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Out-of-Hospital Use of Proton Pump Inhibitors and Hypomagnesemia at Hospital Admission: A Nested Case-Control Study

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Abstract

Background—Case series suggest that chronic use of proton pump inhibitors (PPIs) is associated with hypomagnesemia but current literature lacks systematically collected data. Our

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SUPPLEMENTARY MATERIAL LEGENDS

Table S1: Review of case reports of proton pump inhibitor-induced hypomagnesemia in current literature.

Table S2: ICD-9-CM diagnosis codes used to define variables of interest.

Table S3: Multivariable analysis examining factors associated with low serum magnesium level.

aim was to examine whether hypomagnesemia at time of hospital admission is associated with out-of-hospital use of PPIs.

Study Design—Nested case-control study matched for age and sex.

Setting & Participants—Data was collected retrospectively from a tertiary acute care facility. Eligible cases consisted of 402 adults with hypomagnesemia (serum magnesium <1.4 mEq/L) at time of hospital admission to medical services, age- and sex- matched with 402 control subjects with normal serum magnesium level (1.4–2.0 mEq/L).

Predictor—Out-of-hospital PPI use was identified in the hospital record. An omeprazole equivalent dose was calculated when possible. Covariates included the Charlson-Deyo comorbidity index, diabetes, diuretic use, estimated glomerular filtration rate (eGFR), and gastro-esophageal reflux.

Outcome—Multivariable conditional logistic regression analyses were used to examine the association of PPI use with hypomagnesemia at time of hospital admission.

Results—PPI use was not associated with hypomagnesemia (adjusted odds ratio [OR] 0.82; 95% CI 0.61, 1.11). Neither PPI type nor omeprazole-equivalent daily dose was associated with hypomagnesemia. Sensitivity analyses of PPI use restricted to patients with esophageal disorders (adjusted OR 1.00; 95% CI 0.69, 1.45), severe hypomagnesemia (1.0 mEq/L) (adjusted OR 0.78; 95% CI 0.13, 4.61), or eGFR ≥ 60 ml/min per 1.73m² (adjusted OR 0.84; 95% CI 0.53, 1.34) were unrevealing.

Limitations—Exposure misclassification; hospitalized patients on medical services may not be representative of a broader ambulatory-based population.

Conclusion—In a hospital-based adult population, out-of-hospital PPI use is not associated with hypomagnesemia at time of hospital admission to medical services. In light of these inconclusive results, prospective cohort studies are needed to address this rare potential medication-related adverse effect.

Keywords

hypomagnesemia; proton pump inhibitors; PPIs; electrolyte disorders

INTRODUCTION

Proton pump inhibitors (PPIs) are among the most widely used drugs for the treatment of gastro-esophageal reflux disease (GERD), peptic ulcer disease, and conditions associated with increased gastric acid secretion. Prolonged therapy may be required for adequate symptom control in patients with GERD¹. While the recommended duration of therapy is 4–8 weeks for acute gastric and duodenal ulcer², the Food and Drug Administration (FDA) advises that no more than three 14-day courses of PPI therapy be used in one year³. More prolonged use of PPIs is common in the elderly, especially among those taking non-steroidal anti-inflammatory drugs⁴. In 2003, PPIs became available over-the-counter in the U.S.⁵, further increasing their widespread use. By 2009, they constituted the third highest drug class in sales after antipsychotics and lipid lowering drugs⁶.

Proton pump inhibitors are generally considered safe drugs with rare associated side effects, including pneumonia diarrhea, vitamin B₁₂ and iron deficiency, *Clostridium difficile* colitis, and the recent description of hypomagnesemia^{7,8}. A total of 38 cases of hypomagnesemia associated with the use of PPIs have been reported to date^{9–27}. A common characteristic was the long-term use of PPIs of more than one-year duration and the presence of severe hypomagnesemia (Table S1). Fifteen additional cases were reported to the FDA, which recently recognized hypomagnesemia related to the chronic use of PPI with a safety announcement^{28,29}. This safety announcement is based only on isolated cases, underlining the lack of systematically collected data linking use of PPIs with hypomagnesemia. To help address this knowledge gap, we conducted a case-control study nested within a large cohort of hospitalized adults to examine whether the presence of hypomagnesemia at the time of hospital admission is associated with out-of-hospital use of PPIs.

METHODS

Data Source

The dataset contained hospital discharges at a tertiary acute care facility (Saint Elizabeth's Medical Center) over a 7-year period (October 2000 to September 2007). Institutional Review Board approval was obtained. Discharge abstracts provided information on patient's age, sex, race/ethnicity, hospital service type (medical, surgical, and other), up to 15 International Classification of Diseases-9th Edition-Clinical Modification (ICD-9-CM) diagnosis codes, and procedural codes. Each discharge abstract was linked to the hospital's electronic laboratory database.

Study Design

This was a single-center, age- and sex-matched nested case-control study with a 1:1 matching ratio. The source population consisted of all hospitalized adults (age ≥ 18 years) with an ICD-9-CM diagnosis code for disorders of the esophagus, stomach, or duodenum. Cases were patients with a low serum magnesium level, defined as <1.4 mEq/L (<1.7 mg/dL), in accordance with the clinical laboratory's lower cut-off value. Control subjects were patients with a normal serum magnesium level of 1.4–2.0 mEq/L (1.7–2.5 mg/dL). Magnesium levels at time of hospital admission or the following day were used for both cases and controls. Controls were sex- and age-(±1 year) matched to cases using the MatchIt R package³⁰.

Inclusion and Exclusion Criteria

Assessment of inclusion and exclusion criteria was performed electronically using ICD-9-CM diagnosis codes. Controls were randomly sampled from patients meeting eligibility criteria using computerized simple random allocation. The population was restricted to the first available hospitalization on medical services, with a documented ICD-9-CM diagnosis code for a disease of the upper gastrointestinal tract (Table S2). This restriction produced a study population that was more likely to use PPIs chronically. Restriction to first available hospitalization increased the likelihood that cases of hypomagnesemia were newly diagnosed.

Coexisting conditions that may confound the association of low serum magnesium levels with PPI use were avoided by excluding patients with ICD-9-CM diagnosis codes for acute and chronic diarrheal syndromes, surgery, alcoholism, pancreatitis, and kidney transplantation (Table S2). We also excluded hospitalizations on surgical, obstetrical, psychiatric, oncological, and substance abuse services, as well as hospitalizations with missing service assignment or admission serum magnesium value.

Ascertainment and Validation of Out-of-Hospital PPI Use

Out-of-hospital use of PPIs was ascertained by reviewing physician admission and discharge notes in the electronic medical record (*method 1*) using a structured data collection form. If the hospital admission medication list was not reported in these source documents, the nursing electronic medication administration record (*method 2*) for the corresponding hospitalization was used instead. In this case, PPI use was presumed only if the medication was prescribed during the total length of the hospitalization *and* at time of hospital discharge.

In a randomly selected subgroup of 239 patients (97 cases and 142 controls), a manual chart review was conducted and was used as the gold standard test to calculate performance tests of the two methods employed to ascertain PPI use.

Using a dose conversion factor, a daily omeprazole equivalent dose was also calculated whenever the daily dose of the PPI was documented. In brief, a 20 mg oral dose of omeprazole was considered to have equivalent therapeutic efficacy to 20 mg of esomeprazole, 30 mg of lansoprazole, 40 mg of pantoprazole, and 20 mg of rabeprazole^{31,32}.

Description of Covariates

Based on review of the literature^{24,33} and clinical relevance, several covariates of interest were collected: age, sex, race/ethnicity, diabetes mellitus, the Charlson-Deyo comorbidity index (and its individual components), GERD and other disorders of the upper gastrointestinal tract, out-of-hospital use of medications that might affect serum magnesium level (diuretics, aminoglycosides, and anti-fungal, chemotherapeutic, immunosuppressive, and anti-protozoal drugs), and selected laboratory variables (serum creatinine, calcium, and albumin) obtained at time of hospital admission or, if missing, within the first day of hospitalization. The Charlson-Deyo comorbidity index incorporates a history of comorbidities, using ICD-9-CM diagnosis codes^{34,35}. A Charlson-Deyo score between 0 and

3 was generated, with increasing numerical value reflecting greater comorbidity. Presence of diabetes and disorders of the upper gastrointestinal tract were ascertained using an expanded list of ICD-9-CM diagnosis codes (Table S2). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation³⁶.

Statistical Analysis

Continuous variables were described as mean (standard deviation) or median (25th and 75th percentile), and categorical variables as count (percentage). With the identification of 402

pairs, the study had adequate power to detect an unadjusted odds ratio of 1.52 in exposed relative to unexposed subjects, with a power of 80% and a type-I error of 0.05.

Comparisons between cases and controls were conducted using McNemar's test for binary variables, paired t-test for normally distributed continuous variables, and Wilcoxon signed-rank test for non-normally distributed continuous variables. Global p values of multilevel categorical variables were estimated using the likelihood ratio test.

Multivariable conditional logistic regression analyses were performed to examine the association of low serum magnesium level with out-of-hospital PPI use, type of PPI and daily omeprazole equivalent dose. The covariates of interest included the Charlson-Deyo comorbidity index, diabetes, GERD, out-of-hospital use of diuretics, and eGFR at time of hospital admission. We tested for interactions between PPI use and each covariate, and used the likelihood ratio test to compare the models with and without interaction terms. The results are displayed as odds ratio (OR) with 95% confidence interval (CI).

Several sensitivity analyses were conducted to explore the robustness of the findings, including the removal of influential points (identified using DFBETAS and standardized DFBETAS), the restriction to cases with severe hypomagnesemia (< 1.0 mEq/L or < 1.2 mg/dL), cases with esophageal disorders (including GERD), and cases with preserved kidney function (eGFR ≥ 60 ml/min/1.73 m²).

All analyses were conducted using R system software³⁷ Version 2.14.0. All p values were two-sided and considered to be statistically significant at the 0.05 level.

RESULTS

Derivation of the Study Population

A flow diagram describing the derivation of the study population is depicted in Figure 1. In brief, during the 7-year study period, there were a total of 97,472 hospitalizations representing 51,207 patients. Hospitalizations on surgical, obstetrical, psychiatric, oncological, and substance abuse services were excluded (31,353 hospitalizations, 17,027 patients). Other reasons for exclusion were absence of serum magnesium value on the day of admission (20,522 hospitalizations, 7,802 patients), and missing service assignment (4,994 hospitalizations, 2,798 patients). By limiting to the first hospitalization per patient, 17,023 hospitalizations were excluded. Of the 23,580 patients with first hospitalization on medical services, 20,334 were excluded based on age < 18 years, serum magnesium > 2.0 mEq/L (> 2.5 mg/dL), and absence of diagnosis codes for disorders of the esophagus, stomach and duodenum. After applying these criteria, 3,246 eligible patients were identified for the case-control study. After excluding patients with insufficient data on medication use, the final study population included 402 matched pairs of cases and controls (804 patients).

Population Characteristics

Table 1 displays the characteristics of the study participants. Mean age was 70 years and 40% of patients were men. Comorbidities were more prevalent in cases compared to controls, as evidenced by a higher Charlson-Deyo comorbidity index scores (global P =

0.04), and a higher prevalence of diabetes ($P = 0.01$). Cases also had a higher prevalence of out-of-hospital thiazide diuretic use ($P = 0.02$) and lower serum calcium levels ($P < 0.001$) compared to controls. GERD was unexpectedly more prevalent in controls compared to cases ($P = 0.03$).

Diagnostic Performance of PPI Use Ascertainment Methods

Based on a manual chart review of 239 hospitalizations as the gold standard, the diagnostic performance of *method 1* to ascertain use of PPIs (review of physician admission and discharge notes in the electronic medical record) was better than that of *method 2* (review of nursing electronic medication administration record), as depicted in Table 2.

Primary Analyses

In the unadjusted and adjusted analysis (Table 3), out-of-hospital PPI use was not associated with higher odds for low serum magnesium levels at time of hospital admission (adjusted OR 0.82; 95% CI 0.61, 1.11). There was no significant interaction between PPI use and each covariate (data not shown). Similarly, there was no association between type of PPI (global $P = 0.129$) or the omeprazole equivalent daily dose (adjusted OR 0.98; 95% CI 0.88, 1.10) and serum magnesium levels. Other factors independently associated with low serum magnesium levels were diabetes (adjusted OR 1.42; 95% CI 1.01, 1.98; $P = 0.04$) and out-of-hospital thiazide diuretic use (adjusted OR 1.95; 95% CI 1.18, 3.22; $P = 0.009$) (Table S3).

Sensitivity Analyses

There was no association between PPI use and low serum magnesium levels in sensitivity analyses restricted to case-control pairs where ascertainment of PPI use was based on *method 1* that had better diagnostic performance, patients with severe hypomagnesemia, those with preserved kidney function, or esophageal disorders (Table 3). Although out-of-hospital PPI use was associated with a 1.16 higher adjusted odds for low serum magnesium levels in an analysis restricted to patients with GERD, this association did not reach statistical significance (OR 1.16; 95% CI 0.76, 1.76).

We identified and removed 7 potentially influential observations from our primary multivariable model, which consisted of cases (with 6 women), as well as their matched pair control. The adjusted OR for PPI use without these observations remained approximately the same (OR 0.76; 95% CI 0.56, 1.03) as when using the full dataset (OR 0.82; 95% CI 0.61, 1.11).

DISCUSSION

In the present nested case-control study, we found that out-of-hospital PPI use among patients with disorders of the upper gastrointestinal tract was not associated with low serum magnesium levels at time of hospital admission. Our results remained unchanged after taking into consideration the type or the dose of the prescribed PPI. While we defined hypomagnesemia in accordance with the hospital's clinical laboratory serum magnesium lower cut-off value of 1.4 mEq/L, the cases reported in the literature (Table S1) presented

with lower serum magnesium levels with the highest value being at 1.0 mEq/L¹⁹. When restricting our analysis to cases with serum magnesium levels of less than 1.0 mEq/L, no association between PPI use and low serum magnesium level was found.

Although not statistically significant, our analysis unexpectedly indicated a favorable effect of PPI use against low serum magnesium levels, with observed odds ratios of less than 1.0. If not attributable to chance, a possible explanation might be bias introduced by an unanticipated higher prevalence rate of GERD in the control group. The strong association between GERD and chronic PPI use¹ could potentially introduce confounding by indication, although GERD is not known to be a predictor of low serum magnesium levels. To address this potential bias, we adjusted our multivariable analysis for GERD and performed sensitivity analyses restricted to patients with esophageal disorders or GERD specifically. Although none of these analyses revealed a statistically significant association between PPI use and hypomagnesemia, in the analysis of patients with GERD only, PPI use was associated with non-significant 1.16-fold higher odds for low serum magnesium level. As highlighted above, patients with GERD are most likely to be chronic PPI users¹.

PPI-induced hypomagnesemia has been described primarily among chronic users of these drugs^{18,20}. The potential underlying mechanism remains elusive. The reported rarity of PPI-associated hypomagnesemia is in accordance with our inability to confirm a statistically significant association in a hospital-based patient population and points to uncertainties regarding this potential drug-related adverse effect. Since the urinary excretion of magnesium has been reported to be consistently low in the published case reports (Table S1)^{9,13,18,19}, it is more likely that the putative cause is magnesium loss via the gastrointestinal tract. Indeed, in several reports, oral supplementation with high-dose magnesium was only partially effective, suggesting impaired intestinal magnesium absorption^{11,16}. Speculations that PPIs might affect the function of the Transient Receptor Potential Melastatin-6 (TRPM₆) channel^{11,19}, a magnesium channel that is expressed in the intestine and renal distal tubules³⁸, need confirmation.

The potential deleterious effect of PPIs on serum magnesium levels in patients with impaired kidney function might be confounded by the concomitant oral administration of magnesium-containing antacids^{1,39}, which would attenuate the decline in serum magnesium levels due to impaired GFR¹⁸. Our sensitivity analysis restricted to patients with eGFR ≥ 60 ml/min/1.73m² attempted to address the confounding effect of impaired kidney function, but yet found no association between PPI use and hypomagnesemia. Moreover, by excluding patients with a high serum magnesium level of >2.0 mEq/L (>2.5 mg/dL), we further minimized the potential influence of impaired kidney function on elevating serum magnesium levels.

Although PPI-associated hypomagnesemia was initially reported in users of omeprazole, it has also been described with other PPI compounds (Table S1)^{9,11,16,18,27}. This finding justifies our approach to analyze PPI use in general. This potential drug-related adverse effect has been described as “non-dose related”¹⁸, and we failed to demonstrate an association between the omeprazole equivalent daily dose and serum magnesium level.

Our study is the second epidemiological investigation of the potential association between PPI use and hypomagnesemia other than case series^{40,41}. Our results were consistent, irrespective of the statistical method used. The nested design allowed random sampling of controls from a fully enumerated source population and PPI information was abstracted from the electronic chart only after case and control selection, thereby ensuring that control subjects were sampled independently of exposure status and minimizing the potential for selection bias. Second, during the study period of the hospitalizations, a possible association between PPI use and hypomagnesemia had not been formally recognized in the literature. Consequently, prescription of these drugs was unlikely to have been influenced by physician awareness of a possible association, thereby limiting confounding by indication. Finally, matching and multivariable analyses taking into account the most important potential confounders of the association of PPI use with hypomagnesemia were used to minimize the threat of confounding bias.

Exposure misclassification is an important limitation, as out-of-hospital use of PPIs was ascertained by review of electronic medical records using 2 complementary methods. The poor performance of *method 2* (based on the nursing electronic medication administration records) is indicative of this potential ascertainment bias, which in turn, might have attenuated our effect estimates. Our sensitivity analysis restricted to patients where ascertainment of out-of-hospital PPI use was conducted using *method 1* (based on physician documentation in the electronic medical record) was an attempt to account for this limitation. However, the power of this subgroup analysis was reduced due to a substantially smaller resulting sample size. In addition, we were unable to ascertain duration of PPI therapy. Since PPI-associated hypomagnesemia has been described in long-term users, ranging from 1 to 13 years (Table S1), we restricted the analysis to patients admitted to medical services with disorders of the upper gastrointestinal tract in order to limit the study population to patients most likely to be *chronic* users of PPIs. This choice also enabled us to adequately power our study while keeping the sample size within a feasible limit because our sample was enriched with PPI users. Since exposure misclassification is expected to be non-differential with respect to case status either regarding the poor performance of *method 2* or our inability to ascertain duration of PPI therapy, we anticipate an attenuation of effect estimates rendering conclusions difficult upon potentially rare adverse events, such as the PPI-induced hypomagnesemia.

The possibility of confounding by indication cannot be ruled out since the greater prevalence of GERD in the control subjects may have obscured the potential association between PPI use and hypomagnesemia, even though we adjusted our multivariable analysis for GERD, and performed sensitivity analyses restricted to patients specifically with this diagnosis. Another limitation is that while published case series on PPI use and magnesium levels identify primarily severe cases of hypomagnesemia (<1.0 mEq/L), our subgroup analysis restricted to cases with such severe hypomagnesemia was underpowered, and therefore likely inconclusive.

The criteria applied to select the study population likely limits the external validity of our results. Our dataset derived from a single center and was restricted to hospitalized patients; therefore, it may not be representative of a broader ambulatory-based population. To address

this issue, our analysis was restricted to serum magnesium levels measured on day 1 or day 2 of hospitalization. Also, we restricted our analysis to the first hospitalization of all patients, assuring independence between pairs.

Finally, our study was not powered to examine a rare adverse event. It was however adequately powered to detect a clinically meaningful rate with an unadjusted odds ratio of approximately 1.50, taking under consideration reports that the incidence rate of PPI-induced hypomagnesemia might be considerably underestimated due to a low index of suspicion^{14–16,22}.

Our findings support that magnesium loss in PPI users should be considered in the differential diagnosis of hypomagnesemia, but not as a highly likely cause. The risk of this potential side effect is likely small and should not drive clinical decision against the use of these drugs, unless the patient has a history of PPI-induced hypomagnesemia.

In conclusion, in a hospital-based adult population, out-of-hospital use of PPI is not strongly associated with presence of low serum magnesium levels at time of hospital admission to medical services. In light of these inconclusive results, further studies with more detailed information on cumulative exposure and duration of PPI use are needed to address this potential, and most likely rare, medication-related issue.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow diagram describing the derivation of the analytical dataset.

Table 1

Baseline characteristics of the study population

Variable	Number of pairs	Cases	Control subjects	P value
Serum magnesium, mEq/L *	402	1.23 (1.15, 1.32)	1.64 (1.56, 1.81)	-
Age, years	402	70 (14.4)	70 (14.4)	-
Men, n (%)	402	161 (40.0)	161 (40.0)	-
White ethnicity, n (%)	400	327 (81.8)	336 (84.0)	0.5
Charlson-Deyo comorbidity index, n (%)	402			0.04
0		140 (34.8)	158 (39.3)	
1		121 (30.1)	141 (35.1)	
2		70 (17.4)	51 (12.7)	
3		71 (17.7)	52 (12.9)	
Diabetes mellitus, n (%)	402	139 (34.6)	106 (26.4)	0.01
GERD, n (%)	402	293 (72.9)	322 (80.1)	0.03
Esophageal disorders (including GERD), n (%)	402	333 (82.8)	348 (86.6)	0.2
Gastro-duodenal disorders, n (%)	402	100 (24.9)	90 (22.4)	0.5
Serum creatinine, mg/dL	399	1.29 (1.15)	1.19 (1.02)	0.2
eGFR, ml/min/1.73m ²	397	67.6 (28.6)	68.9 (25.9)	0.5
Serum calcium, mg/dL	399	8.42 (0.76)	8.63 (0.70)	<0.001
Serum albumin, gm/dL	140	3.13 (0.65)	3.21 (0.70)	0.1
Proton pump inhibitor use, n (%)	402	219 (54.5)	238 (59.2)	0.2
Proton pump inhibitor type, n (%)	402			0.1
Omeprazole		38 (9.5)	48 (11.9)	
Lansoprazole		93 (23.1)	88 (21.9)	
Pantoprazole		58 (14.4)	51 (12.7)	
Rabeprazole		3 (0.7)	5 (1.2)	
Esomeprazole		27 (6.7)	46 (11.4)	
Omeprazole equivalent daily dose, mg/day *	322	5 (0, 20)	12.5 (0, 20)	0.9
Diuretics				
Loop, n (%)	402	66 (16.4)	75 (18.7)	0.5
Potassium sparing, n (%)	402	21 (5.2)	17 (4.2)	0.6
Thiazide, n (%)	402	56 (13.9)	35 (8.7)	0.02

* Median with 25th and 75th percentiles; GERD denotes gastro-esophageal reflux disease; eGFR, estimated glomerular filtration rate; P values are calculated using paired t-test, McNemar's test or Wilcoxon signed-rank test, where appropriate. Multilevel factorial variables are presented with global P values and were analyzed using conditional logistic regression.

Table 2

Diagnostic performance characteristics of *method 1* (use of physician admission and discharge notes in the electronic medical record) and *method 2* (use of nursing electronic medication administration record) for assessment of proton pump inhibitor use.

Performance characteristic	Method 1	Method 2
Sensitivity, %	91.1 (82.6, 96.4)	84.5 (72.6, 92.7)
Specificity, %	96.0 (86.3, 99.5)	46.2 (32.2, 60.5)
Positive predictive value, %	97.3 (90.6, 99.7)	63.6 (51.9, 74.3)
Negative predictive value, %	87.3 (75.5, 94.7)	72.7 (54.5, 86.7)
Accuracy, %	93.0 (87.2, 96.8)	66.4 (56.7, 75.1)

Manual chart review of 239 randomly selected hospitalizations was used as the gold standard. The parentheses correspond to the 95% confidence interval for the estimates. To ascertain the exposure variable, *method 1* was used in 39.1% of cases and 48.3% of controls, and *method 2*, in 60.9% and 51.7%, respectively.

Table 3

Unadjusted and adjusted analyses examining the association of proton pump inhibitor use with hypomagnesemia.

Predictor variable (conditional logistic regression)	Unadjusted analysis			Adjusted analysis		
	Number of pairs	OR (95% CI)	P value	Number of pairs	OR (95% CI)	P value
<i>PPI use</i>						
All matched cases	402	0.83 (0.63, 1.09)	0.2	397	0.82 (0.61, 1.11)	0.2
Matched cases with GERD	215	1.20 (0.81, 1.78)	0.4	210	1.16 (0.76, 1.76)	0.5
Matched cases with esophageal disorders (including GERD)	285	1.00 (0.71, 1.41)	0.9	282	1.00 (0.69, 1.45)	0.9
Matched cases with serum magnesium 1.0 mEq/L	31	0.55 (0.20, 1.48)	0.2	26	0.78 (0.13, 4.61)	0.8
Matched cases with eGFR 60 ml/min per 1.73m ²	178	0.77 (0.51, 1.16)	0.2	178	0.84 (0.53, 1.34)	0.5
Matched cases with admission medication list	127	0.78 (0.47, 1.27)	0.3	125	0.77 (0.44, 1.36)	0.4
<i>PPI type</i>	402		0.1	397		0.1
None		1.00			1.00	
Omeprazole		0.75 (0.47, 1.18)			0.76 (0.47, 1.24)	
Lansoprazole		0.95 (0.66, 1.36)			0.96 (0.66, 1.42)	
Pantoprazole		1.02 (0.66, 1.58)			0.97 (0.61, 1.53)	
Rabeprazole		0.54 (0.13, 2.31)			0.58 (0.13, 2.65)	
Esomeprazole		0.52 (0.30, 0.89)			0.47 (0.26, 0.83)	
<i>Omeprazole equivalent daily dose (per 10 mg/day increase)</i>	322	0.99 (0.89, 1.10)	0.9	317	0.98 (0.88, 1.10)	0.8

Analyses adjusted for Charlson-Deyo comorbidity index (0, 1, 2, 3), diabetes mellitus (yes/no); GERD (yes/no); use of diuretics (yes/no for each diuretic type), and eGFR (ml/min/1.73m²). GERD denotes gastro-esophageal reflux disease; eGFR, estimated glomerular filtration rate