

Appropriateness of treatment recommendations for PPI in hospital discharge letters

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Abstract

Purpose The reasons for the dramatic increase in proton pump inhibitors (PPI) prescriptions remain unclear and cannot be explained solely by increased morbidity, new indications or a decrease in alternative medication. Inappropriate use and discharge recommendations in hospitals are considered to be possible explanations. As the quality of PPI recommendations in hospital discharge letters in Germany has not been investigated to date, we have studied the appropriateness of these referrals.

Methods Hospital discharge letters with recommendations for PPI medication from 35 primary care practices in the county of Mecklenburg-Western Pomerania (MV; North-east Germany) were collected and analysed, and the appropriateness of the PPI indication was rated.

Results No information justifying the recommendation for continuous PPI medication could be identified in 54.5% of the discharge letters; in 12.7%, the indication was uncertain, and in 32.7%, we found an evidence-based indication for PPI medication. The most common indication for adequate PPI use was nonsteroidal anti-inflammatory drug-prophylaxis in high-risk patients.

Conclusions Inadequate recommendations for PPIs in discharge letters are frequent. This may lead to a continu-

ation of this therapy in primary care, thereby unnecessarily increasing polypharmacy and the risk of adverse events as well as burdening the public health budget. Hospitals should therefore critically review recommendations for PPI medication and the dosage thereof in their discharge letters and clearly document the reason for PPI use and the need for continuous prescription in primary care.

Keywords Proton pump inhibitors · Germany

Introduction

Proton pump inhibitors (PPIs) are the most potent medications currently available to reduce gastric acid secretion. Their use is widespread and on the increase, with annual sales worldwide that have surpassed US \$25 billion. The prescribing of PPIs in Germany rose from 44 million defined daily doses (DDD) in 1993 to 1,674 million DDD in 2008 (+3,805%), with an associated cost of 540 million Euros per year. The reasons for this are unclear and cannot be explained solely by increased morbidity, new indications [1] or a decrease in alternative medication.

PPIs are indicated for the treatment of gastro-oesophageal reflux disease (GERD) [2], peptic ulcer [3] and, in combination with two suitable antibiotics, for the eradication of *Helicobacter pylori* infection. After eradication, continuation of PPI medication is not necessary [4]. PPIs also are recommended to prevent nonsteroidal anti-inflammatory drug (NSAID)- and aspirin-induced ulcers in high-risk patients [5–7] (Table 1) and for the treatment of gastritis. In intensive care, PPIs are indicated for stress ulcer prophylaxis in patients with a risk of bleeding [8]. The use of PPI for patients with Barrett–Oesophagus is controversial, and its role, if any, in the prevention of carcinoma

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Table 1 Rating of indications for proton pump inhibitors

Indications for proton pump inhibitors

Indications rated as adequate

- Gastroesophageal reflux disease [2]
- Treatment and recurrent prophylaxis of peptic ulcer [3, 37]
- Eradication of *Helicobacter pylori* [4]
- Pathologic hypersecretory conditions (e.g. Zollinger–Ellison syndrome) [38]
- Histological proven diagnosis of gastritis [31, 32]
- Prevention of medication-induced ulcers: [5–7]
 - NSAID at patients >65 years
 - NSAID and corticosteroid
 - NSAID and warfarin /coumadin
 - NSAID and patient history of ulcer/ GI bleeding
 - Aspirin and corticosteroid
 - Aspirin and warfarin/coumadin
 - Aspirin and NSAID

Indications rated as uncertain

- Dyspepsia
- Barrett–Oesophagus [9]
- Oesophageal varices [10, 11]
- Ulcer prophylaxis with clopidogrel and low dose aspirin [13, 14]
- Patient underwent upper gastrointestinal endoscopy and biopsy, result outstanding at discharge [31, 32]
- History of gastritis, no endoscopy, no further information
- Anaemia, no endoscopy

NSAID, Nonsteroidal anti-inflammatory drug

induction has not yet been demonstrated [9]. A Cochrane Review reported that PPIs could be effective in a small proportion of patients with dyspepsia, but studies have shown a significant heterogeneity. Some guidelines recommend testing for *H. pylori* and eradication if necessary, others suggest an empirical PPI treatment 4–8 weeks as an alternative treatment [10]. Also, there is no clear evidence to support the assumption that PPIs prevent bleeding and promote quicker healing after ligation in patients with liver cirrhosis and oesophageal varices [11]. Some authors recommend ulcer prophylaxis for patients on a combination of aspirin and clopidogrel [12], but there has been some concerns about the interaction of clopidogrel and PPIs reducing cardiovascular protection and increasing arterio-sclerotic complications [13, 14].

The prescription of PPIs without clear indications has been frequently observed in many countries in hospitals [15–19] and primary care [20] alike. Reported rates of non-indicated prescriptions on general medical wards range from 40 to 81% [15–19], while inadequate acid-suppressive medication is often continued after discharge for long time [19, 21].

Although PPIs are generally considered safe, it has been shown that long-term use might be associated with hip fractures [22, 23], pseudomembranous colitis [24] and

respiratory infections, such as pneumonia [25]. In addition, the cost of unnecessary medication burdens the national health budget.

The aim of this study was to analyse the appropriateness of PPI treatment recommendations in patients discharged from hospital in a large German county.

Methods

This cross-sectional observational study was conducted in 35 primary care practices in the state of Mecklenburg-Vorpommern (MV), North-Eastern Germany.

Recruitment of practices We invited all 933 registered general practitioner (GP) practices in MV to participate in the study. Addresses were obtained from the Association of Statutory Health Insurance Physicians (*Kassenaerztliche Vereinigung*). A total of 97 GPs agreed to participate the study, representing 35 practices (Fig. 1) The sample was stratified by area: two practices from each of 12 rural districts and six major towns in MV were randomly selected.

Identification of patients Patients included in this study were members of the AOK (*Allgemeine Ortskrankenkasse*)

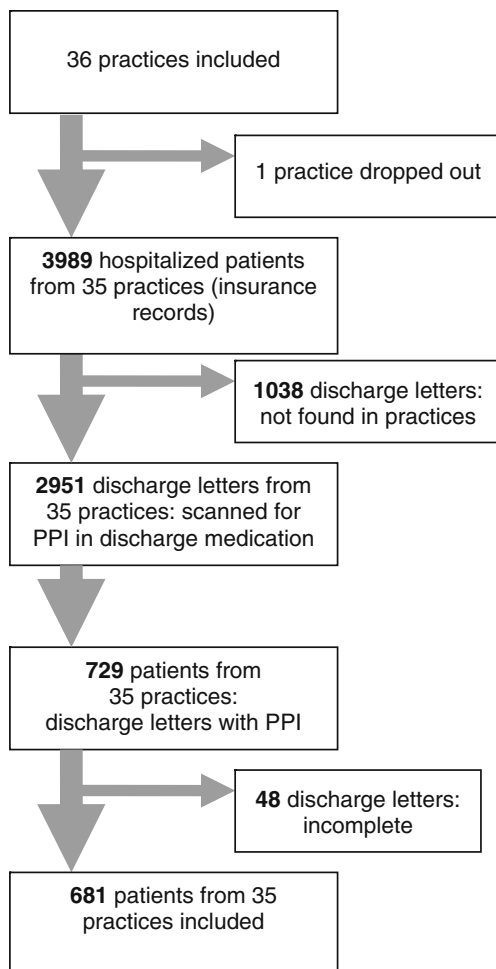


Fig. 1 Patient flow. PPI Proton pump inhibitor

MV, the largest statutory health insurance organization, covering 27% of the population in MV. All patients from the participating practices >18 years of age discharged from hospital between 1 July 2006 and 30 June 2007 were identified from insurance records. In patients with multiple hospital admission, only the first discharge was included. Patients who have received intensive care treatment were excluded.

Data collection Practice nurses received an instruction folder containing the names of all PPI preparations available in Germany. They were asked to screen discharge letters of all the patients identified for PPIs in the discharge medication. Letters recommending PPIs were copied, anonymized and sent to the study centre.

Two raters (DA and GB) assessed all clinical information available in the discharge letter (including co-medication) justifying a recommendation for continuous treatment with PPIs. The indication was rated as adequate, inadequate or uncertain (Table 1). Adequate use of a PPI was defined on the basis of approved indications (as written

in the official product information) and indications supported by clinical guidelines and scientific literature. If the PPI recommendation was rated as inadequate, we analysed the discharge letter to assess what may have triggered the decision. Differences in judgment between the authors were resolved by discussion.

The study was approved by the Ethics Committee of the medical school of the University of Göttingen.

Statistical analysis Simple descriptive statistics were used. To explore factors associated with inadequate recommendation of PPI, we conducted univariate analyses comparing patients who received an adequate PPI recommendation with those who did not. In a second step, we performed logistic regression analysis to calculate the probability of receiving an inadequate PPI recommendation. We excluded patients with an uncertain indication from the regression model. Covariates retained in the final model were selected with the score procedure. Goodness of fit was assessed with the Hosmer Lemshow test. The software package SAS 9.2 (SAS, Cary, NC) was used for the analysis.

Results

In the participating practices, a total of 2,951 patients discharged from hospitals were identified in the respective time period. Practice nurses identified 681 (23%) hospital discharge letters containing a recommendation for PPIs. The patient flow is shown in Fig. 1. Of the participating patients, 382 (57%) were female, and the mean age (\pm standard deviation) was 70.7 (\pm 13.7) years. Demographic data on the patient cohort and co-medications used by these patients discharged with PPI are shown in Table 2. *H. pylori* testing was performed in 96 (14.2%) of 209 patients who had a documented upper gastrointestinal endoscopy, of whom 44 tested positive. Seventeen patients had no pathologic findings on endoscopy and did not take any ulcer-inducing medication.

No information justifying the recommendation for continuous PPI medication could be identified in 371 (54.5%) of all discharge letters; in 12.7%, the indication was uncertain, and in 32.7%, we found an evidence-based indication for PPI medication. The most common indication for adequate PPI use was NSAID-prophylaxis in high-risk patients, followed by endoscopically proven gastritis. In patients without an adequate indication, the most common “finding” in the discharge letter was that there was no reason given for the continuous prescription of the PPI; the next most common reason was ulcer prophylaxis in patients taking low-dose aspirin alone (Table 3).

Table 2 Baseline socio-demographic and clinical characteristics and univariate analysis of the association with inadequate prescription of PPI

Baseline socio-demographic and clinical characteristics (<i>n</i> =681)	Values ^b	Comparison of inadequate with adequate PPI recommendation (<i>n</i> =594) ^c
Age ^a , years (±SD)	71 (±14)	n.s.
Sex ^a		
Female	382 (57.0)	OR 0.87 (0.6–1.2)
Male	299 (43.0)	
Length of stay median, days ^a (IQR)	9 (6–14)	n.s.
Hospital category ^a		n.s.
Primary/regional care	214 (31.4)	
Secondary care centres	266 (39.0)	
Tertiary care centres	100 (14.7)	
Specialty care centres	101 (14.8)	
Endoscopy ^a	209 (30.7)	OR 0.18 (0.12–0.16)
Testing for <i>H. pylori</i> ^a	96 (15.0)	OR 0.1 (0.06–0.18)
Co-medication ^a		
None	16 (2.3)	OR 0.26 (0.09–0.77)
NSAID	85 (12.5)	OR 0.15 (0.08–0.25)
Aspirin (low dose)	243 (36.0)	OR 1.2 (0.8–1.73)
Coxib	23 (3.4)	OR 1.96 (0.71–5.4)
Corticoid	59 (8.7)	OR 0.66 (0.38–1.1)
Warfarin/coumadin	54 (7.9)	OR 0.4 (0.22–0.69)
Polypharmacy ^a (>5 substances)	520 (76.4)	OR 1.15 (0.79–1.68)

NSAID, Non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SD, standard deviation; IQR, interquartile range; n.s., not significant

^aSignificant associations

^bUnless stated otherwise, data are given as the number (*n*) with the percentage in parenthesis

^cPatients with indeterminate indication for PPI were excluded. Values are given as the odds ratio (OR) with the 95% confidence interval in parenthesis

Univariate analysis revealed that factors associated with a lower risk of inadequate recommendation for PPIs were endoscopy [odds ratio (OR) 0.18, 95% confidence interval (CI) 0.12–0.16], testing for *H. pylori* (OR 0.1, 95% CI 0.06–0.18), NSAID (OR 0.15, 95% CI 0.08–0.25) or oral anticoagulation (OR 0.4, 95% CI 0.22–0.69). No association was found with age, gender, polypharmacy (defined as >5 concomitant medications) and hospital type (Table 2). After adjustment with multivariate analysis, endoscopy (OR 0.13, 95% CI 0.08–0.22), testing for *H. pylori* (OR 0.1, 95% CI 0.06–0.18), co-medication of NSAIDs (OR 0.14, 95% CI 0.09–0.21) or oral anticoagulation (OR 0.24, 95% CI 0.12–0.49) remained significant factors that decreased the risk of inadequate PPI recommendation (R^2 0.48).

The most commonly prescribed PPI was pantoprazole (*n*=487, 72%). Recommended daily doses are shown in Table 4.

Discussion

Our study confirms that PPIs in hospitals are often prescribed without a clear indication. In 54.5% of the discharge letters recommending PPIs analysed, no appro-

priate indication justifying continuous prescription could be identified, and in 12.8%, the indication was uncertain.

Current guidelines recommend peptic ulcer prophylaxis only for intermediate- to high-risk patients; in the absence of risk factors, no peptic ulcer prevention is necessary in patients using NSAID or low-dose acetylsalicylic acid (ASA) [5, 7]. In addition, there is evidence that concomitant use of PPIs might reduce the cardiovascular protection provided by aspirin [26]. Concerns also exist about the interaction of PPI and clopidogrel with respect to possible increases in arteriosclerotic complications [13, 14]. We therefore rated ulcer prophylaxis in the combination of aspirin and clopidogrel as an uncertain indication, but it should be taken into account that the studies reporting these associations were published after our study sampling period. Steroids without concomitant NSAID therapy do not significantly increase the risk of peptic ulcers [27]. No ulcer prophylaxis is necessary for oral anticoagulation drugs administered in the therapeutic range to patients without a history of ulcer/bleeding or concomitant NSAID treatment [28].

Stress ulcer prophylaxis is recommended only for high risk-patients in intensive care units (ICU) wards. For these

Table 3 Rating of indication, results and categories (n=681)

Rating of indication for PPI	Presumed reason for recommendation of continuous prescription of PPIs	Number (%)
Adequate documented indication (n=223; 32.8%)	NSAID in high-risk patients	90 (40.4)
	Gastric or duodenal ulcer	46 (20.6)
	GERD	45 (20.2)
	Proven gastritis with/ without helicobacter	37 (16.6)
	Macroscopic erosion or erythema, no biopsy because of oral anticoagulation	5 (2.2)
Documented indication uncertain (n=87; 12.8%)	Clopidogrel and low dose aspirin	43 (49.4)
	Macroscopic gastric erythema or erosion, result outstanding at discharge	13 (15.0)
	History of gastritis, no endoscopy, no further information	10 (11.5)
	Oesophageal varices	10 (11.5)
	Barrett–Oesophagus	5 (5.7)
	Dyspepsia	4 (4.6)
	Anaemia, no endoscopy	2 (2.3)
No documented adequate indication (n=371; 54.4%)	No reason for PPI found	140 (37.8)
	Low-dose aspirin, no documented history of bleeding	108 (29.1)
	Macroscopic gastric erythema or erosion, no biopsy, no <i>H. pylori</i> testing	27 (7.3)
	NSAID <65y, no history of bleeding	23 (6.2)
	Clopidogrel alone	23 (6.2)
	Corticosteroid alone	21 (5.7)
	Oral anticoagulation	15 (4.0)
	Coxib alone	9 (2.4)
	PPI after completed <i>H. pylori</i> -treatment, eradication, no ulcer	3 (0.8)
	Corticosteroid and oral anticoagulation	2 (0.5)

GERD. Gastroesophageal reflux disease

patients, respiratory failure requiring mechanical ventilation and coagulopathy have been identified as strong independent risk factors [29]. The American Society of Health Service guidelines also denote sepsis and specific illnesses, such as spinal cord injury, as determining factors for stress ulcer prophylaxis [30]. Patients from ICU wards were excluded from our study.

The diagnosis of gastritis is based on histological examination of the gastric mucosa. Macroscopic signs, such as erythema or erosion, are of very limited value in the evaluation of gastritis and *H. pylori* infection [31, 32]. We consider the recommendation of continuous PPI therapy based only on visual findings of macroscopic erythema or

erosion to be inadequate if there were no contraindications for biopsy and no biopsy was taken.

We assume that low-dose aspirin or NSAIDs in low-risk patients, steroid therapy or oral anticoagulant treatment may have been a frequent trigger for inappropriate prescriptions (Table 3). For more than one third of inappropriate PPI prescriptions, we found no explanation.

Doctors may not be aware of existing guidelines and use PPIs uncritically in good faith as stress ulcer prophylaxis without indication. Inappropriate assumptions about the risk of ulcer development during hospitalization may also be an explanation for the prescribing behaviour. Although endoscopy, testing for *H. pylori* and co-medication with

Table 4 Recommended PPI/ daily doses

PPI type: n =	Pantoprazole 487 (71.5%)	Esomeprazole 116 (17.0%)	Omeprazole 77 (11.3%)	Lansoprazole 1 (0.2%)
No dosage	4 (0.8%)	1 (0.9%)	3 (3.9%)	
20 mg	104 (21.3%)	60 (51.7%)	49 (63.6%)	
40 mg	312 (64.1%)	47 (40.5%)	20 (26%)	1 (100%)
80 mg	65 (13.4%)	8 (6.9%)	5 (6.5%)	
120 mg	2 (0.4%)			

NSAIDs or oral anticoagulation were factors that significantly decreased the risk of inadequate PPI prescribing, more than half of these patients had no identifiable indication for PPI prescription. It is notable that 17 patients in our sample underwent endoscopy and were subsequently prescribed PPIs, although no pathology was found and no ulcerogenic medication was administered.

The high rates of inappropriate PPI prescriptions in hospitals observed in our study are consistent with rates published from other studies. Two Swedish studies found that 59–81% of hospitalized patients received acid suppression therapy without appropriate indication [16, 18], while two Italian studies reported 41.5% [17] and 68%, respectively. [21] A 1-day survey at an Irish hospital revealed that 30% of patients were on PPI medication; of these, 71% were started on PPIs in hospital and 33% had no evidence-based indication [15]. An American study found that 60% of PPI treatments started in the hospital had no medical basis [19]; after discharge 46–80% and 50% of these patients were still on PPIs after 3 and 6 months, respectively [19, 21].

Inappropriate prescribing of PPIs is an important issue mainly for two reasons. First, the administration of unnecessary medication leads to polypharmacy and can lead to side-effects and pharmacological interactions. PPI use has been found to have a significant association with community-acquired pneumonia [25] and *Clostridium difficile*-associated diarrhoea [24]. Long-term PPI therapy has been suspected to be associated with an increased risk of hip fractures [22, 23].

PPIs are a major burden for the national healthcare budget. It was very noticeable that more than two thirds of the discharge letters analysed recommended pantoprazole which, at the time of the study, was much more expensive than the generic omeprazole. At equipotent doses, different PPIs are considered to be equally efficient in inhibiting gastric acid secretion [33, 34]. Hospitals significantly influence drug prescription behaviour in the primary care setting [35]. Moreover, in Germany, many hospitals receive PPIs at no or minimal cost, and manufacturers expect that continued prescribing in primary care will reimburse them for this initial “loss” [36].

This is the first study in Germany to assess the appropriateness of PPI prescribing in hospital discharge letters. Theoretically, it is possible that the GP practices participating in our study failed to identify all discharge letters with a PPI recommendation. However, it is unlikely that such an omission would have introduced a significant selection bias. Our assessment of the appropriateness of the drug recommendation is solely based on information available in the discharge letter; consequently, the numbers of inappropriate PPI recommendations may be slightly overestimated. Nevertheless, discharge letters should provide sufficient information to allow the GP to understand

the recommendation when specific hospital drugs are to be continued in the primary care setting.

Hospitals should critically review their practice of recommending PPIs in their discharge letters and clearly document the reason for continued PPI use after discharge. Likewise, GPs should carefully assess the need for continuous prescription. The reasons why evidence-based clinical guidelines are obviously not observed merits further research.

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Conflict of interests None

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