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Appropriateness of treatment recommendations for PPI in hospital discharge letters

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Abstract

Purpose: The reasons for the dramatic increase of 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 one of several possible explanations. Since in Germany the quality of PPI recommendations in hospital discharge letters has not been investigated so far we studied the appropriateness of these referrals.

Methods: Hospital discharge letters with recommended 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 PPI-indication was rated.

Results: In 54.5% of discharge letters no information justifying the recommendation for continuous PPI recommendation could be identified. In 12.7% indication was uncertain, and in 32.7% we found an evidence based indication for PPI medication. Most common indication for adequate PPI use was NSAID-prophylaxis in high risk-patients.

Conclusions: Inadequate recommendations for PPIs in discharge letters are frequent. This may lead to continuation of this therapy in primary care, unnecessarily increasing polypharmacy, the risk of adverse events and burdening the public health budget. Therefore hospitals should critically review recommendations and dosage for PPI in their discharge letters and clearly document the reason for PPI use and the need for continuous prescription in primary care.

Introduction

Proton pump inhibitors (PPIs) are the most potent medications available to reduce gastric acid secretion. Their use is widespread and increasing and annual sales of PPIs worldwide have surpassed \$ 25 billion. Prescription of PPI in Germany rose from 44 Million DDD in 1993 to 1674 million DDD in 2008 (+3805%) with an associated costs 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 is not necessary [4]. PPIs also are recommended for prevention of NSAID and aspirin induced ulcers in high risk patients [5-7] (Table 1) and treatment of gastritis. In intensive care, PPIs are indicated for stress ulcer prophylaxis in patients with risk of bleeding [8]. The use of PPI for patients with Barrett-Oesophagus is controversial and prevention of carcinoma induction has not yet been demonstrated [9]. A Cochrane Review reported that PPI could be effective in a small proportion of patients with dyspepsia, but studies showed a significant heterogeneity. Some guidelines recommend testing for *H. pylori* and eradication if necessary. Alternatively, an empirical PPI-treatment could be tried for 4-8 weeks [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 interaction of clopidogrel and proton pump inhibitors reducing cardiovascular protection and increasing arteriosclerotic complications [13;14].

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 ranged from 40% to 81% [15-19]. 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

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3 respiratory infections such as pneumonia.[25] In addition the cost of unnecessary
4 medication burdens the national health budget.
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7 The aim of this study was to analyse the appropriateness of PPI treatment
8 recommendations in patients discharged from hospital in a large German county.
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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 GP practices in MV to participate in the study. Addresses were obtained by the Association of Statutory Health Insurance Physicians (*Kassenaerztliche Vereinigung*). A total of 97 GPs agreed to join the study and 35 practises were included in this study (Figure 1) The sample was stratified by area; two practices from each of 12 rural districts and 6 major towns in MV were randomly selected.

Identification of patients: Patients included in this study were members of the AOK (*Allgemeine Ortskrankenkasse*) MV, the largest statutory health insurance covering 27% of the population in MV. All patients from the participating practices > 18 years of age discharged from hospital between July 1 2006 and June 30 2007 were identified from insurance records. In patients with multiple hospital admission only the first discharge was included. Patients with intensive care treatment were excluded.

Data collection: Practice nurses received an instruction containing the names of all PPI preparations available in Germany. They screened discharge letters of all identified patients 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. Indication was rated as adequate, inadequate or uncertain (Table 1). Adequate use of PPI was defined according to approved indications (as written in the official product information) and indications supported by clinical guidelines and scientific literature. If PPI recommendation was rated as inadequate, we analysed the discharge letter to assess what might 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: We use simple descriptive statistics. To explore factors associated with inadequate recommendation of PPI, we conducted univariate analyses comparing patients who received adequate PPI recommendation with those

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3 who did not. In a second step, we performed logistic regression analysis to calculate
4 the probability of receiving an inadequate PPI recommendation. We excluded
5 patients with uncertain indication from the regression model. Covariates retained in
6 the final model were selected with the score procedure. Goodness of fit was
7 assessed with the Hosmer Lemshow-test. The software package SAS 9.2 was used
8 for analysis.
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Results

In the participating practices a total of 2951 patients discharged from hospitals were identified in the respective time period. Practice nurses identified 681 (23%) hospital discharge letters with PPI recommendations. The patient flow is shown in figure 1. Of the participating patients, 382 (57%) were female; the mean age was 70.7 years (SD \pm 13.7). Demographic data and relevant medication of patients discharged with PPI is shown in table 2. In 96 (14.2%) of 209 patients with documented upper gastrointestinal endoscopy H. pylori testing was performed (44 tested positive). 17 patients had no pathologic findings on endoscopy and did not take any ulcer inducing medication.

In 371 (54.5%) of all discharge letters no information justifying the recommendation for continuous PPI recommendation could be identified. In 12.7% 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 adequate indication most commonly no reason for PPI-administration could be found in the discharge letters, followed by ulcer prophylaxis in patients taking low dose aspirin alone (Table 3).

Factors associated with lower risk of inadequate recommendation for PPI in univariate analysis were endoscopy (OR 0.18 CI₉₅ 0.12-0.16), testing for H. pylori (OR 0.1 CI₉₅ 0.06-0.18), NSAID (OR 0.15 CI₉₅ 0.08-0.25) or oral anticoagulation (OR 0.4 CI₉₅ 0.22-0.69). No association was found with age, gender, polypharmacy (defined as more than 5 concomitant medications) and hospital type (Table 2). After adjustment with multivariate analysis endoscopy (OR 0.13 CI₉₅ 0.08-0.22) testing for H. pylori (OR 0.1 CI₉₅ 0.06-0.18), comedication of NSAID (OR 0.14 CI₉₅ 0.09-0.21) or oral anticoagulation (OR 0.24 CI₉₅ 0.12-0.49) remained significant factors decreasing the risk of inadequate PPI recommendation (R square 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 given without a clear indication. In 54.5% of analysed discharge letters recommending PPI no appropriate indication justifying continuous prescription could be identified and in 12.8% indication was uncertain.

Guidelines recommend peptic ulcer prophylaxis only for intermediate to high risk patients. Without risk factors no peptic ulcer prevention is necessary in patients using NSAID or low-dose ASA [5;7]. In addition there is evidence that concomitant use of PPIs might reduce the cardiovascular protection by aspirin [26]. Concerns also exist about the interaction of PPI and clopidogrel, increasing arteriosclerotic complications [13;14]. Hence we rated ulcer prophylaxis in the combination of aspirin and clopidogrel as an uncertain indication, but it should be considered that the relating studies were published after the study sampling period. Steroids without concomitant NSAID therapy do not significantly increase the risk of peptic ulcers [27]. For oral anticoagulation in therapeutic range without history of ulcer/ bleeding or concomitant NSAID treatment no ulcer prophylaxis is necessary [28].

Stress ulcer prophylaxis is recommended only for high risk patients at intensive care wards. For these patients, respiratory failure requiring mechanical ventilation and coagulopathy have been identified as strong independent risk factors [29]. Aside these factors, American Society of Health Service guidelines note sepsis and specific illnesses as spinal cord injury as determining factors for stress ulcer prophylaxis [30]. Patients from ICU wards have been excluded from our study.

Diagnosis of *gastritis* is based on the histological examination of the gastric mucosa. Macroscopic signs like erythema or erosion are of very limited value in the evaluation of gastritis and helicobacter pylori infection [31;32]. We considered 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 might have been a frequent trigger for inappropriate prescriptions (Table 3). For more than one third of inappropriate PPI prescriptions we found no explanation.

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3 Doctors might not be aware of existing guidelines and use PPI uncritically in good
4 faith for stress ulcer prophylaxis without indication. Inappropriate assumptions about
5 the risk of ulcer development during hospitalisation might be an explanation.
6 Although endoscopy, testing for *H. pylori* and comedication with NSAID or oral
7 anticoagulation were factors decreasing significantly the risk of inadequate PPI
8 recommendation more than half of these patients had no identifiable indication for
9 PPI prescription. It is noticeable that 17 patients in our sample underwent endoscopy
10 and were subsequently prescribed PPIs although no pathology was found and no
11 ulcerogenic medication was administered.
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20 The high rates of inappropriate PPI prescriptions in hospitals observed in our study
21 are consistent with previous reports. Two Swedish studies found 59-81% of
22 hospitalised patients receiving acid suppression therapy without appropriate
23 indication [16;18], an Italian study 41,5% [17] and 68%. [21] A one-day-survey at an
24 Irish hospital showed 30% of patients on PPI-medication; 71% of them were started
25 in hospital and 33% had no evidence-based indication [15]. An American study found
26 60% of medically unfounded PPI treatment started in hospital [19]. After discharge
27 46-80% of patients were still on PPIs after 3 months and 50% after 6 months [19;21].
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37 Inappropriate recommendation of PPI is an important issue mainly for two reasons.
38 First, administration of unnecessary medication leads to polypharmacy and could
39 cause side-effects and pharmacological interactions. PPI use has been found to have
40 a significant association with community acquired pneumonia [25] and *Clostridium*
41 *difficile* associated diarrhoea [24] Long term PPI therapy has been suspected to be
42 associated with increased risk of hip fractures [22;23].
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48 PPI are a major burden for the national health care budget. It is noticeable, that more
49 than two thirds of letters recommended pantoprazole which was much more
50 expensive than generic omeprazole at the time of the study. At equipotent doses
51 proton pump inhibitors are considered to be equally efficient in inhibition of gastric
52 acid secretion [33;34]. It has been shown previously that hospitals significantly
53 influence drug prescription in primary care [35]. Moreover, in Germany many
54 hospitals receive PPIs at no or minimal cost and manufacturers expect that continued
55 prescribing in primary care will reimburse them for this initial "loss" [36]
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3 This is the first study in Germany to assess appropriateness of PPI recommendation
4 in hospital discharge letters. Theoretically it is possible that practices failed to identify
5 all discharge letters with PPI recommendation. However, it seems unlikely to have
6 introduced a significant selection bias. Our assessment of appropriate drug
7 recommendation is solely based on the available information in the discharge letter
8 and numbers of inappropriate PPI recommendations might be slightly overestimated.
9 Nevertheless discharge letters should provide sufficient information to the GP to
10 understand the recommendation in case specific hospital drugs are to be continued
11 in primary care.
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20 Hospitals should critically review their practice of recommending PPI in their
21 discharge letters and clearly document the reason for continued PPI use after
22 discharge. Likewise GPs should carefully assess the need for continuous
23 prescription. The reasons why evidence-based clinical guidelines are obviously not
24 observed merits further research.
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31 Conflict of interests: None.
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36 Acknowledgements:
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41 identify discharged patients.
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Table 1: Rating of 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= Non-steroidal anti-inflammatory drug

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Table 2: Baseline socio-demographic and clinical characteristics and univariate analysis of association with inadequate prescription of PPI (significant associations are bold)

n = 681	Comparison of inadequate with adequate PPI recommendation n = 594*	
Age	71 (SD ±14)	n.s.
Sex		
female	382 (57.0%)	OR 0.87 (CI ₉₅ 0.6-1.2)
male	299 (43.0%)	
Length of stay median (days)	9 (IQR 6-14)	n.s.
Hospital category		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	209 (30.7%)	OR 0.18 (CI ₉₅ 0.12-0.16)
Testing for H. pylori	96 (15.0%)	OR 0.1 (CI ₉₅ 0.06-0.18)
Comedication		
none	16 (2.3%)	0.26 (CI ₉₅ 0.09-0.77)
NSAID	85 (12.5%)	0.15 (CI ₉₅ 0.08-0.25)
Aspirin (low dose)	243 (36.0%)	1.2 (CI ₉₅ 0.8-1.73)
Coxib	23 (3.4%)	1.96 (CI ₉₅ 0.71-5.4)
Corticoid	59 (8.7%)	0.66 (CI ₉₅ 0.38-1.1)
Warfarin/ Coumadin	54 (7.9%)	0.4 (CI ₉₅ 0.22-0.69)
Polypharmacy (> 5 substances)	520 (76.4%)	OR 1.15 (CI ₉₅ 0.79-1.68)

* Patients with indeterminate indication for PPI were excluded

OR: odds ratio, CI₉₅ 95% confidence interval, SD = standard deviation, IQR interquartile range
NSAID= Non-steroidal anti-inflammatory drug, PPI Proton pump inhibitor

Table 3: Rating of indication- Results and categories (n = 681)

Rating of indication for PPI	Presumed reason for recommendation of continuous prescription of PPIs	
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%)
No documented adequate indication n=371 (54.4%)	- Anaemia, no endoscopy	2 (2.3%)
	- 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 HP-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 HP- eradication, no ulcer	3 (0.8%)	
- Corticosteroid and oral anticoagulation	2 (0.5%)	

PPI = Proton pump inhibitor, NSAID= Non-steroidal anti-inflammatory drug,

GERD = Gastroesophageal reflux disease

Table 4: Recommended PPI / daily doses

PPI Type	Pantoprazole	Esomeprazole	Omeprazole	Lansoprazole
n=	487 (71.5%)	116 (17.0%)	77 (11.3%)	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%)			

For Peer Review

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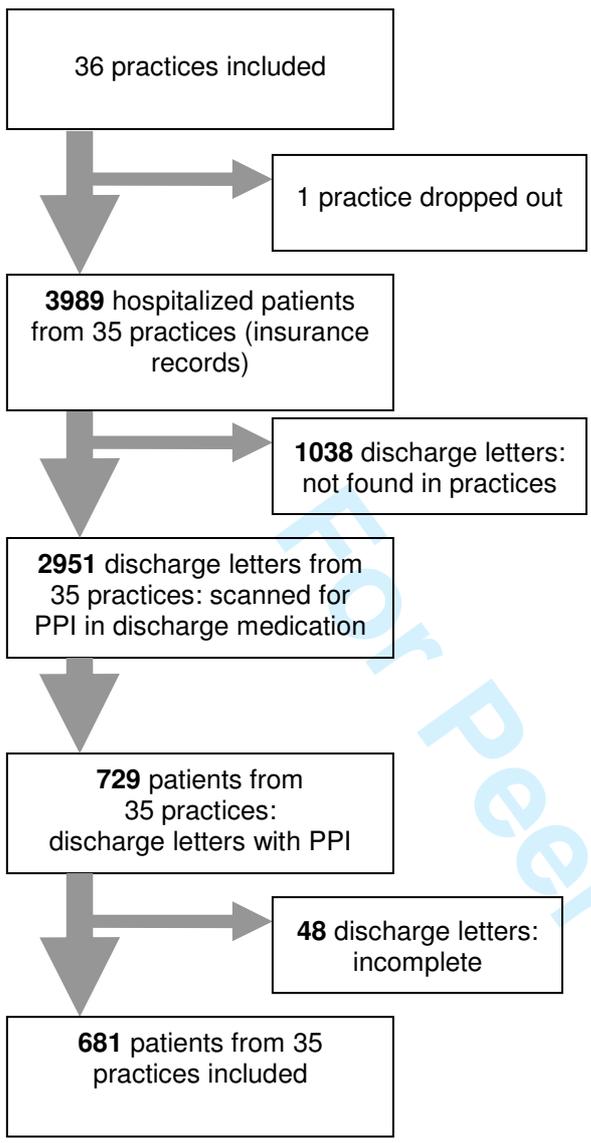


Figure1: Patient flow