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Research

Prescribing, deprescribing and potential adverse effects of proton pump inhibitors in older patients with multimorbidity: an observational study

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Abstract

Background: Proton pump inhibitors (PPIs) contribute to polypharmacy and are associated with adverse effects. As prospective data on longitudinal patterns of PPI prescribing in older patients with multimorbidity are lacking, we sought to assess patterns of PPI prescribing and deprescribing, as well as the association of PPI use with hospital admissions over 1 year in this population.

Methods: We conducted a prospective, longitudinal cohort study using data from the Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM) trial, a randomized controlled trial testing an intervention to reduce inappropriate prescribing (2016–2018). This trial included adults aged 70 years and older with at least 3 chronic conditions and prescribed at least 5 chronic medications. We assessed prevalence of PPI use at time of hospital admission, and new prescriptions and deprescribing at discharge, and at 2 months and 1 year after discharge, by intervention group. We used a regression with competing risk for death to assess the association of PPI use with readmissions related to their potential adverse effects, and all-cause readmission.

Results: Overall, 1080 (57.4%) of 1879 patients (mean age 79 yr) had PPI prescriptions at admission, including 496 (45.9%) patients with a potentially inappropriate indication. At discharge, 133 (24.9%) of 534 patients in the intervention group and 92 (16.8%) of 546 patients in the control group who were using PPIs at admission had deprescribing. Among 680 patients who were not using PPIs at discharge, 47 (14.6%) of 321 patients in the intervention group and 40 (11.1%) of 359 patients in the control group had a PPI started within 2 months. Use of PPIs was associated with all-cause readmission (n = 770, subdistribution hazard ratio 1.31, 95% confidence interval 1.12–1.53).

Interpretation: Potentially inappropriate use of PPI, new PPI prescriptions and PPI deprescribing were frequent among older adults with multimorbidity and polypharmacy. These data suggest that persistent PPI use may be associated with clinically important adverse effects in this population.

Although proton pump inhibitors (PPIs) are among the most frequently prescribed medications worldwide,[1] they are associated with adverse events, including fractures (relative risk 1.33, 95% confidence interval [CI] 1.15–1.54; absolute risk of hip fracture 0.51 per 1000 person-years), pneumonia (odds ratio [OR] 1.27, 95% CI 1.11–1.46), bacterial intestinal infections (OR 1.73, 95% CI 1.47–2.85 for *Clostridium difficile* infection) and vitamin B_{12} deficiency (OR 1.95, 95% CI 1.77–2.15).[2,3] Therapy with PPIs is often started in hospital, despite a lack of appropriate indication in more than two-thirds of cases.[4,5] Financial costs associated with inappropriate continuation of PPIs after discharge are high.[5] In response to those concerns, a guideline has been developed, aimed at decreasing inappropriate prescribing of PPIs.[6] Recommendations alone may not be sufficient to significantly reduce inappropriate prescribing; specific interventions may need to be developed.[7] To this end, it is important to study the current state of PPI prescribing, the risk of adverse effects and the safety of stopping PPI therapy for older patients with multimorbidity, an understudied population that is particularly vulnerable to adverse effects of medications.[8]

In this study of older patients with multimorbidity and polypharmacy, we sought to assess the prevalence of appropriate and potentially inappropriate PPI prescriptions at hospital

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admission; the incidence of PPI deprescribing and new PPI prescriptions at discharge, 2 months and 1 year after hospital admission; the association between persistent PPI use and potential adverse effects; and potentially serious risks associated with stopping PPIs.

Methods

Study design and population

We used data from the Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM) trial, a European, multicentre study of an intervention to reduce inappropriate prescribing.[9,10] The OPERAM trial included patients aged 70 years or older with multimorbidity and polypharmacy (≥ 5 chronic medications) who were admitted to an acute hospital between December 2016 and December 2019. Multimorbidity was defined as 3 or more chronic conditions (i.e., *International Classification of Diseases, 10th Revision* [ICD-10] codes with an estimated duration of ≥ 6 mo or based on a clinical decision). Participating countries were Belgium, Ireland, the Netherlands and Switzerland, as part of a consortium funded by the European Union. Participants were identified based on medical records. The results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Exposure and potential confounders

We assessed comorbidities at baseline using ICD-10 codes on discharge letters of the index hospital admission.[11] We captured medication information using Anatomic Therapeutic and Chemical (ATC) codes,[12] and standardized doses using the defined daily dose (Appendix 1, Supplemental Text S1 and S2 available at www.cmajopen.ca/content/11/1/E170/suppl/DC1).[12] We defined persistent PPI use as a PPI prescription at discharge (including new prescriptions at discharge and prescriptions present at admission and discharge) and at 2 months after discharge. According to guidelines and expert consensus, potentially appropriate indications for PPIs in adults aged 65 years or older include the following: gastroesophageal reflux disease with acid-related complications (i.e., erosive esophagitis or peptic stricture) or symptomatic gastroesophageal reflux disease; Barrett esophagus; current treatment of gastroduodenal ulcer; current treatment of *Helicobacter pylori*; acute gastritis; peptic gastrointestinal bleeding; persistent use of nonsteroidal anti-inflammatory drug or with antiplatelet medication (given that all patients in OPERAM were older than 60 years, as an additional risk factor).[6,13–15] We considered prescription of PPIs without at least 1 of those indications as potentially inappropriate. We used ICD and ATC codes to identify indications (Appendix 1, Supplemental Text S3).

Potential confounders included variables that could be potentially associated with PPI prescribing and readmission risk, namely age, sex, Charlson Comorbidity Index, number of medications at baseline, admission ward (surgical v. medical), study site, discharge destination (nursing home or home v. other destination), number of previous hospital admissions, anticoagulant use and intervention arm in the OPERAM trial.[16]

Outcomes

The primary outcome of the OPERAM trial was the first drug-related readmission. In the present study, we assessed the following 1-year outcomes: first all-cause readmission, first readmission related to potential adverse effect of PPIs (defined as pneumonia, fracture, bacterial intestinal infection or nephritis) and first readmission related to potential adverse effects of stopping PPI (defined as gastrointestinal bleeding; Appendix 1, Supplemental Text S4). In the OPERAM trial, an independent committee at each trial site, blinded to intervention and control groups, adjudicated the cause and drug-relatedness of hospital readmissions (without recording what specific drug was potentially related to the hospital admission).[9,10] We also assessed the prevalence of appropriate and potentially inappropriate PPI prescriptions at hospital admission, and the incidence of PPI deprescribing and new PPI prescriptions at discharge, 2 months and 1 year after hospital admission.

Statistical analysis

We assessed the proportion of patients with prescriptions for PPIs at admission, and the proportion with potentially appropriate or inappropriate indications for PPIs. We compared baseline characteristics and PPI indications among patients with and without PPI prescriptions using χ^2 tests for categorical variables, and Student *t* tests for continuous variables.

We conducted descriptive analyses of patterns of PPI prescribing, separating control and intervention groups, because the OPERAM intervention addressed inappropriate PPI prescribing. In patients using PPIs at admission, we assessed the incidence of deprescribing at discharge, distinguishing between patients with a potentially appropriate indication versus those with a potentially inappropriate indication. In patients without a PPI prescription at admission, we assessed the incidence of new PPI prescription at discharge, distinguishing again between those with a potentially appropriate indication versus those with a potentially inappropriate PPI indication. We assessed change in PPI prescribing (e.g., deprescribing, stable treatment, dose increase, new prescription) at 2 months and 1 year after discharge.

We performed a competing-risk regression using Fine and Gray's proportional subhazards model,[17] with death as a competing event, to assess the association between persistent PPI use (compared with nonpersistent use) and our outcomes. For readmissions related to potential adverse effects of PPIs, we analyzed any adverse effects together and each specific adverse effect separately. For the competing-risk regression, follow-up started at 2 months after discharge to ensure that patients with PPI at discharge were persistent users. We tested for an interaction between persistent PPI use and intervention arm because the OPERAM intervention addressed potentially inappropriate prescribing of PPIs. We conducted crude, minimally adjusted (i.e., adjusted for age, sex and Charlson Comorbidity Index) and fully adjusted analyses (i.e., adjusted for all potential confounders). We conducted the minimally adjusted analysis because of the low number of readmissions related to potential adverse effects of PPIs. We performed all analyses using Stata/MP version 16.0 (StataCorp).

Ethics approval

This study was approved by all ethical committees of the sites that recruited patients for the OPERAM trial.

Results

Among the 2008 patients included in the OPERAM trial, 10 were lost of follow-up and 119 withdrew consent, yielding 1879 patients available for this analysis, including 835 (44.4%) female patients. The mean age was 79 (standard deviation [SD] 6) years, 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 prescriptions at admission (n = 799) were more frequently female (47.2% v. 40.7%, p = 0.005), had a higher mean Charlson Comorbidity Index (2.9 v. 2.5 points, p < 0.002) and had more medications (mean 11.3 v. 8.7, p < 0.001) than patients without PPI prescriptions at admission (n = 1080) (Table 1). Within 1 year, 377 (20.1%) patients had died. The main cause of death was cancer (n = 99, 26.3%), followed by infection (n = 78, 20.7%), heart failure (n = 64, 17.0%) and bleeding (n = 16, 4.2%).

Prevalence and indications for PPIs at admission

At admission, 1080 (57.5%) patients had a PPI prescription, including 584 (54.1%) patients with a potentially appropriate indication. Gastroesophageal reflux disease was more frequent among patients with PPI prescriptions than among those without (4.8% v. 1.6%, p < 0.001) (Table 1). The most frequent, potentially appropriate indication was antiplatelet medication (n = 874, 46.5% of all patients), followed by nonsteroidal anti-inflammatory medication (n = 145, 7.7%). Gastrointestinal disorders were uncommon indications (Table 1).

Change in PPI prescribing between admission and discharge

At discharge, 133 (24.9%) of 534 patients with PPIs at admission in the intervention group had deprescribing, compared with 92 (16.8%) of 546 patients in the control group. The incidence of deprescribing was similar among patients with and without a potentially appropriate indication (Figure 1A, Figure 2A). A new PPI prescription at discharge occurred in 80 (21.5%) of 372 patients in the intervention group and 82 (19.2%) of 427 patients in the control group (Figure 1B, Figure 2B).

Table 1: Baseline patient characteristics at admission

Characteristic	No. (%) of patients*		p value
	Without PPI n = 799	With PPI n = 1080	
Age, yr, mean ± SD	79.5 ± 6.2	79.3 ± 6.4	0.39
Sex, female	325 (40.7)	510 (47.2)	0.005
Surgical ward	131 (16.4)	172 (15.9)	0.78
Charlson Comorbidity Index, mean ± SD	2.5 ± 2.0	2.9 ± 2.1	0.002
No. of chronic medications at admission, mean ± SD	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
Gastrointestinal bleeding	4 (0.5)	4 (0.4)	0.67
Gastroduodenal ulcer	12 (1.5)	30 (2.8)	0.06
Barrett esophagus	0	1 (0.1)	0.38
Acute gastritis	0	0	NA
Gastroesophageal reflux disease	13 (1.6)	52 (4.8)	< 0.001
Helicobacter pylori infection	0	1 (0.1)	0.39
Nonsteroidal anti-inflammatory drug	54 (6.7)	91 (8.4)	0.18
Antiplatelet cotherapy	361 (45.2)	513 (47.5)	0.32

Note: NA = not applicable, OPERAM = Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults, SD = standard deviation.
*Unless indicated otherwise.
†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 1 indication.

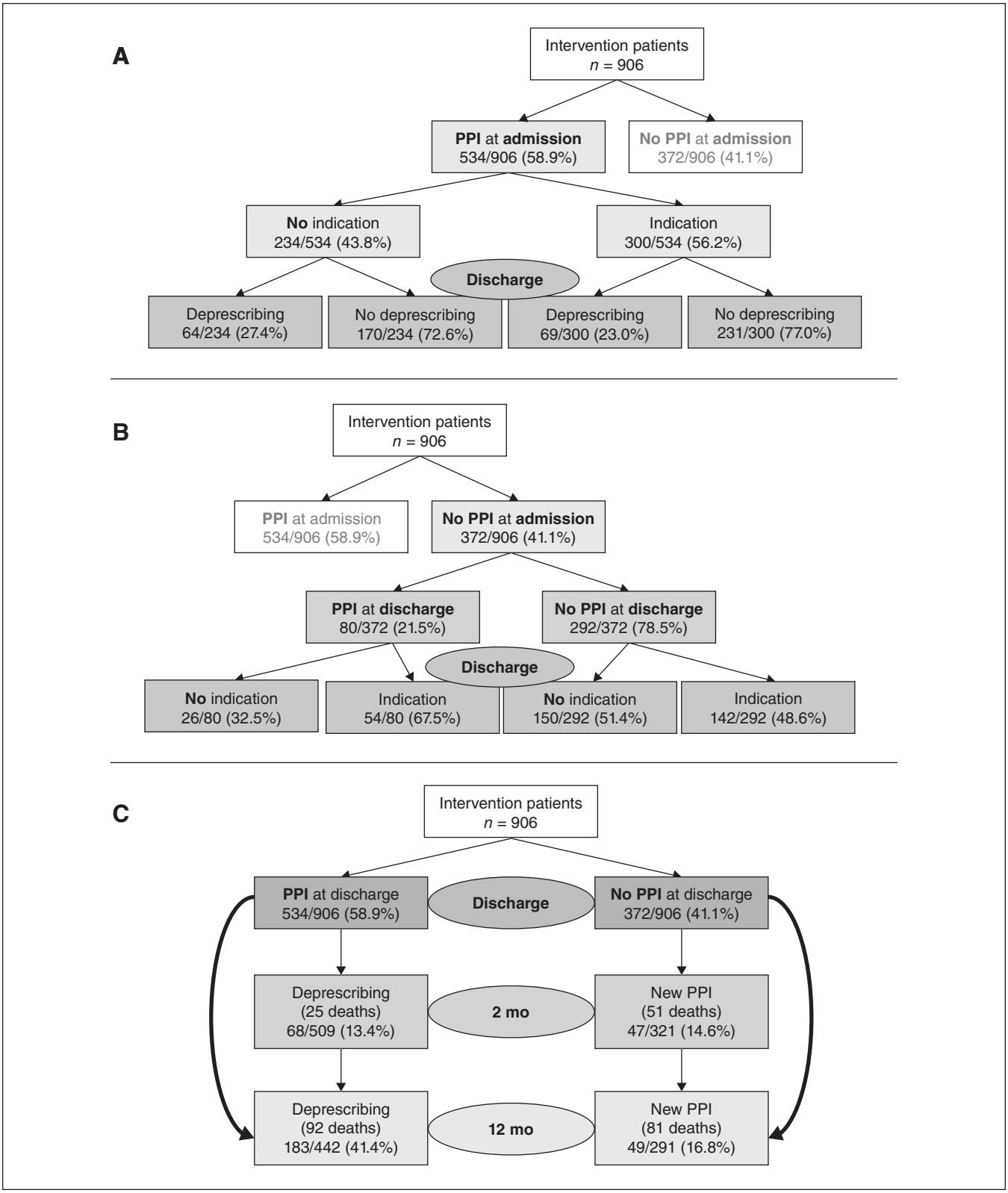

Figure 1: Longitudinal patterns of proton pump inhibitor (PPI) prescribing and deprescribing among patients in intervention group. (A) Patterns of PPI prescribing and deprescribing among patients using PPIs at admission, from admission to discharge. (B) Patterns of PPI prescribing and deprescribing among patients not using PPIs at admission, from admission to discharge. (C) Patterns of deprescribing among patients with PPI prescriptions at admission, and of prescribing among patients without prescriptions at admission, from discharge to 12 months after discharge. Note: Diagnoses were not available after discharge, except among patients with readmissions, so we could not ascertain the potential appropriateness of PPI prescribing at 2 months and 12 months after discharge.

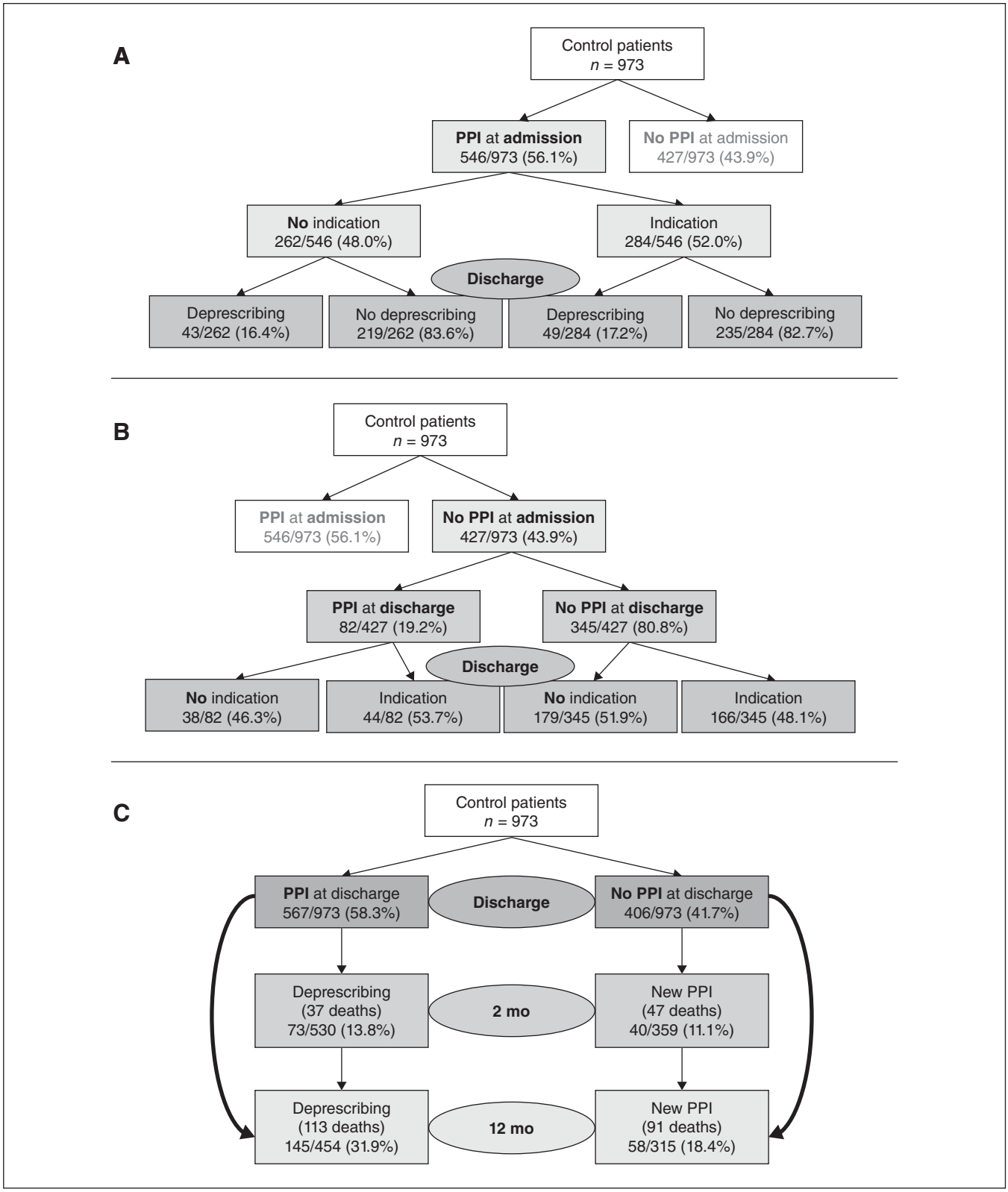

Figure 2: Longitudinal patterns of proton pump inhibitor (PPI) prescribing and deprescribing among patients in control group. (A) Patterns of PPI prescribing and deprescribing among patients using PPIs at admission, from admission to discharge. (B) Patterns of PPI prescribing and deprescribing among patients not using PPIs at admission, from admission to discharge. (C) Patterns of deprescribing among patients with PPI prescriptions at admission, and of prescribing among patients without prescriptions at admission, from discharge to 12 months after discharge. Note: Diagnoses were not available after discharge, except among patients with readmissions, so we could not ascertain the potential appropriateness of PPI prescribing at 2 months and 12 months after discharge.

Change in PPI prescribing at 2 months and 1 year

Of 1039 patients with PPI prescriptions at discharge who were alive at 2 months after discharge, 68 (13.4%) of 509 patients in the intervention group and 73 (13.8%) of 530 patients in the control group had deprescribing within 2 months (Figure 1C, Figure 2C). Among the 680 patients without PPI prescriptions at discharge who were alive at 2 months after discharge, 47 (14.6%) of 321 patients in the intervention group and 40 (11.1%) of 359 patients in the control group had a PPI started within 2 months of discharge. Of 896 patients with PPI prescriptions at discharge who were alive at 1 year after discharge, 183 (41.4%) of 442 patients in the intervention group and 145 (31.9%) of 454 patients in the control group had deprescribing within 1 year of discharge. Among the 606 patients without PPI prescriptions at discharge who were alive at 1 year after discharge, 49 (16.8%) of 291 patients in the intervention group and 58 (18.4%) of 315 patients in the control group had a PPI started within 1 year of discharge.

Persistent PPI use, stopping PPIs and adverse events

Among 1719 patients who were alive at 2 months after discharge, 1039 (60.4%) had persistent PPI use, and 62 (3.6%) had a readmission for potential adverse effects from PPIs within 1 year; 809 (47.1%) were using anticoagulant drugs. Patients with potential adverse effects included 34 (2.0%) with pneumonia, 25 (1.4%) with fractures, 3 (0.2%) with bacterial intestinal infections and 1 (0.1%) with nephritis. We observed no readmissions for gastrointestinal bleeding.

Table 2 shows the crude, minimal adjusted and fully adjusted analyses with death as competing event. Persistent PPI use was independently associated with an increased risk of all-cause readmission (subdistribution hazard ratio [SHR] 1.31, 95% CI 1.12–1.53), and with a nonsignificantly increased risk of PPI-related readmission (SHR 1.24, 95% CI 0.74–2.08), pneumonia-related readmission (SHR 1.40, 95% CI 0.68–2.87) and fracture-related readmission (SHR 0.96, 95% CI 0.42–2.23) in the fully adjusted model (Table 2, Figure 3). We did not observe a significant interaction between persistent PPI use and OPERAM intervention arm. Bacterial intestinal infection and acute interstitial nephritis could not be assessed as individual outcomes given their very low incidence (n = 3 and n = 1, respectively).

Interpretation

In this study of 1879 older adults with multimorbidity and polypharmacy from 4 European countries, more than half of patients were prescribed a PPI, despite a potentially inappropriate indication in almost 50% of cases. This finding was consistent over a 1-year follow-up period. Deprescribing occurred between admission and discharge for one-fifth of patients, and between discharge and 2 months for 13% of patients, which 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 who were not on a PPI at discharge. Use of PPIs was associated with an increased risk of 1-year all-cause readmission.

The high prevalence of PPI use, particularly among patients with potentially inappropriate indications for PPIs, is consistent with previous studies conducted in hospital settings, although prevalence rates were highly variable across studies.[18–20] This may be owing to differences in patient characteristics (e.g., age, comorbidities) and settings. For example, one study did not limit the assessment to older patients with multimorbidity and polypharmacy.[19] Interestingly, the incidence of PPI deprescribing during hospital admission was almost twice as high in our study than in the preintervention period of the study from McDonald and colleagues.[19] It is possible that efforts to curb the use of PPIs and raise awareness of the high prevalence and potential adverse effects of potentially inappropriate use of PPIs have helped to reduce PPI prescribing. However, it is also possible that clinicians

Table 2: Unadjusted and adjusted analyses of association between persistent use of proton pump inhibitors and hospital readmission*

Outcome	Crude SHR (95% CI)	Minimally adjusted SHR (95% CI)	Fully adjusted SHR (95% CI)
All-cause readmission (n = 767)	1.44 (1.25–1.67)	1.40 (1.21–1.63)	1.31 (1.12–1.53)
Potentially PPI-related readmission (n = 62)	1.39 (0.83–2.32)	1.33 (0.80–2.22)	1.24 (0.74–2.08)
Pneumonia-related readmission (n = 34)	1.70 (0.83–3.49)	1.56 (0.76–3.20)	1.40 (0.68–2.87)
Fracture-related readmission (n = 25)	1.03 (0.47–2.28)	1.04 (0.48–2.30)	0.96 (0.42–2.23)

Note: CI = confidence interval, PPI = proton pump inhibitor, SHR = subdistribution hazard ratio.
*Competing-risk regression based on the method by Fine and Gray,[17] with death as competing event. Minimal adjustment model adjusted for age, sex and Charlson Comorbidity Index. Full adjustment model adjusted for age, sex, Charlson Comorbidity Index, medication count, anticoagulant use, study site, admission ward, number of previous hospital admissions, intervention arm and discharge destination. Potentially PPI-related readmissions included readmissions with pneumonia, fracture, nephritis or bacterial intestinal infection.

may deprescribe medications that are not indicated more often for older patients with polypharmacy and multimorbidity (as with our study population) than for younger ones, for whom clinician focus may be less on medications.

Although several studies have assessed patterns of PPI prescribing over time after the introduction of an intervention (before–after studies), or of a new policy, we conducted a prospective study to assess the evolution of prescribing in

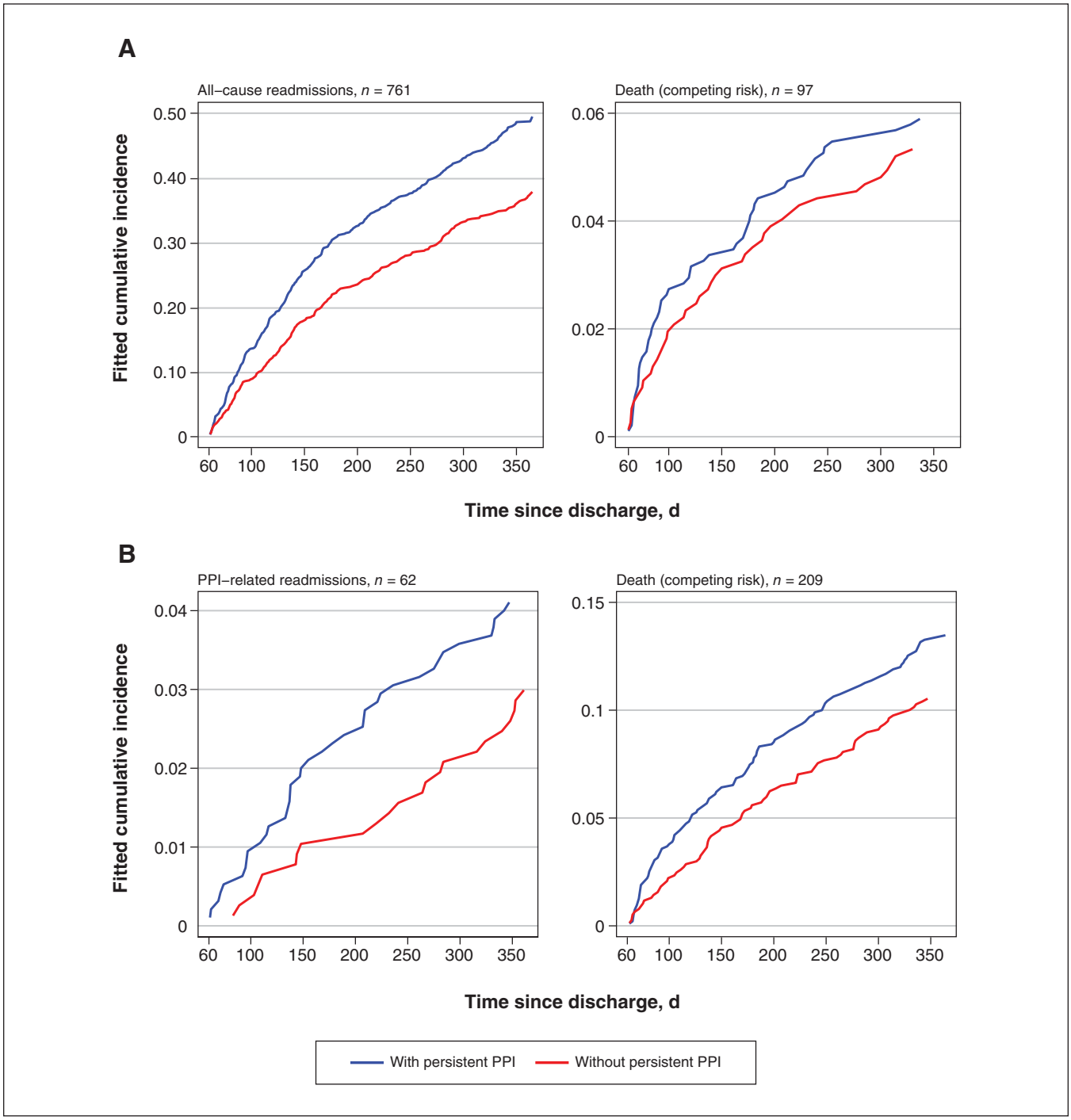

Figure 3: Predicted cumulative incidence of (A) all-cause readmissions, and (B) PPI-related readmissions, and competing risk of death, among patients with or without persistent use of PPIs. Note: CI = confidence interval, *n* = number of events, PPI = proton pump inhibitor, SHR = subdistribution hazard ratio. Results of competing-risk regression based on the method by Fine and Gray,[17] with death as competing event, adjusted for age, Charlson Comorbidity Index, medication count, study site, admission ward, number of previous hospital admissions, anticoagulant use, intervention arm and discharge destination. Potential PPI-related readmissions included readmissions with pneumonia, fracture, nephritis or bacterial intestinal infection.

individual patients during a 1-year follow-up period after discharge of an acute care hospital admission.[19,21–23] We observed similar proportions of patients with PPIs who were receiving deprescribed PPIs as patients without PPIs who received new PPI prescriptions 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 draw conclusions on the appropriateness of deprescribing and of starting a PPI, this finding suggests that prescribers may be increasingly aware of inappropriate PPI prescribing. It is also possible that knowledge that patients had been included in the OPERAM trial stimulated health care professionals to conduct medication reviews.

The most prevalent potentially appropriate indication for PPI prescribing was antiplatelet medication. However, a large proportion of patients with antiplatelet medications were not prescribed PPIs. This suggests that prescribers may not be fully aware of this indication, potentially because of a lack of evidence and expert agreement. Although PPIs may reduce the risk of gastrointestinal 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.[6,13–15]

Although PPIs were independently associated with all-cause readmissions within 1 year, the association did not reach statistical significance for PPI-related readmissions. This association was found in several studies, but 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 owing to a real lack of association or of power, given the low number of observed events. Finally, it is possible that our definition of persistent use as 2 months was insufficient to observe associations between PPI use and adverse effects.

Our study reinforces previous work on adverse effects of PPIs and adds new knowledge in the vulnerable population of older adults with multimorbidity and polypharmacy. Given the potential association of PPI use with clinically important adverse effects, it is important to develop interventions to reduce their inappropriate use, particularly for older multimorbid patients with polypharmacy, who are more vulnerable to adverse effects related to medications. Although reducing inappropriate PPI use alone is unlikely to eliminate the risks associated with polypharmacy among older adults, it could contribute to risk reduction.

Limitations

The assessment of indications for PPI using ICD codes was incomplete, since we did not know when a condition was diagnosed. For example, a patient with a diagnosis of gastroduodenal ulcer that had since resolved may not have actually had an appropriate indication for PPI. However, using the most sensitive definition (i.e., including all diagnoses), we still found that a high proportion of patients had a potentially inappropriate indication. We used only the first readmission diagnosis to define readmissions that were potentially related to adverse effects of PPIs. This yielded a low event rate with broad CIs, suggesting we may have lacked power. 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. The OPERAM trial was not powered to assess the safety of PPI use, and we may not have had sufficient power to detect differences in adverse effects of PPIs between groups; results should be interpreted cautiously. We might not have been able to capture subtle changes in dose and, thus, the impact of those modifications. Finally, since this was not a randomized trial on PPI use, we cannot exclude unmeasured confounders, or that PPI use may be a marker of sickness, rather than the cause of the relationship with adverse outcomes.

Conclusion

Use of PPIs was frequent in this multicountry sample of older adults with multimorbidity and polypharmacy. The indication for PPI was potentially inappropriate in almost 50% of patients at admission and discharge, as well as 2 months and 1 year after discharge. Deprescribing was as frequent as new prescriptions at discharge and at 2 months after discharge, and was slightly more frequent at 1 year after discharge. Use of PPIs was associated with an increased risk of adverse clinical outcomes. Our study provides long-term insight on PPI use in older adults with multimorbidity, and suggests that 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 among older patients with multimorbidity and polypharmacy, who are more vulnerable to adverse effects related to medications.

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