(De-)prescribing and potential adverse effects of proton pump inhibitors in older multimorbid patients: an observational study

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ABSTRACT

Background: Proton pump inhibitors (PPIs) contribute to polypharmacy and are associated with adverse effects. However, we lack prospective data on longitudinal patterns of PPI prescribing in older multimorbid patients. We assessed patterns of (de-)prescribing of PPIs and association with adverse effects over 1 year in older multimorbid adults.

Methods: Prospective longitudinal cohort study using data from the OPERAM trial (2016-2018, 1-year follow-up, four European countries). In adults aged ≥70 years with ≥3 chronic conditions and ≥5 chronic medications, we assessed PPI prevalence at admission, and new prescriptions and deprescribing (discontinuation or dose reduction) at discharge, 2 months and 1 year. We used cox regression with competing risk for death to assess the association of PPI use with potential PPI adverse effects (pneumonia, fracture, nephritis, bacterial intestinal infection) leading to readmission, and all-cause readmission.

Results: 58% (1,080/1,879) patients (mean age 79 years) had PPI at admission, 496 (46%) with a potentially inappropriate indication. At discharge, 224 (21%) PPI users were deprescribed. Among PPI users, 13% were deprescribed at 2 months, and 30% at 1 year. Among patients without PPI at discharge, 8% had a PPI at 2 months, and 14% at 1 year. PPI use was associated with all-cause readmission (N=770, subhazard ratio 1.32, 95%CI 1.13-1.54).

Interpretation: PPI use was frequent in older multimorbid adults, with potentially inappropriate indication in almost 50% of them. At discharge, one fifth of patients had PPI deprescribing, while another fifth had a new prescription. PPI use was associated with increased 1-year readmission risk.

INTRODUCTION

While proton pump inhibitors (PPIs) are among the most frequently prescribed medications worldwide,[1] they are associated with several adverse events, such as fractures, pneumonia, bacterial intestinal infections, and vitamin B12 deficiency.[2] PPIs are often started at hospital, despite a lack of appropriate indication in over two thirds of cases.[3,4] While PPIs are frequently continued at discharge despite the lack of an appropriate indication, total costs attributed to PPIs have been estimated over 3 million US dollars within 30 days of discharge.[4] In response to those concerns, guidelines have been developed to leverage inappropriate PPIs prescribing.[5] However, recommendations alone may not be sufficient to significantly reduce inappropriate prescribing, so that specific interventions should be developed.[6] Before doing that, it is important to increase knowledge on current state of PPI prescribing, risks of adverse effects, and safety of discontinuation in older multimorbid patients, a population particularly vulnerable to adverse effects of medications.[7]

The aims of this study were to assess, in a multicountry study of older patients with multimorbidity and polypharmacy: 1) the prevalence of appropriate and potentially inappropriate PPI prescriptions at hospital admission; 2) the incidence of PPI deprescribing and new PPI prescriptions at discharge, 2 months and 1 year; 3) the association between persistent PPI use and potential adverse effects (i.e., fractures, pneumonia, bacterial infections, and acute interstitial nephritis leading to readmission, and all-cause readmissions); 4) potential risks associated with PPI discontinuation . We hypothesized that persistent potentially inappropriate PPI prescribing would be frequent, and that persistent PPI use would be associated with an increased risk of adverse events.

METHODS

Study design and population

We used data from the OPERAM ("OPtimising thERapy to prevent Avoidable hospital admissions in Mulimorbid older people") trial, a European multicenter study which aimed at reducing inappropriate prescribing. The population, design, and main results of the OPERAM trial have been described in details elsewhere.[8,9] Shortly, this trial (study period December 2016 to October 2019) included patients aged ≥70 years, had multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 chronic medications), and were acutely admitted to a medical or surgical hospital ward. Participating countries were Belgium (Louvain), Ireland (Cork), the Netherlands (Utrecht), and Switzerland (Bern) The primary outcome of the trial was the first drug-related readmission.

Exposure and other variables of interest

Comorbidities at baseline were assessed using International Classification of Diseases (ICD)-10 codes,[10] based on discharge letters of index hospitalization. We captured the name, dose, and start and end dates of each medication, using Anatomical Therapeutic and Chemical (ATC) codes.[11] To allow comparison across different PPI ingredients, we standardized doses using the Defined Daily Dose (DDD) from the World Health Organization (**Supplemental Text S1 and S2**).[11] We defined persistent PPI use as a PPI prescription at discharge and 2 months after. According to guidelines and expert consensus of the ACCF/ACG/AHA, potentially appropriate indications for PPIs in adults aged ≥65 years include:[5,12-14] 1) gastro-esophageal reflux disease (GORD) with acid-related complications (i.e., erosive esophagitis or peptic stricture) or symptomatic GORD; 2) Barrett's esophagus; 3) current treatment of gastro-duodenal ulcer; 4) current treatment of Helicobacter pylori; 5) acute gastritis; 6) peptic gastro-intestinal bleeding; 7) persistent use of non-steroidal anti-inflammatory drug (NSAID); 8) antiplatelet medication. We used ICD and ATC codes to identify those indications (**Supplemental Text S3**).

Outcomes

In patients with PPI at admission, the primary outcome was the incidence of PPI deprescribing (discontinuation or dose reduction) during hospitalization. In those without PPI at admission, the primary outcome was the incidence of new PPI prescription at discharge. For both, we distinguished between potentially appropriate vs. potentially inappropriate indications. Secondary outcomes included change in PPI prescribing at 2 months and

1 year after discharge, all-cause readmissions, and readmissions for potential adverse effect of PPI use (defined as fracture, pneumonia, bacterial intestinal infection, acute interstitial nephritis) and of PPI discontinuation (defined as gastrointestinal bleeding; **Supplemental Text S4**). Readmissions for potential adverse effect of PPI use were assessed both as combined and distinct outcomes.

Statistical analyses

We assessed the proportion of patients with PPI at admission, and the proportion of them with potentially appropriate vs. inappropriate indication. We compared baseline characteristics and PPI indications in patients with and without PPI, using chi square tests for categorical variables, and t-tests for continuous variables. In patients with PPI at admission, we assessed the incidence of deprescribing at discharge, distinguishing between patients with a potentially appropriate vs. potentially inappropriate indication. In patients without PPI at admission, we assessed the incidence of new PPI prescription at discharge, distinguishing again between those with potentially appropriate vs. potentially inappropriate PPI indication. Then, we assessed change in PPI prescribing (i.e., deprescribing / stable treatment / dose increase / new prescription) at 2 months and 1 year. Finally, we performed a competing-risk regression based on Fine and Gray's proportional subhazards model,[15] with death as a competing event, to assess the risk associated with persistent PPI use (compared to non-persistent use), including: a) all-cause readmissions, b) readmissions related to potential adverse effects of PPIs, and c) readmissions related to potential adverse effects of PPI discontinuation. We tested for interaction between PPI prescription and intervention arm (because OPERAM intervention aimed at improving prescribing appropriateness) and adjusted for all available covariates potentially associated with the exposure and outcome of interest: age, sex, Charlson comorbidity index,[16] baseline medication count, admission ward (surgical vs. medical), study site, discharge destination (nursing home or home, vs. other destination), number of previous hospitalizations, OPERAM trial intervention arm. We performed all analyses using Stata/MP 16.0 (StataCorp LP, College Station, Texas).

RESULTS

Baseline characteristics

Among the 2,008 patients included in the OPERAM trial, 10 were lost of follow-up, and 119 withdrew consent, yielding 1,879 patients available for this analysis. The mean age was 79 (standard deviation [SD] 6) years, with 835 (44%) women. The mean Charlson comorbidity index was 3 (SD 2) points, and the mean number of medications at admission was 10.2 (SD 4.2). Patients with PPI at admission were more frequently women (47% vs. 41%, p=0.005), had a higher Charlson comorbidity index (mean 2.9 vs. 2.5 points, p<0.002), and had more medications (mean 11 vs. 9, p<0.001) than patients without PPI at admission (Table 1).

Prevalence and indications for PPIs at admission

At admission, 1,080 (58%) patients had a PPI prescription, 584 (54%) of which with a potentially appropriate indication (Figure 1A&B). GORD was more frequent in patients with PPI (5%, vs. 2% in those without, p<0.001) (Table 1). The most frequent potentially appropriate indication was antiplatelet medication (N=874, 47% of all patients), followed by non-steroidal anti-inflammatory medication (N=145, 8%). Gastro-intestinal disorders as indication were rare (Table 1).

Change in PPI prescribing at discharge

At discharge, 21% of patients with PPI at admission had deprescribing, including 63% with complete discontinuation, and 37% with dose reduction only. The incidence of deprescribing was similar among patients with and without potentially appropriate indication (20% vs. 22%, p=0.59; Figure 1A). Among PPI users, 6% had a dose increase, while 20% of the patients without PPI at admission had a new PPI prescription at discharge. Among those, 40% had a potentially inappropriate indication (Figure 1B).

Change in PPI prescribing at 2 months and 1 year

Of 1,039 patients with PPI at discharge and alive at 2 months, 9% had deprescribing (Figure 1C). Among the 680 patients without PPI at discharge and alive at 2 months, 13% had a PPI started within 2 months. Of 896 patients with PPI at discharge and alive at 1 year, 27% had deprescribing. Among the 606 patients without PPI at discharge and alive at 1 year, 14% had a PPI started within 1 year.

Association between persistent PPI use, PPI discontinuation, and adverse events

Among 1,719 alive at 2 months after discharge, 55% had persistent PPI use, and 4% had a readmission for a diagnosis compatible with an adverse effect of PPI use. These comprised 34 (2%) patients with pneumonia, 25 (2%) with fracture, 3 (0.2%) with bacterial intestinal infection, and 1 (0.06%) with nephritis. We observed no readmission for gastrointestinal bleeding. Using the Fine and Gray's method with death as competing event, persistent PPI use was independently associated with an increased risk of 1-year all-cause readmission (SHR 1.30, 95%CI 1.12-1.54, p<0.001), and with a non-significantly increased risk of PPI-related 1-year readmission (SHR 1.23, 95%CI 0.78-2.06, p=0.44), pneumonia-related 1-year readmission (SHR 1.36, 95%CI 0.67-2.77, p=0.39) and fracture-related 1-year readmission (SHR 1.00, 95%CI 0.44-2.29, p=0.99), after adjusting for age, Charlson comorbidity index, medication count, sex, admission ward, study site, discharge destination, number of previous hospitalizations, and intervention arm (Table 2, Figure 2). There was no significant interaction between persistent PPI use and OPERAM intervention arm. Bacterial intestinal infection and acute interstitial nephritis could not be assessed as individual outcome because of the too low incidence (N=3 and N=1, respectively).

DISCUSSION

In this study including 1,879 older adults with multimorbidity and polypharmacy from four European countries, over half of the patients were prescribed a PPI, despite a potentially inappropriate indication in almost 50% of the cases. This finding was consistent over time, during a 1-year follow-up. Deprescribing occurred in one fifth of patients between admission and discharge, and in 13% of them between discharge and 2 months, and was as frequent as new PPI prescriptions. Within 1 year, over one third of PPI users had deprescribing, while a PPI was started in 18% of patients free of PPI at discharge. PPI use was associated with an increased risk of 1-year all-cause readmission, while the risk of 1-year readmission related to potential adverse effects of PPIs showed a pattern of increase not reaching statistical significance.

The high prevalence of PPI use and of potentially inappropriate indication is consistent with previous studies conducted in hospital settings, although prevalence rates were highly variable across studies.[17-19] This may be due to differences in patient characteristics (e.g., age, co-morbidities) and settings. For example, McDonald et al. did not limit the assessment to older patients with multimorbidity and polypharmacy.[18] Interestingly, the incidence of PPI deprescribing during hospitalization was almost twice higher in our study than in the pre-intervention period of McDonald's study.[18] It is possible that efforts to curb down the use of PPIs so far and studies raising awareness of the high prevalence and potential adverse effects of potentially inappropriate use of PPIs have helped to reduce somewhat PPI prescribing. However, it is also possible that clinicians may pay more attention to deprescribe medications that are not indicated in older patients with polypharmacy and multimorbidity (our study population) than in younger ones where the focus may be less on medications.

While several studies assessed patterns of PPI prescribing over time after the introduction of an intervention (before – after study), or of a new policy, we are not aware of a prospective study like ours that assessed the evolution of prescribing in individual patients during a 1-year follow-up period after discharge of an acute care hospitalization.[18,20-22] We observed about the same proportion of patients with PPI receiving deprescribing than of PPI-free patients receiving a new prescription between admission and discharge, and within 2 months of discharge. However, within 1 year of discharge, the proportion of new prescriptions was less than 18%, while over one third of patients had deprescribing. Although our data are limited to conclude on the appropriateness of deprescribing and of starting a PPI, this suggests that prescribers may start to pay more attention to the issue related to

inappropriate PPI prescribing. It is also possible that primary care provider information about the fact that their patient had been included in the OPERAM trial has stimulated physicians to conduct medication reviews.

The most prevalent indication for PPI prescribing was antiplatelet medication. However, a large proportion of patients with antiplatelet medication were yet not prescribed a PPI. This suggests that prescribers may not be well aware of this indication, potentially because of a lack of evidence and expert agreement. While PPIs may reduce the risk of gastro-intestinal bleeding associated with antiplatelet medications, they are also not free of adverse effects, and physicians and patients may be reluctant to add an additional medication when benefits do not clearly outweigh potential risks.[5,12-14]

While PPIs were independently associated with a all-cause 1-year readmissions, the association did not reach statistical significance for PPI-related readmissions. Although an association was found in several studies, a recent review underscored that the evidence is low to very low for the risk of fractures, intestinal bacterial infections, and pneumonia associated with long-term PPI use.[2] The lack of significant association found in our study may be due to a real lack of association or of power, given the low number of observed events. Finally, it is possible that a longer duration than the minimum of 2 months used to define persistent use in our study, may have been needed to lead to such side effects.

Limitations and strengths

We must acknowledge several limitations. First, the assessment of indications for PPI using ICD codes was incomplete, since we had no information on the timeline of diagnoses. However, using the most sensitive definition (i.e., including all diagnoses), we still found a high proportion of patients with a potentially inappropriate indication. Second, we used only the first readmission diagnosis to define readmissions potentially related to PPI adverse effects. This yielded a low number of outcomes and the broad confidence intervals suggest that we might not have had not enough power to find a significant effect. Third, new diagnoses that may have represented appropriate indications for PPI were not available after discharge, so that the proportions of appropriate or inappropriate indications for new prescriptions and deprescribing at 2 months and 1 year are to be taken with caution. Finally, we cannot exclude that unmeasured confounders, and that PPI may be a marker of sickness, rather than the cause of the relationship with adverse outcomes.

This study has several strengths as well. First, all data were collected systematically and prospectively, following OPERAM trial standard protocol. Second, exclusion criteria were very limited, and we evaluated both

surgical and medical patients, increasing result generalizability. Finally, we recorded not only presence vs. absence of prescriptions, but also dose increase and decrease allowing us to capture more subtle change in prescribing. This is particularly important for PPIs, given that tapering may prevent withdrawal symptoms.[5]

Conclusion

PPI use was frequent in this multicountry sample of older multimorbid adults with polypharmacy. The indication for PPI was potentially inappropriate in almost 50% of them at admission, discharge, 2 months and 1 year. Deprescribing was as frequent as new prescriptions at discharge and 2 months, and slightly more frequent at 1 year. PPI use was associated with an increased risk of adverse clinical outcomes. Our study provides the first long-term insight on PPI use in older multimorbid adults, and suggests that their use may be associated with clinically important adverse effects. Interventions are required to help reduce the use and potential burden of inappropriate use of PPIs, particularly in older multimorbid patients with polypharmacy, who are more vulnerable to medication adverse effects.

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None.

CONFLICTS OF INTEREST

The authors declare that they do not have a conflict of interest.

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Table 1. Baseline characteristics according to PPI at admission.

Characteristics	Without PPI (N=799)	With PPI (N=1,080)	p-value
Age, years	79.5 (6.2)	79.3 (6.4)	0.39
Female	325 (40.7)	510 (47.2)	**0.005**
Surgical ward	131 (16.4)	172 (15.9)	0.78
Charlson comorbidity index, points	2.5 (2.0)	2.9 (2.1)	**<0.002**
Medications, n	8.7 (3.4)	11.3 (4.4)	**<0.001**
OPERAM intervention arm	372 (46.6)	534 (49.4)	0.22
Study site			**<0.001**
Belgium (Louvain)	122 (15.3)	284 (26.3)	
Ireland (Cork)	187 (23.4)	151 (14.0)	
The Netherlands (Utrecht)	116 (14.5)	214 (19.8)	
Switzerland (Bern)	374 (46.8)	431 (39.9)	
Potential PPI indication	406 (50.8)	584 (54.1)	0.16
Gastro-intestinal bleeding	4 (0.5)	4 (0.4)	0.67
Gastro-duodenal ulcer	12 (1.5)	30 (2.8)	0.06
Barrett's esophagus	0 (0.0)	1 (0.1)	0.38
Acute gastritis	0 (0.0)	0 (0.0)	NA
Gastro-esophageal reflux disease	13 (1.6)	52 (4.8)	**<0.001**
Helicobacter pylori infection	0 (0.0)	1 (0.1)	0.39
Non-steroidal anti-inflammatory drug	54 (6.7)	91 (8.4)	0.18
Antiplatelet	361 (45.2)	513 (47.5)	0.32

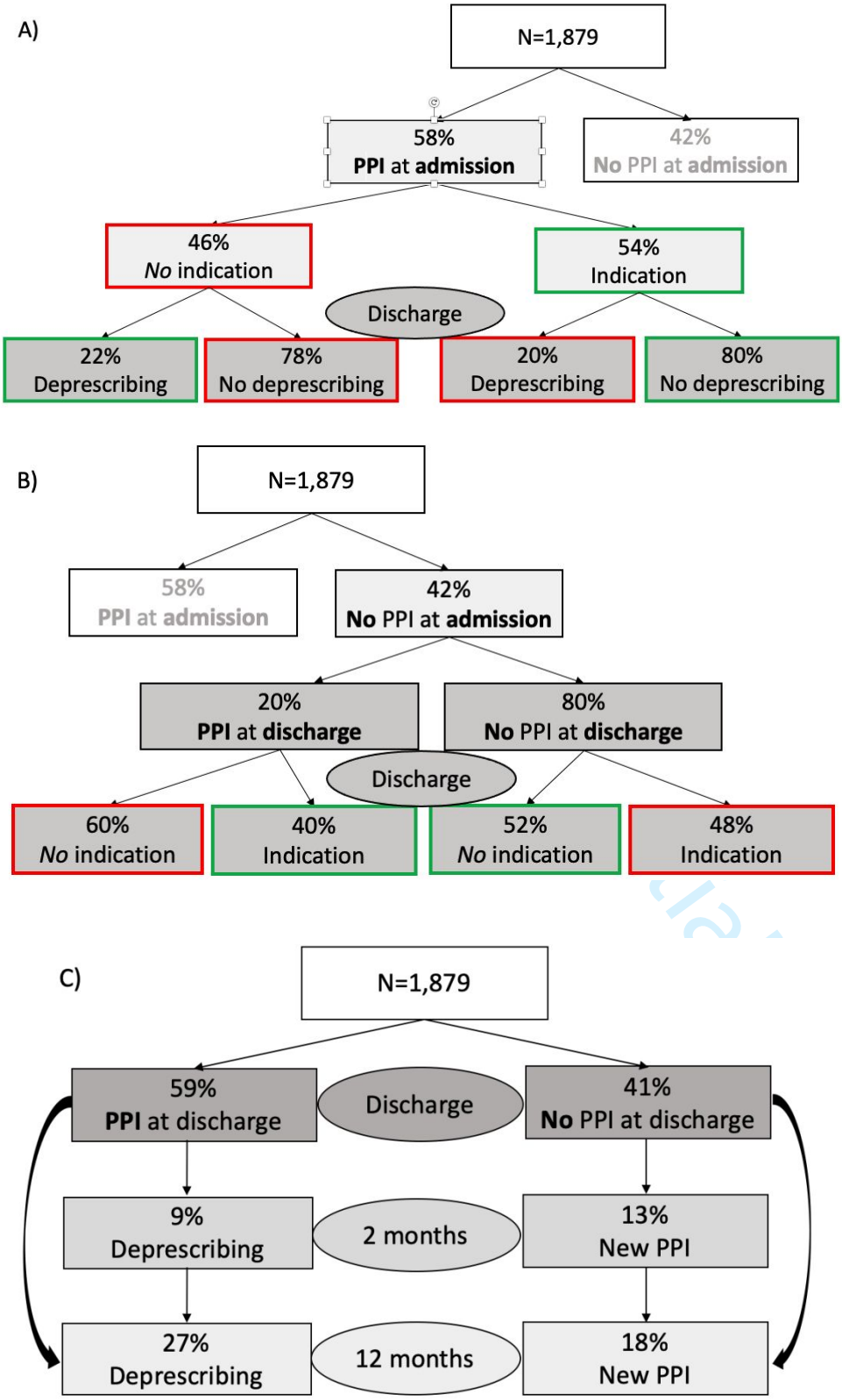
Abbreviations: PPI, proton pump inhibitor.
Legend: Categorical variables are presented as n (%), and continuous variables as mean with standard deviation. The sum of all potential PPI indications is more than the number of patients with a potential PPI indication, because some patients had more than one indication.

Table 2. Association between persistent proton pump inhibitor use and outcomes.

Outcomes	Subhazard ratio (95% CI)	p-value
All-cause readmission (N=767)	1.30 (1.12-1.54)	<0.001
Potentially PPI-related readmission (N=62)	1.23 (0.78-2.06)	0.44
Pneumonia-related readmission (N=34)	1.37 (0.67-2.77)	0.39
Fracture-related readmission (N=25)	1.00 (0.44-2.29)	0.99

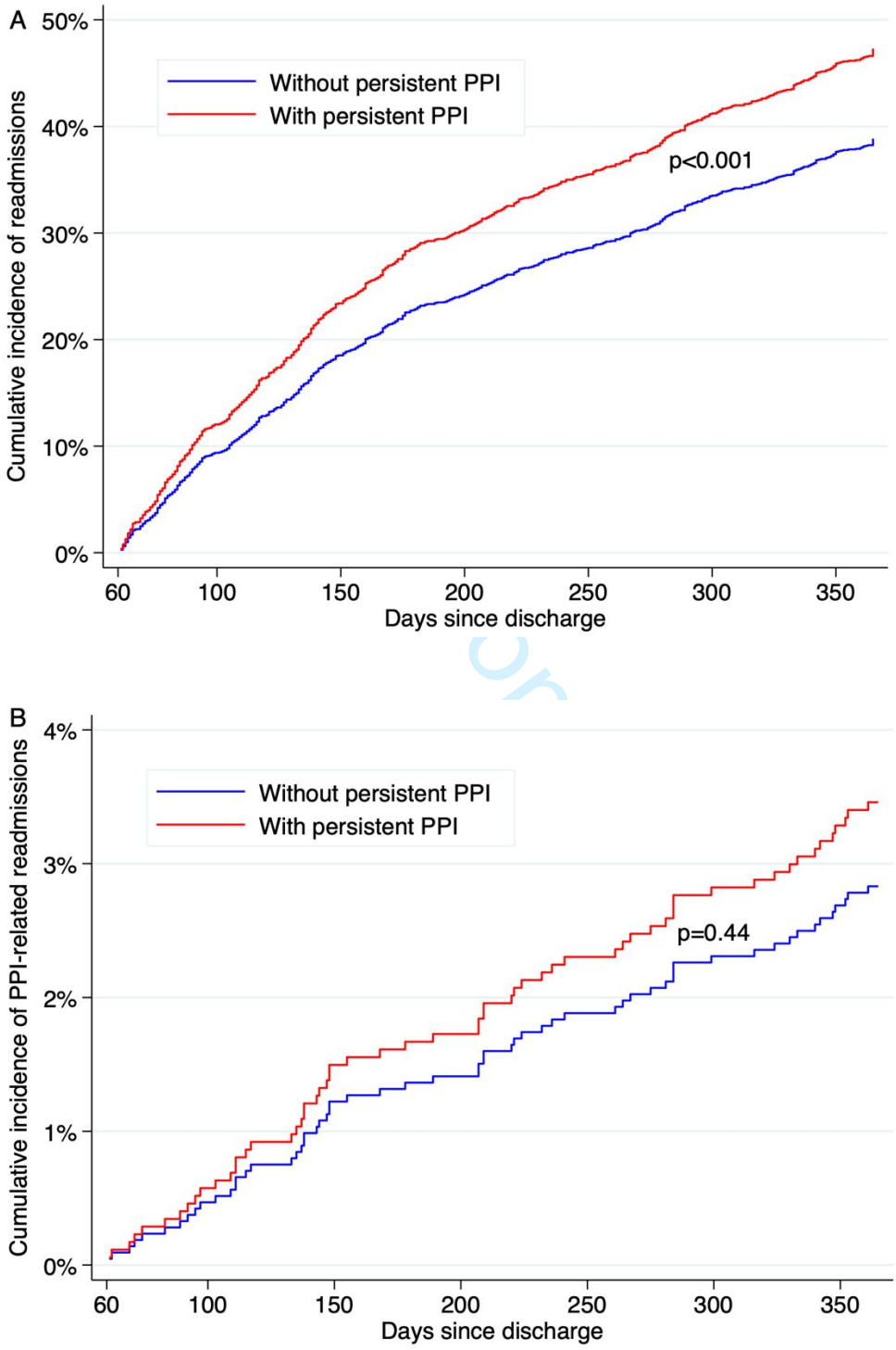
Abbreviations: CI, confidence interval; N, number; PPI, proton pump inhibitor.
Legend: 483/770 (62.7%) patients with readmission had persistent PPI use, and 40/62 (64.5%) a potentially PPI-related readmission. Results of competing-risk regression based on the method by Fine and Gray,[15] with death as competing event, adjusted for age, Charlson comorbidity index, medication count, study site, admission ward, number of previous hospitalzations, OPERAM intervention arm, and discharge destination. Follow-up starting at 2 months after discharge to ensure that patients with PPI were persistent users (defined as PPI use both at discharge and 2 months after), because the assessed adverse PPI effects are related to persistent use. Patients who died within 2 months after discharge could not be included, leaving 1,719 patients for analysis. PPI-related readmissions included readmissions with one of the following as first diagnosis: pneumonia, fracture, nephritis, bacterial intestinal infection.

Figure 1. Longitudinal patterns of PPI prescribing and deprescribing: A) Admission to discharge in PPI users at admission; B) Admission to discharge in non-PPI users at admission; C) Discharge to 12 months in PPI users and non-PPI users at discharge.



Abbreviations: PPI, proton pump inhibitor.
Legend: Diagnoses were not available after discharge, except for readmissions, so that we could not ascertain the potential appropriateness of prescribing at 2 months and 12 months. Red displays cases with indication but no PPI, or without indication but with PPI. Green displays cases with PPI and indication, or without PPI and without indication.

Figure 2. Predicted cumulative incidence of A) all-cause readmissions, and B) PPI-related readmissions, according to persistent use of PPI.



Abbreviations: PPI, proton pump inhibitor.

Legend: Patients who died within 2 months after discharge could not be included, leaving 1,719 patients for analysis. Among them, 950 (55.3%) had persistent PPI use, 767 (44.6%) were readmitted, and 62 (3.6%) had a PPI-related readmission. Results of competing-risk regression based on the method by Fine and Gray,[15] with death as competing event, adjusted for age, OPERAM intervention arm, discharge destination, and study site (all without any significant association). Follow-up starting at 2 months after discharge to ensure that patients with PPI were persistent users (defined as PPI use both at discharge and 2 months after), because the assessed adverse PPI effects are related to persistent use of PPI. PPI-related readmissions included readmissions with one of the following as first diagnosis: pneumonia, fracture, nephritis, bacterial intestinal infection.

SUPPLEMENTAL MATERIAL

Supplemental Text S1. Defined Daily Doses (DDD) for proton pump inhibitors (PPIs):

1) Omeprazole: 20 mg
2) Pantoprazole: 40 mg
3) Lansoprazole: 30 mg
4) Rabeprazole: 20 mg
5) Esomeprazole: 30 mg
6) Dexlansoprazole: 30 mg

Supplemental Text S2. Defined Daily Doses (DDD) for PPIs: A02BC01-08, A02BC53, A02BD01-07, A02BD09, A02BD10-13, B01AC56.

Supplemental Text S3. PPI indications, and related International Classification of Diseases (ICD) German Modification version 10 or ATC codes.

1) Gastro-oesophageal reflux disease with oesophagitis: ICD K21.0
2) Gastro-oesophageal reflux disease without oesophagitis: K21.9;
3) Barrett's oesophagus: ICD K22.5;
4) H. pylori infection: ICD B98.0!;
5) Acute gastritis: ICD K29.0, K29.1, K29.7;
6) Gastro-duodenal ulcer: ICD K26.x, K27.x;
7) Peptic gastro-intestinal bleeding: ICD K21.0x, K21.9x, K22.1x, K22.7x, K25.x, K26.x, K27.x, K29.0 (with x = 0, 2, 4, or 6);
8) Non-steroidal anti-inflammatory drug (NSAID): ATC M01AA01-06, M01AB01-09, M01AB12-17, M01AB51, M01AB55, M01AC01-06, M01AC56, M01AE01-18, M01AE51-53, M01A5E6, M01AG01-04, M01AH01-07, M01AX01-02, M01AX04-05, M01AX07, M01AX12-14, M01AX17-18, M01AX21-26, M01AX68;
9) Antiplatelet medication: ATC B01AC01-27, B01AC30, B01AC56.

Supplemental Text S4. ICD codes for clinical outcomes:

- Fracture: ICD S02.x, S12.x, S22.x, S32.x, S42.x, S52.x, S62.x, S72.x, S82.x, S92.x, T02.x, T08.x, T10.x, T12.x, T14.2x;
- Pneumonia: ICD J12.x-J18.x;
- *C. difficile*: ICD A04.7, A04.70, A04.71, A04.72, A04.73, A04.79;
- Other intestinal bacterial infection: ICD A00.0-1+9, A01.0-4, A02.0-2, A02.8-9, A03.0-3, A03.8-9, A04 A04.0-9, A09.0;
- Acute interstitial nephritis: ICD N10;
- Gastrointestinal bleeding: ICD K21.0x, K21.9x, K22.1x, K22.7x, K25.x, K26.x, K27.x, K29.0 (with x = 0, 2, 4, or 6).