Appropriateness of proton pump inhibitor recommendations at hospital discharge and continuation in primary care

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Introduction

Prescriptions of proton pump inhibitors (PPI) are increasing and annual sales of PPI worldwide have surpassed $17.5 billion Euros. In the last decade, prescription of PPI in Germany raised from 322 million DDD in 2000 to 1973 million DDD in 2009 (+613%), with associated costs of 1058 billion Euros per year (1). Increased morbidity or new indications cannot explain the rise in PPI prescriptions. Inappropriate prescriptions of PPI have been widely reported, with 40–80% of all PPI prescriptions not being in agreement with guidelines (2–5).

PPIs are first choice in the treatment of gastro-esophageal reflux disease (GERD) (6) and peptic ulcers (7,8). In combination with antibiotics, they are used for eradication of Helicobacter pylori. After eradication for symptomatic H. pylori infection, continuation of PPI is usually not necessary unless there is another indication for PPI (9). PPI are also indicated as a concomitant medication to prevent non-steroidal anti-inflammatory drug (NSAID) and aspirin associated ulcers in high-risk patients (10–12). Some authors recommend ulcer prophylaxis for patients on a combination of aspirin and clopidogrel but there have been some concerns about interaction of clopidogrel and PPI reducing cardiovascular protection and increasing arteriosclerotic complications (13,14). In intensive care, PPI are indicated for stress ulcer prophylaxis in patients with risk of bleeding (15). Benefit from PPIs in patients with Barrett-Oesophagus is controversial, prevention of carcinoma

SUMMARY

Background: Inappropriate prescriptions of proton pump inhibitors (PPI) in hospital and primary care have been widely reported. Recommendations from hospital have been implicated as one reason for inappropriate prescriptions of PPI in primary care. Objective: To quantify the amount of appropriate PPI recommendations in hospital discharge letters and the influence of these recommendations on general practitioners’ (GPs’) PPI-prescriptions. Materials and Methods: This is an observational study in 31 primary care practices. We identified patients discharged from hospital with PPI recommendation between 2006 and 2007 and assessed practice records and PPI prescription six months prior and after hospital admission. Hospital recommendation for continuous PPI-treatment and continuation by GPs was classified as appropriate, inappropriate or uncertain. Logistic regression analysis was used to calculate factors associated with indicated and non-indicated PPI continuation. Results: In 263 (58%) out of 506 patients discharged from 35 hospitals with a PPI recommendation no indication could be found. Non-indicated PPIs were continued by GPs in 58% for at least 1 month. Indicated PPIs were discontinued in 33%. Two thirds of non-indicated PPIs were initiated in hospital. The strongest factor associated with non-indicated continuation was a PPI-prescription prior to hospital admission [OR: 3.0; 95% confidence interval (CI): 1.7–5.4]. This was also the strongest factor for continuation of an indicated PPI medication [OR: 3.2; 95% CI: 1.4–7.5]. Conclusions: We found a strong influence of hospital recommendations and previous prescriptions on PPI prescriptions after discharge. Hospitals should critically review their practice of recommending PPI and document indications. GPs should carefully assess hospital recommendations and their medication prior to admission to avoid over- and under-prescribing.

What’s known
• Prescriptions of proton pump inhibitors (PPI) are increasing worldwide.
• Previous studies have shown over and underuse of PPIs.
• Evidence of clinically relevant adverse effects of long term PPI use is accumulating.

What’s new
• Hospitals induce non-indicated PPI prescriptions.
• GPs continue non-indicated PPI recommendation and discontinue indicated PPI recommendations.
• GPs should carefully assess hospital recommendations for PPIs in discharge letters and medication prior to admission.

Introduction

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induction has not yet been demonstrated (16). A Cochrane Review concluded that PPI could be effective in some patients with dyspepsia, but studies showed a significant heterogeneity (17). Some guidelines recommend testing for Helicobacter pylori and eradication if necessary, an empirical PPI-treatment for 4–8 weeks is an alternative option (18). In patients with liver cirrhosis and oesophageal varices there is no clear evidence that PPI prevent bleeding and promote quicker healing after ligation (19).

Inappropriate recommendation of PPIs is a matter of concern. Administration of unnecessary medication could cause adverse effects and pharmacological interactions and lead to polypharmacy. PPI intake has been found to have a significant association with community acquired pneumonia (20,21) and Clostridium difficile associated diarrhea (22–24). Long term PPI therapy is suspected to be associated with increased risk of hip fractures (25,26) and to reduce the therapeutic effects of bisphosphonates (27) and low-dose aspirin (28). Increase of serum potassium levels associated with PPI has been described (29). Last but not least overuse of PPI unnecessarily burdens national health care budgets.

One important factor for a widespread and inadequate use of PPI seems to be the beginning of a PPI medication during a patient’s hospitalisation and its recommendation for continuation in primary care without apparent reason. The appropriateness of PPI medication in hospital and continuation in primary care have been studied in two chart reviews in an Italian and a US hospital (5,30). In both studies more than 60% of acid suppression therapy lacked an indication and about 50% of these patients received this treatment 3 months after discharge. However, for valid conclusions about problems at the primary-secondary-care interface it is important to consider a broad range of hospitals and not only a single one. More importantly, we should also consider whether patients received a PPI before hospitalisation from their general practitioner (GP) to determine whether an inappropriate PPI prescription in the hospital may have been started in general practice. In Germany hospitals have no prescription privileges, therefore patients need to see their personal physician (mostly a GP) after discharge for prescription of discharge medication.

The aim of this study was threefold: (i) to analyze the appropriateness of PPI treatment recommendations in patients discharged from different hospitals; (ii) to quantify the continuation of appropriate and inappropriate hospital prescriptions by GPs; and (iii) to identify factors associated with the continuation of appropriately and inappropriately prescribed PPI, including a prior prescription of a PPI by the GP.

Materials and methods
We conducted a cross sectional observational study in 36 primary care practices in the state of Mecklenburg-West Pomerania (MWP), North-Eastern Germany. Parts of the data set have been published elsewhere (31). The study was approved by the ethics committee of the medical school of the University of Göttingen.

Recruitment of practices
All 933 registered GPs in MWP were invited to participate in the study. A total of 35 practices out of 97 who agreed to participate were included. We stratified the sample by area and selected randomly two practices from each of 12 rural districts and 6 major towns in MWP (n = 36).

Identification of patient and inclusion criteria
Patients of the participating practices older than 18 years and discharged from hospital between July 1, 2006 and June 30, 2007 were identified from insurance records. We only included patients insured by AOK (Allgemeine Ortskrankenkasse), which covers about 37% of the population in MWP. In patients with multiple hospital admissions only the first discharge was included. Patients with intensive care treatment were excluded.

Data collection
We instructed practice nurses to screen discharge letters of all identified patients for documented PPI recommendations. Discharge letters usually contain a list of all diagnoses, a detailed hospital course, results of all medical procedures and a final recommendation with discharge medication. Practice records 6 months prior and after hospital admission and discharge letters of all patients with PPI recommendation were copied, anonymised and sent to the study centre.

Two raters (DA and GB) reviewed all available clinical information from practice records and discharge letters independently. Based on this information, hospital recommendation for PPI-treatment and continuation by GPs was classified as adequate, inadequate or uncertain (Table 1). The raters resolved disagreements by consensus. Adequate use of PPI was defined according to approved indications (as documented in the official product information) and indications indorsed by scientific literature. PPI recommendation was also rated to be adequate, if patients had PPI prior to admission plus a justifying diagnosis documented in practice records. PPI treatment was assumed to be induced by hospital, if it was continued within a period of 3 weeks after dis-
charge and no new indication was documented in practice records.

Statistical analysis
To explore factors associated with continuation of PPI we first performed a univariate analysis calculating crude odds ratios. In a second step, we performed multivariate logistic regressions to calculate adjusted odds ratios of continuation of indicated and non-indicated PPI recommendation respectively. We excluded patients with uncertain indication from the regression model. Goodness of fit was assessed with the Hosmer-Lemeshow-test. The software package SAS 9.2 was used for analysis.

Results
One rural practice dropped out. GPs from the remaining practices were on average 54 years old (national average 53 years) and 13 years in practice, 42% of them were female (national average 42%).

A total of 2951 patients discharged from hospital were identified by AOK from the participating practices in the respective time period. In 681 (23%) of these patients, practice nurses found PPI recommendations. As a result of incomplete discharge letters or missing practice records, we excluded 175 patients so that 506 patients from 31 practices remained (56% female; mean age 73 years [range 18-99]). They were discharged from 35 different hospitals. The patient flow is shown in Figure 1. Demographic data and relevant medication of patients discharged with PPI are shown in Table 2.

### Table 1  Rating of indications for proton pump inhibitors

<table>
<thead>
<tr>
<th>INDICATIONS rated as ADEQUATE</th>
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<tbody>
<tr>
<td>Gastro-oesophageal reflux disease (16)</td>
<td></td>
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<tr>
<td>Treatment and recurrent prophylaxis of peptic ulcer (7,8)</td>
<td></td>
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<tr>
<td>Eradication of Helicobacter pylori (9)</td>
<td></td>
</tr>
<tr>
<td>Pathologic hypersecretory conditions (e.g. Zollinger-Ellison-Syndrome) (41)</td>
<td></td>
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<tr>
<td>Histological proven diagnosis of gastritis (42,43)</td>
<td></td>
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<tr>
<td>Prevention of medication induced ulcers (10–12):</td>
<td></td>
</tr>
<tr>
<td>- NSAI at patients &gt; 65 years</td>
<td></td>
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<tr>
<td>- NSAID and corticosteroid</td>
<td></td>
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<tr>
<td>- NSAID and warfarin / coumadin</td>
<td></td>
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<tr>
<td>- NSAID and patient history of ulcer/gastrointestinal bleeding</td>
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<tr>
<td>- Aspirin and corticosteroid</td>
<td></td>
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<tr>
<td>- Aspirin and warfarin / coumadin</td>
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<tr>
<td>- Aspirin and NSAID</td>
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<table>
<thead>
<tr>
<th>INDICATIONS rated as UNCERTAIN</th>
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<tbody>
<tr>
<td>Dyspepsia (17)</td>
<td></td>
</tr>
<tr>
<td>Barrett's Oesophagus</td>
<td></td>
</tr>
<tr>
<td>Oesophageal varices (18)</td>
<td></td>
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<tr>
<td>Ulcer prophylaxis with clopidogrel and low dose aspirin (11–13)</td>
<td></td>
</tr>
<tr>
<td>Patient underwent upper gastrointestinal endoscopy and biopsy, result outstanding at discharge (34,35)</td>
<td></td>
</tr>
<tr>
<td>History of gastritis, no endoscopy, no further information</td>
<td></td>
</tr>
<tr>
<td>Anaemia, no endoscopy</td>
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</tbody>
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NSAID, non-steroidal anti-inflammatory drug

![Figure 1 Patient flow](image.png)
indicated according to our assessment, was continued in 151 patients (58%) for at least one month. Continuous Prescription of non-indicated PPI over a period of 6 months is shown in Figure 3. In contrast, indicated PPI medication was discontinued in 33% of cases. Hospital diagnoses of these patients are shown in Table 3.

In univariate analyses, factors associated with continuation of non-indicated medication were PPI medication prior to hospital admission, low dose aspirin, age above 70 years and hospitalisation in a regional care centre (p = 0.03) (Table 4). In multivariate analyses, only prescription of PPI prior to hospital admission remained a significant factor [odds ratio (OR): 3.0; 95% confidence interval (CI): 1.7–5.4]. This was also the strongest factor associated with continuation of indicated PPI medication while indicated ulcer prophylaxis because of NSAID prescription (OR: 0.4; 95% CI: 0.2–0.8) was associated with inadequate discontinuation of PPI (Table 4).

**Discussion**

**Summary of main findings**

In more than half of the PPI recommendations in hospital discharge letters, an appropriate indication was missing. In 57% of these cases, GPs followed this recommendation and continued the prescription for more than one month. A clear evidence-based indication for PPI could be identified in 35% of patients, but the PPI was not continued for one third of these patients. The strongest factor associated with appropriate and inappropriate continuation of PPIafter discharge was PPI-prescription prior to hospitalisation.
Strengths and limitations of the study
This is the first study to assess appropriateness of PPI recommendation in hospital discharge letters in Germany, and the first European study including GP records prior and after hospital stay. Previous studies only analysed patients discharged from one hospital which is limiting generalisability. We included a representative sample of GPs based on demographics and regional distribution and patients discharged from various hospitals in Germany in our study, however our sample was not stratified by population. All included patients were insured by AOK, the largest public health insurance in Germany, covering 37% of the population in MV. Although there is no evidence that AOK patients are treated differently compared with patients insured by other public health insurances (which by law all cover the same health care services) we cannot exclude selection bias.

Although practice nurses received an instruction to identify all available PPI preparations in Germany, it is possible that they failed to identify all discharge letters with PPI recommendation. However, this is unlikely a significant source of selection bias. Since our classification of PPI treatment is based on all clinical information provided by the discharge letters and practice records, we cannot exclude that we missed unrecorded indications for PPI.

We analysed practice records 6 months prior and after hospital admission. If a PPI indication was not documented in this period, we might have underestimated the number of patients with indicated PPI therapy prior to admission. Nevertheless discharge letters should provide all necessary information for GPs including indications for all drugs to be continued in primary care. Since two thirds of inappropriate PPI treatments were initiated in hospital, this is a negligible source of bias.

Comparison with existing literature
High rates of inappropriate PPI prescriptions in hospital have been reported from other countries. Between 42 and 81% patients in Sweden and Italy received acid suppression therapy without appropriate indication (4,30,32). According to an Irish one-day-survey, 71% of PPI-medication was started in hospital, one-third of them lacked evidence-based indication (2). In a recent Spanish study, 55% of patients in a tertiary hospital received PPI at discharge, 80% of them without indication (33).

Two thirds of inappropriate PPI medications in our study were initiated in hospital, 42% of them were continued by GPs after discharge. Only few studies observed continuation of PPI prescriptions after discharge. An American study found 60% of medically unfounded PPI treatment started in hospital (5). After discharge 46–80% of patients were still on PPIs after 3 months and 50% after 6 months (5).

Similar rates were found in an Italian hospital (30). Remarkably, despite differences in health care systems, we observed similar rates of continuation of non-indicated PPI medication.

In an American ambulatory care setting, 35% of patients with PPI prescription had appropriately documented indications, 10% received PPI empirically, 18% for gastroprotection and 36% had no documented indication for PPI (34).

The reasons for PPI overprescribing in hospital are not well studied. Doctors might have inappropriate

<table>
<thead>
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<th>Table 4 Factors associated with continuation of non-indicated or indicated proton pump inhibitor prescriptions</th>
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<tr>
<td><strong>Factor</strong></td>
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<tr>
<td><strong>Factors associated with recommendation of non-indicated PPI prescription (n = 263)</strong></td>
</tr>
<tr>
<td>Age &gt; 70 years</td>
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<tr>
<td>Sex (female)</td>
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<tr>
<td>PPI-prescription prior to admission</td>
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<tr>
<td>NSAID</td>
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<tr>
<td>Low dose Aspirin</td>
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<tr>
<td>Polypharmacy (≥ 5 drugs)</td>
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<tr>
<td><strong>Factors associated with continuation of indicated PPI prescription (n = 176)</strong></td>
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<tr>
<td>Age &gt; 70 years</td>
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CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor
assumptions about the risk of ulcer development during hospitalisation, using PPI in good faith without awareness of existing guidelines (3). We previously reported that in a larger study sample, low dose aspirin, NSAIDs in low risk patients, steroid therapy or oral anticoagulant treatment were assumed to be the most common triggers for inappropriate prescriptions (31).

Our study shows a significant influence of inadequate hospital recommendations on GPs’ prescribing, leading to continuation of non-indicated PPI medication, increasing overuse of PPI with the risk of adverse effects and interactions, and unnecessarily burdening the public health budget.

We observed that GPs continued a high proportion of non-indicated PPI therapy, particularly in patients who received PPIs prior to hospital admission. This might have different explanations: GPs might prescribe PPI pre-discharge medication without reassessment and unaware of existing guidelines. Another reason might be trust in the authority of hospital recommendations. Also, when interacting with patients, GPs might feel uncomfortable if they do not follow hospital recommendations. This is supported by a British qualitative study which found GPs under approval pressure if the hospital suggested a certain drug (35). In addition, general attitudes might influence doctors’ decision: Jaye and Tilyard analysed GPs’ prescribing profiles and concluded that high-cost prescribers frequently show an activist approach and have a positive attitude towards medical intervention (36).

Surprisingly, continuation of inadequate PPI medication was associated with discharge from a regional/primary care centre. Whether GPs make important distinctions as to the trustworthiness of recommendations from different hospitals remains unclear.

Little is known about GPs’ strategies of handling medical recommendations from hospital. At the interface between specialists and GPs, Crowe et al. identified six factors influencing GPs decision making in prescribing drugs. These included GPs lack of expertise in using specialist drugs, the shared care arrangement, the influence of locally agreed advisory lists, financial and resource considerations, patient convenience and GPs’ specific interests (37). The authors, however, did not examine and discuss whether the recommendations were adequate.

Apart from overprescribing, in one third of patients PPIs were not continued despite a clear evidence-based indication which puts them at a preventable risk of complications like gastrointestinal bleeding (Table 3). In these patients, 56% had a PPI indication because of ulcer prophylaxis and concomitant NSAID use. The problem of under-prescription of gastroprotective particularly with NSAIDs has been described repeatedly (38–40).

As mentioned before, also in patients with non-indicated PPI medication, low dose aspirin comedication was a significant factor for continuation. GPs might be unaware of current guidelines regarding ulcer prophylaxis related to NSAID/ aspirin use. Recently, a French study reported high rates of underutilisation of gastroprotective drugs in patients receiving non-steroidal anti-inflammatory drugs. Likewise the authors also observed overprescribing in patients without risk factors (38). It is also conceivable that some GPs are aware of routine prescribing of PPIs in hospitals and might therefore routinely discontinue hospital initiated PPI use. German GPs have to manage a budget for medication, which might also influence the decision to discontinue medication.

Not surprisingly, the best predictor for continuation of PPI therapy after discharge was PPI therapy prior to admission, even if no indication could be found. This could be because of non-reflective continuation of GPs medication by hospitalists, which is then again continued after discharge. However, one should keep in mind that two thirds of inappropriate medication was started in hospital.

Implications for clinical practice and future research

Our study found high rates of inadequate PPI recommendations in hospital discharge letters and continuation in primary care, showing a strong influence of hospital recommendations on GPs. Hospitals should critically review their practice of recommending PPIs and clearly document indication for PPI recommendations. GPs should carefully assess hospital recommendations in discharge letters and medication prior to admission, focusing on the indication for continuous prescription of PPIs to avoid under- and overprescribing of PPIs. Indication for PPI prescription should be assessed periodically.

Reasons for inadequate PPI prescriptions need to be explored in more depth to tailor interventions promoting appropriate PPI prescribing.

Ethics committee

Ethics committee University of Göttingen Medical School.

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**References**


**Authors’ contributions**

DA, MMK and WH contributed to concept/design; JFC, DA and GB performed data analysis/interpretation; JFC, DA and WH drafted the article; DA and MMK secured funding; GB helped in data collection; all authors reviewed and approved the final manu- script.

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