanation of this discrepancy may be related to increasing use of ulcer prophylaxis, even for low-risk patients, especially in the presence of selected clinical conditions (i.e. heart diseases, acute renal failure) which are perceived as risk factors despite their lack of evidence (33). However, it is important to recall that long-term use of PPIs has been associated with several negative outcomes. For example, the use of PPIs was found to be associated with functional decline (1, 34) and mortality (8) among older patients discharged from hospital. PPIs are known to increase the risk of cardiovascular events (35) and infections (10, 25). Long-term use of PPIs is also associated with a reduced absorption of calcium, vitamin B12, iron, and magnesium (36). Additionally, use of PPIs was found associated with lower insulin-like growth factor-1 (IGF-1), suggesting a potential mechanism by which PPIs may exert negative effects of nutritional status and adverse outcomes among older people (37). Osteoporotic fractures have been reported as potential negative effects of PPIs (26). Finally, since PPIs are mainly metabolized by the cytochrome P450 system, interactions with other drugs using this system are expected (13). The above evidence, together with our results, raises the need to make further efforts to identify specific appropriateness for PPI prescriptions, especially in older patients vulnerable to negative outcomes. Considering that hospitalization for an acute event may create a potential basis for drug treatment strategies, studies are needed to show specific indications (as from guidelines), for the appropriate use of PPI prescribing at discharge.

Interestingly, we found that an underprescription of PPI was associated with older age, use of aspirin and systemic steroids, and overall comorbidity. Although comorbidity is widely correlated with polypharmacy, our results are in accordance with a previous study report by McDonald et al. (17) showing that the number of drugs was a risk factor for underprescription. Additionally, advanced age may be a risk factor that is considered negligible at the time of discharge in patients receiving no prophylaxis compared to patients receiving antiplatelet therapy (38). Current evidence suggests that polypharmacy and older age should not discourage from prescribing PPIs when there is a clear clinical indication. Indeed, the extensive use of gastroprotective agents can substantially reduce the morbidity and mortality associated with long-term NSAID and aspirin use (39), especially in

older patients (40). Recent cohort studies in France (41) and Japan (42) have demonstrated significant reductions in upper gastrointestinal bleeding through appropriate prescribing of PPIs. Our findings suggest that a treatment-risk paradox (i.e. treatment selection bias in which high-risk patients are less likely to receive therapy than low-risk ones) might affect PPI prescribing. Since the absolute benefits of PPI treatment are substantially necessary in patients with a high risk profile, physicians should be aware of such paradox in order to avoid negative clinical outcomes. Additionally, this paradox is an important confounder and needs to be recognized when drawing conclusions about treatment effects on the basis of associations between treatment exposure and outcomes (43).

Our study design includes some limitations. This study was only performed in geriatric and internal medicine units, which might result in an under-representation of selected indications for the use of PPIs (e.g. peptic ulcer). Additionally, the cross-sectional design does not allow to capture information regarding the duration of PPI use. Finally, factors related to the organization of participating wards, as well as internal policies of participating hospitals might influence the use of PPIs.

However, our study protocol holds a multicenter design and the population enrolled did not have stringent inclusion/exclusion criteria to allow for a greater awareness of appropriateness of PPI prescribing in a general population of older patients.

Conclusion

In conclusion, our study indicates that overprescribing and, to a lesser extent, underprescribing of PPIs are frequent among patients discharged from hospital. Accordingly, the hospital setting may improve the quality of PPI prescription only to some extent. Patients receiving PPIs without any recognized indication at discharge are younger with less comorbidities compared to those receiving appropriate PPI prescriptions. Given the potential for associated negative consequences, individuals not meeting prescribing indications would create a basis for future trials investigating withdrawal of PPIs. On the contrary, underprescribed patients are characterized by a high-risk profile. Hospitalization provides an important opportunity to improve the quality of PPI prescriptions.

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Conflict of interest disclosure form: All authors declare to have no conflict of interest with this manuscript.

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