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Proton Pump Inhibitor Usage and the Risk of Mortality in Hemodialysis Patients

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Introduction: Long-term inappropriate proton pump inhibitors use (PPIs) is a matter of concern because of the risks associated with their long-term use in older patients with chronic conditions. The risk of PPI treatment in hemodialysis patients remains unexplored.

Methods: We assessed the relationship between the use of PPIs and the risk of death in hemodialysis patients throughout a retrospective multicenter propensity score–matched study. Information about demographic, hemodialysis treatment, laboratory data, and concomitant medication was obtained from the EuCliD database (Fresenius Medical Care). We studied 1776 hemodialysis patients on PPI therapy compared to 466 patients not receiving PPIs. The resulting population comprising 2 groups of 410 matched patients was studied.

Results: PPI use was associated with hypomagnesemia (Mg $<$1.8 mg/dl (0.75 mmol/l); odds ratio [OR] = 2.70, 95% confidence interval [CI] = 1.38−5.27, $P < 0.01$). The exposure to PPIs in the full patient cohort was identified as an independent predictor for all-cause mortality in both univariate (HR = 3.16, 95% CI = 1.69–5.90, $P < 0.01$) and multivariate (HR = 2.70, 95% CI = 1.38–5.27, $P < 0.01$) Cox regression models. Moreover PPI use was identified as a predictor of CV mortality (HR = 1.51, 95% CI = 1.05−2.20, $P = 0.03$) Of the 820 patients matched throughout the propensity score analysis, the hazard ratios for all-cause mortality (HR = 1.412, 95% CI = 1.04–1.93, $P = 0.03$) and CV mortality (HR = 1.67, 95% CI = 1.03−2.71, $P = 0.04$) were higher among patients on PPIs versus those not on PPIs.

Conclusion: The study data suggest that the PPI treatment should be regularly monitored and prescribed only when indicated.

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Proton pump inhibitors (PPI) are among the most commonly prescribed drugs. However the uncritical use of PPIs to treat symptoms that are not caused by an underlying acid-related disease is a widespread problem. Recent findings suggest that PPIs may be inappropriately prescribed in 50% to 80% of patients who are admitted to geriatric and internal medicine wards in acute care hospitals.[1] Strid *et al.* concluded that PPIs were prescribed to 41% of chronic kidney disease (CKD) patients who lacked an adequate indication; this figure was 13% in hospitalized patients and 18% in patients with chronic lung disease.[2]

Although there may have been some confounding factors, recent studies have associated PPI use with complications such as vitamin B_{12} deficiency,[3] neurological disturbances,[4] impaired magnesium absorption,[5] fracture risk,[6] *Clostridium difficile* infection,[7] and community-acquired pneumonia.[8] Other studies have shown increased hazards of cardiovascular (CV) disease and death with PPI use,[9–11] and it is also associated with a higher risk of incident CKD.[12] Recently Xie *et al.* studied the risk of renal outcomes in 1:1 propensity score−matched cohorts of patients taking H2 blockers versus patients taking PPIs and in patients taking PPIs versus controls.[13] The authors concluded that PPI exposure is associated with increased risk of incident CKD, CKD progression, and ESRD.

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Both CV problems and PPI use are very prevalent in hemodialysis (HD) patients. Notably, CV diseases are the leading cause of death among HD patients. Risk factors for CV diseases include hypertension, diabetes mellitus, hyperlipidemia, anemia, left ventricular hypertrophy, and chronic inflammation.[14,15] In the prospective observational Dialysis Outcomes and Practice Patterns Study, PPI prescribing patterns were investigated in 8628 HD patients from 7 countries. That study found that PPI use was very prevalent and that PPIs were more likely to be prescribed in France (25.7% of HD patients), Spain (26.9%), and the United Kingdom (27.3%) than in the United States (19.3%).[16] PPI use has been associated with hypomagnesemia,[5,17] and lower serum magnesium levels are associated with higher mortality in HD patients, including those with hypoalbuminemia.[18,19]

The aim of this study was to investigate associations among the use of PPIs, hypomagnesemia, and the risk of CV and all-cause mortality in a large, unselected cohort of HD patients. By mimicking the randomization used in clinical trials, propensity score matching (PSM) aims to achieve balance between treatment groups with regard to measured confounders and thus to minimize bias when estimating the effect of therapies. This study aimed to use PSM to control for systematic differences between HD patients on PPIs and those not on PPIs, and to investigate the effect of PPI therapy on mortality.

METHODS

Patients and Study Design

This retrospective, multicenter, intention-to-treat, PSM study analyzed the effects of PPIs on all-cause mortality and CV mortality in HD patients. As a secondary outcome, it evaluated the effects of these drugs on serum magnesium levels.

The study population comprised prevalent and stable outpatients who received HD treatment from 1 January 2014 to 30 March 2014. This was considered the baseline period. Patients were followed up until 30 September 2016 at any of the Fresenius Medical Care (FMC) NephroCare dialysis clinics in Spain. Patients were included in the study if they maintained a HD regimen of 3 sessions per week. The exclusion criteria were age less than 18 years and having a prescription for diuretics, which meant any drug in the C03 subgroup of the Anatomical Therapeutic Chemical (ATC) Classification System, or magnesium-containing compounds, which meant any drug with A12CC or A12AX ATC codes. The study included a total of 2242 patients from 40 different HD units. All patients completed informed written consent forms for the use of their clinical and demographical data in accordance with the corresponding Data Protection Agency standards and also to introduce them to the EuCliD database, the FMC clinical data system that has been used in other epidemiological studies[20–22] and that was described previously for the Spanish population.[23]

Treatment Protocol

The attending nephrologist at each center provided routine patient care and managed medication prescriptions. Standard HD (HD) and OL-HDF treatments were performed with FX-class High-Flux Dialysers and High-Flux Hemo*dia*filters with 4008S or 5008 monitors (Fresenius Medical Care, Bad Homburg, Germany). The treatment targets were determined according to Spanish FMC guidelines, which recommends a target weekly treatment length of 720 minutes and a dialysis dose goal of Kt/V>1.4. Patients were dialyzed 3 times per week with ultrapure dialysate containing less than 0.1 colony forming units per milliliter and less than 0.03 endotoxin units per milliliter. The dialysate included sodium (140 mmol/l), magnesium (0.50 mmol/l), glucose (1 g/l), customized potassium (1.5–3 mmol/l), and calcium (1.25–1.75 mmol/l) according to the clinical characteristics of each patient.

Study Variables

We recorded the following baseline data: age (years), gender (female), dialysis vintage (months), diabetes mellitus status (categorized as yes/no) and Charlson Comorbidity Index. We recorded the following HD treatment clinical characteristics: vascular access (categorized as arteriovenous fistula [AVF] or catheter; prosthetic AVF was included in the AVF category); treatment technique, that is, HD or postdilution OL-HDF dialysis mode; Kt/v; effective treatment time (Td, minutes); and systolic blood pressure (SBP), measured before the HD session and calculated as the average of the baseline period measurements. We also measured the average relative overhydration (AvROH) with a body composition monitor, which was calculated as the average during the baseline period. Blood samples for laboratory assessments were drawn routinely, and the following were determined: albumin, hemoglobin (Hb), C-reactive protein (CRP), magnesium, calcium, and 25-hydroxycholecalciferol (VitD). Medication prescriptions during the baseline period were recorded as "yes" or "no" for each studied drug for each patient. We recorded the prescription of any PPI (i.e., any drug in the A02BC ATC subgroup). To look at potential drug−drug interactions between PPIs and some anticoagulant agents, we recorded prescriptions of vitamin K antagonists (drugs in the B01AA ATC subgroup, including acenocoumarol [Sintrom; Madrid, Spain] or warfarin), platelet aggregation inhibitors, excluding

heparin (drugs in the B01AC ATC subgroup, including clopidogrel or acetylsalicylic acid), and systemic corticosteroids (drugs in the H01 ATC subgroup).

Statistical Analysis

Continuous variables are reported as means and standard deviations (SD) or as medians and 25th and 75th percentiles, as appropriate. Categorical variables are reported as percentages. Bivariate comparisons between cohorts were performed using the *t* test for normally distributed variables, the Wilcoxon rank-sum test for continuous parameters that were not normally distributed, or the χ^2 test for categorical variables.

Factors that influence serum magnesium levels were studied 6 months after the individual's baseline data were recorded. To build these subanalyses, we selected those patients with a complete 6-month follow-up period. Univariate and multivariate logistic regression analyses were performed to identify factors that predicted hypomagnesemia, which was defined as total serum magnesium levels lower than 1.8 mg/dl (0.75 mmol/l). The corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable recorded in the study.

For survival analyses, follow-up time was defined as the period between the baseline and the last confirmed follow-up or the date of death. For all-cause mortality, we used several Kaplan−Meier survival curves that were compared using log-rank tests. To investigate possible independent predictors of mortality, univariate and multivariate Cox regression models were used to calculate the corresponding hazard ratios (HRs) and to estimate the 95% CIs.

The linear effects of the continuous variables for both risk models that were used in the study and described above were investigated using several univariate models. The corresponding cut-off values were chosen to ensure balanced groups that were clinically relevant. For age, the cut-offs were ≤55, 56 to 65, 66 to 75, and >76 years. For dialysis vintage, the cut-offs were ≤24, 24.01 to 48.00, 48.01 to 72, and >72.01 months. For SBP, the cut-offs were ≤115, 115.01 to 125.00, 125.01 to 140.0, 140.01 to 155.00, and >155.01 mm Hg. For AvROH, the cut-offs were ≤4.00, 4.01 to 10.00, 10.01 to 15.00, and >15%. For albumin, the cut-offs were ≤3.50, 3.51 to 4.00, and >4.00 g/dl. For Hb, the cut-offs were ≤10.00, 10.01 to 11.00, 11.01 to 12.00, 12.01 to 13.00, and >13.00 g/dl. For CRP, the cut-offs were ≤2.0, 2.01 to 5.0, 5.01 to 13.00, and >13.0 mg/l. For calcium, the cut-offs were ≤8.40, 8.41 to 9.00, 9.01 to 9.50, and 9.51 mg/dl. For VitD, the cut-offs were ≤10.0, 10.01 to 15.00, 15.01 to 30.00, and >30.01 ng/dl. In the Cox models, magnesium levels were introduced as a split covariate with the following cut-off values: ≤2.09, 2.1 to 2.30, 2.31 to 2.50, and >2.51 mg/dl. On the contrary, Kt/V and Td were introduced as continuous variables.

The other covariates that were included in the corresponding risk models were gender (reference: female), diabetes mellitus (reference: none), Charlson Comorbidity Index (excluding age and diabetes mellitus); vascular access (reference AVF); treatment mode (reference: HD); Kt/V, Td, vitamin K antagonists (including acenocoumarol or warfarin; reference: none); platelet aggregation inhibitors, excluding heparin (including clopidogrel or acetylsalicylic acid; reference none); and systemic corticosteroid use.

An additional approach was performed to study the relation between the PPI exposure and the outcomes, considering a competing risks scenario. This consists of constructing several adjusted competing risks regression models to calculate the corresponding subdistribution hazard ratios (SHR) for all-cause mortality following the approach proposed by Fine and Gray.[24]

This was an observational study, so patients were not randomly assigned to receive or not to receive PPIs. Thus, we used PSM to minimize confounding by indication as a sensitivity analysis. Then we calculated the propensity score for each patient by modeling the probability of receiving or not receiving PPIs by the subsequent multivariate logistic regression models. Demographic features, HD clinical parameters, laboratory values, and concomitant antithrombotic medication were included for the proper estimation of the propensity scores. The resulting scores were used to match the groups on a 1:1 basis using a caliper-matching algorithm. We performed PSM by fixing a caliper parameter that was the equivalent of 0.2 of the pooled SD of the logit of the propensity scores.[25] After conducting the PSM, there were 1422 unmatched patients, leaving 820 matched patients for statistical analysis (410 in each group). Finally, to ensure the quality of the pairings from the PSM, we evaluated the balance in the covariates using the standardized differences before and after matching between the groups, considering that differences <0.1 were of negligible imbalance[26] and by making the appropriate bivariate comparisons.

Analyses were performed with IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY). The Fine and Gray competing risks regression models were run using the SPSS extension command COMPRISK, which uses the R "cmprsk" package.[27] The PSM was performed using SPSS R-Menu[28] using in both cases the R statistical free software version R3.1.1. Statistical significance was set at $P < 0.05$.

RESULTS

Demographic and Laboratory Data

This study included 2242 patients who were treated at 40 HD facilities in Spain, 1776 (79.2%) of whom were on PPI therapy. Table 1 shows the baseline characteristics of the patients in this cohort. The patients on PPIs had been treated longer with HD, had more catheters for vascular access, had lower SBP, had lower serum albumin, had lower serum magnesium levels (no PPI mean and 95% CI = 2.41 mg/dl (2.37−2.44)/PPI: 2.30 mg/dl (2.27−2.31), and a lower percentage had online hemodiafiltration (OL-HDF) as a treatment option. In addition, the percentage of patients using antithrombotic agents was higher in the group of patients on PPI therapy compared to the group not on PPI therapy.

Identifying Hypomagnesemia Predictors

Total serum hypomagnesemia was defined as magnesium levels <1.8 mg/dl (<0.75 mmol/l). In all, 137 (6.1%) of the 2242 included patients had hypomagnesemia. The PPI use was higher in the hypomagnesemia group (92.0% vs. 78.4%; $P < 0.01$). Univariate and multivariate logistic regression models were used to identify predictors that might have an impact on hypomagnesemia (Table 2). PPI use was significantly associated with hypomagnesemia, by both univariate (OR = 3.16; 95% CI = 1.69–5.90, $P < 0.01$) and multivariate (OR = 2.70; 95% CI = 1.38–5.27, $P < 0.01$) analysis. Moreover, OL-HDF, pre-HD SBP, and serum calcium levels were independent predictors for hypomagnesemia in HD patients.

Table 1. Baseline characteristics of the entire study population (N = 2242)

	No PPI (n = 466)	PPI (n = 1776)	*P*
Demographics			
Age, yr	68.50 (56–76)	68.00 (57–76)	0.69
Gender, female	33.92%	38.14%	0.09
Dialysis vintage, mo	32.19 (16.56–67.96)	45.60 (21.77–79.15)	<0.01
Diabetes mellitus	31.94%	33.06%	0.65
Charlson Comorbidity Index[a]	2 (2–3)	2 (2–3)	0.24
HD clinical parameters			
AVF	74.45%	69.65%	0.05
OL-HDF	53.74%	44.84%	<0.01
Kt/v	1.9 ± 0.38	1.93 ± 0.4	0.17
Td, min	245.92 ± 11.87	246.22 ± 13	0.65
SBP pre-HD, mm Hg	134.91 ± 21.72	132.58 ± 23	0.04
AvROH	9.79 (4.23–14.39)	9.7 (4.26–14.54)	0.88
Laboratory values			
Albumin, g/dl	3.89 ± 0.36	3.85 ± 0.36	0.03
Hemoglobin, g/dl	11.71 ± 1.36	11.75 ± 1.38	0.62
CRP, mg/l	5.00 (1.80–12.48)	5.92 (2.00–13.58)	0.14
Magnesium, mg/dl	2.41 ± 0.38	2.30 ± 0.36	<0.01
Calcium, mg/dl	9.02 ± 0.53	8.96 ± 0.85	0.15
VitD, ng/dl	15.7 (10.9–24)	15.5 (10.1–25)	0.89
Antithrombotic agents			
Vitamin K antagonists[b]	7.73%	11.71%	0.01
Platelet aggregation inhibitors excluding heparin[c]	40.13%	55.07%	<0.01
Systemic corticosteroids	3.43%	7.55%	<0.01

AVF, arteriovenous fistula; AvROH, average relative overhydration; CRP, C-reactive protein; HD, hemodialysis; OL-HDF, online hemodiafiltration; PPI, proton-pump inhibitor; SBP pre-HD, systolic blood pressure measured before hemodialysis session; Td, effective treatment time; VitD, 25-hydroxycolecalciferol.
[a]Charlson Comorbidity Index: excluding age and diabetes mellitus.
[b]Vitamin K antagonists: including acenocoumarol or warfarin.
[c]Platelet aggregation inhibitors excluding heparin: including clopidogrel or acetylsalicylic acid.

Proton Pump Inhibitors and Mortality

Patients were followed up until they left the FMC clinics for any reason or until death. The overall mean follow-up time was 22.81 ± 9.18 months. During the follow-up period, 560 patients dropped out of the study because of kidney transplantation (45.17%), changes in HD unit (n = 43.77%), or other reasons (11.09%). All of these patients were censored at the time that they dropped out of the study.

There were 515 deaths during the study, including 433 patients who were on PPIs and 82 patients who were not on PPIs. The causes of mortality were CV related (43.30%), infection (19.22%), sudden death (16.12%), oncological disease (7.38%), and other causes (13.98%). The resulting 90% and 80% survival time and the corresponding 95% CIs were 10.97 (10.94−10.98) and 20.23 (20.20−20.25) months for the PPI group and 14.27 (14.23−14.29) and 26.81(26.75−26.86) months for the non-PPI group, respectively. The Kaplan–Meier analysis of the entire patient cohort showed significantly worse survival (log-rank = 7.44; $P = 0.01$) for patients on PPI therapy (Figure 1). The Kaplan–Meier analysis of the entire patient cohort that considered only CV-related disease also showed significantly worse survival (log-rank = 4.889; $P = 0.03$) for patients on PPI therapy (Figure 1).

The independent predictors of all-cause mortality in the entire patient cohort were identified throughout several Cox regression models using the original scale for each variable (Supplementary Table S1) and also by analyzing the nonlinear effects of the continuous variables (Table 3). PPI exposure was identified as an independent predictor of all-cause mortality in the univariate analysis (HR = 1.39, 95% CI = 1.10–1.76, $P = 0.01$) and both multivariate (HR = 1.34, 95% CI = 1.03–1.75 $P = 0.03$; HR nonlinear effects = 1.37, 95% CI = 1.05–1.78, $P = 0.02$) regression models. Also the PPI exposure was also a significant factor in CV mortality (HR = 1.51, 95% CI = 1.05–2.20, $P = 0.03$). Other independent predictors of all-cause mortality were age, dialysis vintage, diabetes mellitus, Charlson Comorbidity Index, vascular access, pre-HD SBP, AvROH, albumin, C-reactive protein level, serum calcium level, and exposure to vitamin K antagonists or platelet aggregation inhibitors.

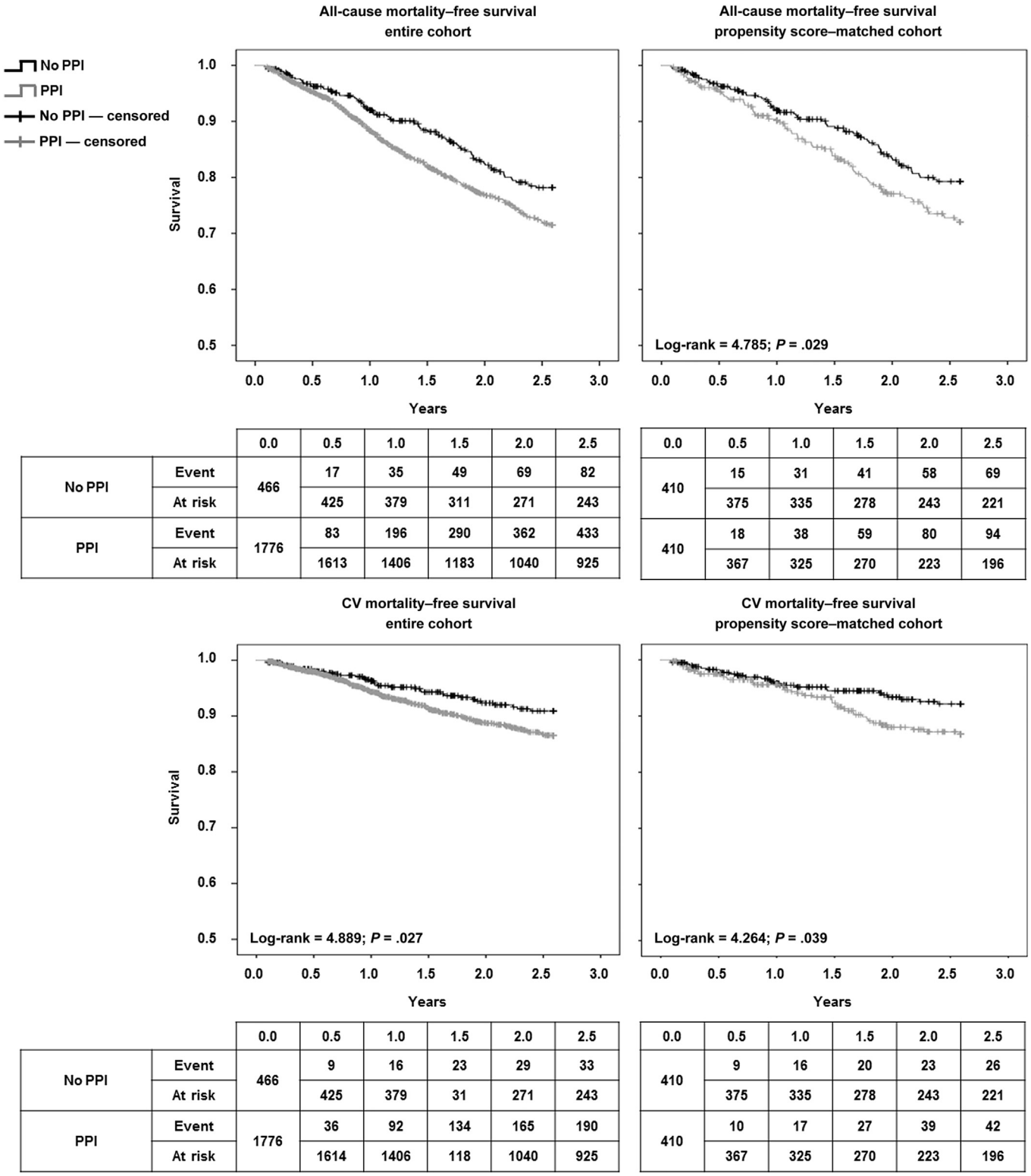
Table 2. Logistic regression models to identify predictors with a potential impact on hypomagnesemia (<1.8 mg/dl or <0.75 mmol/l)

	Univariate analysis				Multivariate analysis			
		95% CI				95% CI		
	OR	Lower	Upper	*P*	OR	Lower	Upper	*P*
PPI								
Ref: no	3.16	1.69	5.90	<0.01	2.70	1.38	5.27	<0.01
Demographics								
Age, yr								
Ref: ≤55	-	-	-	-	-	-	-	-
56–65	0.63	0.35	1.13	0.12	0.49	0.25	0.98	0.04
66–75	0.70	0.40	1.20	0.19	0.69	0.35	1.37	0.29
>76	0.51	0.30	0.85	0.01	0.40	0.21	0.76	0.01
Gender								
Ref: female	0.88	0.61	1.27	0.49	0.75	0.49	1.15	0.19
Dialysis vintage, mo								
Ref: ≤24.0	-	-	-	-	-	-	-	-
24.01–48.00	0.60	0.38	0.96	0.03	0.57	0.34	0.95	0.03
48.01–72.00	0.75	0.44	1.28	0.30	0.92	0.49	1.72	0.080
>72.01	0.92	0.56	1.49	0.73	0.91	0.52	1.59	0.73
Diabetes mellitus								
Ref: no	0.88	0.61	1.26	0.49	0.86	0.56	1.31	0.49
Charlson Comorbidity Index[a]	0.91	0.78	1.06	0.22	0.95	0.80	1.13	0.58
HD clinical parameters								
VCC								
Ref: AVF	0.74	0.52	1.06	0.11	0.98	0.63	1.53	0.92
OL-HDF								
Ref: HD	1.80	1.25	2.60	<0.01	1.71	1.14	2.55	0.01
Kt/V	0.99	0.97	1.00	.086	0.80	0.44	1.43	0.44
Td, min	0.99	0.97	1.00	.086	0.98	0.97	1.00	0.04
SBP pre-HD, mm Hg								
≤115.00	1.29	0.80	2.09	.294	1.96	1.10	3.48	0.02
115.01–125.00	1.16	0.69	1.96	.582	1.14	0.64	2.04	0.65
Ref: 125.01–140.0	-	-	-	-	-	-	-	-
140.01–155.0	1.94	1.15	3.26	0.01	1.85	1.04	3.30	0.04
>155.01	1.79	1.01	3.18	0.05	1.94	1.02	3.68	0.04
AvROH								
≤4.00	0.90	0.55	1.48	0.68	0.87	0.49	1.57	0.65
Ref: 4.01–10.00	-	-	-	-	-	-	-	-
10.01–15.00	0.72	0.45	1.15	0.17	0.62	0.37	1.06	0.08
>15.01	0.92	0.55	1.54	0.76	1.00	0.55	1.81	0.99
Laboratory values								
Albumin, g/dl								
<3.5	0.57	0.38	0.87	0.01	0.66	0.42	1.07	0.09
3.5–4.0	-	-	-	-	-	-	-	-
Ref: >4.0	1.91	1.22	3.01	0.01	1.33	0.79	2.25	0.28
Hemoglobin, g/dl								
<10.0	0.68	0.38	1.20	0.18	0.66	0.33	1.30	0.28
10.0–11.0	0.87	0.54	1.42	0.58	0.88	0.50	1.55	0.67
Ref: 11.0–12.0	-	-	-	-	-	-	-	-
12.0–13.0	1.33	0.79	2.24	0.28	1.21	0.68	2.17	0.52
>13.0	0.89	0.53	1.49	0.66	0.95	0.52	1.73	0.86
CRP, mg/l								
Ref: <2	-	-	-	-	-	-	-	-
2.01–5.0	1.16	0.67	1.99	0.60	1.20	0.65	2.22	0.56
5.01–13.0	1.06	0.65	1.72	0.83	1.23	0.70	2.18	0.47
>13.0	0.76	0.48	1.21	0.25	0.98	0.57	1.70	0.95
Calcium, mg/dl								
Ref: <8.40	-	-	-	-	-	-	-	-
8.41–9.00	1.50	0.98	2.31	0.06	1.80	1.09	2.97	0.02
9.01–9.50	2.58	1.57	4.21	<0.01	2.96	1.65	5.30	<0.01
>9.51	7.74	3.00	19.94	<0.01	8.93	3.01	26.47	<0.01
VitD, ng/dl								
≤10.00	1.35	0.75	2.40	.315	1.25	0.64	2.45	0.52
10.01–15.00	1.45	0.80	2.62	.226	1.26	0.66	2.39	0.48
15.01–30.00	1.12	0.66	1.89	.670	0.96	0.55	1.68	0.89
>30.01	-	-	-	-	-	-	-	-
Antithrombotic agents								
Vitamin K antagonists[b]								
Ref: no	0.52	0.33	0.82	0.01	0.61	0.36	1.03	0.06
Platelet aggregation inhibitors excluding heparin[c]								
Ref: no	1.14	0.81	1.61	0.46	1.15	0.75	1.76	0.51
Systemic corticosteroids								
Ref: no	0.90	0.46	1.76	0.77	1.62	0.63	4.19	0.31

AVF, arteriovenous fistula; AvROH, average relative overhydration; CI, confidence interval; CRP, C-reactive protein; HD, hemodialysis; OL-HDF, online hemodiafiltration; OR, odds ratio; PPI, proton pump inhibitor; Ref, reference; SBP pre-HD, systolic blood pressure measured before the hemodialysis session; Td, effective treatment time; VCC, venous central catheter; VitD, 25-hydroxycolecalciferol.
[a]Charlson Comorbidity Index: excluding age and diabetes mellitus.
[b]Vitamin K antagonists: including acenocoumarol or warfarin.
[c]Platelet aggregation inhibitors excluding heparin: including clopidogrel or acetylsalicylic acid.

Further examination for CV mortality as the outcome of interest was performed using competing risks methods to account for non-CV mortality as a competing event. Moreover, as this study was conducted in a routine clinical practice scenario, both the "other" drop-out reasons as well as the independent predictors of all-cause mortality previously isolated were considered to build these multivariate competing risks regression analysis. Again, the PPI exposure was identified as an independent predictor of all-cause mortality (SHR = 1.33, 95% CI = 1.09–1.56, $P < 0.01$) and CV mortality (SHR = 1.432, 95% CI = 1.05–1.81, $P = 0.04$) in both cases.

Because of the observational nature of this study, we used PSM for the sensitivity analysis for the main outcome to minimize the effects of confounding. We then tried to balance these populations for every covariate. The baseline characteristics after PSM are shown in Table 4. After PSM, mortality was compared in the 410 patients who were on PPIs versus the 410 patients who were not on PPIs. The results were consistent with our findings for the entire patient cohort. Kaplan–Meier analysis for all-cause mortality and CV mortality in the adjusted cohort showed significantly worse survival for patients on PPI therapy (log-rank = 4.785, $P = 0.03$, and log-rank = 4.264, $P = 0.04$, respectively) (Figure 1). Cox models



		0.0	0.5	1.0	1.5	2.0	2.5
No PPI	Event	466	17	35	49	69	82
	At risk		425	379	311	271	243
PPI	Event	1776	83	196	290	362	433
	At risk		1613	1406	1183	1040	925

		0.0	0.5	1.0	1.5	2.0	2.5
410			15	31	41	58	69
			375	335	278	243	221
410			18	38	59	80	94
			367	325	270	223	196

		0.0	0.5	1.0	1.5	2.0	2.5
No PPI	Event	466	9	16	23	29	33
	At risk		425	379	31	271	243
PPI	Event	1776	36	92	134	165	190
	At risk		1614	1406	118	1040	925

		0.0	0.5	1.0	1.5	2.0	2.5
410			9	16	20	23	26
			375	335	278	243	221
410			10	17	27	39	42
			367	325	270	223	196

Figure 1. Kaplan–Meier survival plots for (upper panels) all-cause mortality and (lower panels) cardiovascular (CV) mortality, both (left panels) in the entire population and (right panels) after the propensity score–matching adjustment. The resultant survival curves for patients on proton pump inhibitors (PPIs) are shown in gray, whereas the curves for patients not on PPIs are shown in black. Corresponding log-rank test results and survival tables are also shown.

identified PPI exposure as an independent predictor of all-cause mortality (HR = 1.41, 95% CI = 1.04–1.93, P = 0.03) and CV mortality (HR = 1.67, 95% CI = 1.03–2.71, P = 0.04). The corresponding Fine and Gray regression models performed in the PSM-adjusted population showed the same results as the Cox models for all-cause mortality (SHR = 1.41, 95% CI = 1.11–1.73, P = 0.03) and CV mortality

Table 3. Univariate and multivariate Cox regression analysis of all-cause mortality in the entire study population

	Univariate analysis				Multivariate Cox analysis			
		95% CI				95% CI		
	HR	Lower	Upper	*P*	HR	Lower	Upper	*P*
PPI								
Ref: no	1.39	1.10	1.76	0.01	1.37	1.05	1.78	0.02
Demographics								
Age, yr								
Ref: ≤55	-	-	-	-	-	-	-	-
56–65	1.76	1.23	2.52	<0.01	1.41	0.94	2.12	0.10
66–75	2.61	1.90	3.58	<0.01	2.14	1.49	3.08	<0.01
> 76	3.71	2.72	5.05	<0.01	3.41	2.37	4.90	<0.01
Gender								
Ref: female	1.04	0.87	1.25	0.07	1.11	0.90	1.36	0.33
Dialysis vintage, mo								
Ref: ≤24.0	-	-	-	-	-	-	-	-
24.01–48.00	1.17	0.91	1.50	0.21	1.04	0.79	1.38	0.76
48.01–72.00	1.34	1.03	1.74	0.03	1.38	1.03	1.84	0.03
>72.01	1.30	1.03	1.64	0.03	1.65	1.27	2.15	<0.01
Diabetes mellitus								
Ref: no	1.48	1.25	1.77	<0.01	1.54	1.26	1.90	<0.01
Charlson Comorbidity Index[a]	1.15	1.07	1.24	<0.01	1.12	1.04	1.22	0.01
HD clinical parameters								
VCC								
Ref: AVF	1.50	1.26	1.80	<0.01	1.29	1.06	1.58	0.01
OL-HDF								
Ref: HD	0.93	0.78	1.10	0.40	0.90	0.72	1.11	0.31
Kt/V	1.02	0.82	1.27	0.86	1.03	0.77	1.39	0.83
Td, min	0.99	0.99	1.00	0.01	0.99	0.99	1.00	0.15
SBP pre-HD, mm Hg								
≤115.00	1.25	0.99	1.59	0.06	1.10	0.83	1.44	0.51
115.01–125.00	0.93	0.70	1.24	0.64	0.91	0.66	1.24	0.54
Ref: 125.01–140.0	-	-	-	-	-	-	-	-
140.01–155.0	0.79	0.61	1.02	0.07	0.79	0.59	1.05	0.11
>155.01	0.76	0.56	1.01	0.06	0.81	0.59	1.12	0.20
AvROH								
≤4.00	1.23	0.95	1.60	0.12	1.41	1.05	1.88	0.02
Ref: 4.01–10.00	-	-	-	-	-	-	-	-
10.01–15.00	1.43	1.12	1.83	0.01	1.50	1.14	1.97	0.01
>15.01	1.72	1.34	2.20	<0.01	1.74	1.32	2.29	<0.01
Laboratory values								
Albumin, g/dl								
<3.5	1.68	1.36	2.09	<0.01	1.40	1.10	1.79	0.01
3.5–4.0	-	-	-	-	-	-	-	-
Ref: >4.0	0.62	0.50	0.77	<0.01	0.71	0.55	0.91	0.01
Hb, g/dl								
<10.0	1.68	1.25	2.25	<0.01	1.35	0.97	1.89	0.08
10.0–11.0	1.27	0.99	1.62	0.06	1.12	0.85	1.48	0.41
Ref: 11.0–12.0	-	-	-	-	-	-	-	-
12.0–13.0	1.13	0.88	1.44	0.33	1.06	0.80	1.39	0.68
>13.0	1.06	0.81	1.39	0.68	0.98	0.73	1.34	0.92
CRP, mg/l								
Ref: <2	-	-	-	-	-	-	-	-
2.01–5.0	1.61	1.21	2.16	<0.01	1.69	1.22	2.33	0.01
5.01–13.0	1.85	1.42	2.42	<0.01	1.85	1.36	2.51	<0.01
>13.0	2.53	1.95	3.28	<0.01	2.37	1.77	3.17	<0.01
Magnesium, mg/dl								
<2.09	1.54	1.21	1.96	<0.01	0.91	0.68	1.22	0.52
2.10–2.30	1.40	1.08	1.83	<0.01	1.00	0.75	1.35	0.99
2.31–2.50	1.23	0.93	1.61	0.15	1.06	0.79	1.43	0.71
Ref: >2.51	-	-	-	-	-	-	-	-
Calcium, mg/dl								
Ref: <8.40	-	-	-	-	-	-	-	-
8.41–9.00	0.87	0.63	1.20	0.40	0.61	0.41	0.92	0.02
9.01–9.50	0.94	0.73	1.23	0.67	0.73	0.54	0.98	0.04
>9.51	1.05	0.80	1.37	0.72	0.99	0.74	1.33	0.94
VitD, ng/dl								
≤10.00	1.27	0.95	1.70	0.10	1.14	0.84	1.54	0.40
10.01–15.00	1.08	0.80	1.46	0.60	1.07	0.79	1.46	0.67
15.01–30.00	0.86	0.64	1.14	0.29	0.88	0.65	1.17	0.37
>30.01	-	-	-	-	-	-	-	-
Antithrombotic agents								
Vitamin K antagonists[b]								
Ref: no	1.61	1.28	2.04	<0.01	1.50	1.15	1.96	<0.01
Platelet aggregation inhibitors excluding heparin[c]								
Ref: no	1.33	1.12	1.59	<0.01	1.31	1.07	1.62	0.01
Systemic corticosteroids								
Ref: no	1.12	0.80	1.56	0.52	1.45	1.00	2.11	0.05

AVF, arteriovenous fistula; AvROH, average relative overhydration; CI, confidence interval; CRP, C-reactive protein; HD, hemodialysis; OL-HDF, online hemodiafiltration; PPI, proton pump inhibitor; Ref, reference; SBP pre-HD, systolic blood pressure measured before hemodialysis session; Td, effective treatment time; VCC, venous central catheter; VitD, 25-hydroxycolecalciferol.
[a]Charlson Comorbidity Index: excluding age and diabetes mellitus.
[b]Vitamin K antagonists: including acenocoumarol or warfarin.
[c]Platelet aggregation inhibitors excluding heparin: including clopidogrel or acetylsalicylic acid.

(SHR = 1.64, 95% CI = 1.24–2.24, $P = 0.03$) in both cases.

DISCUSSION

In this observational study, we used PSM to examine the effects of PPI therapy on the mortality of HD patients in Spain. Our data suggest an overall trend toward hypomagnesemia and increased all-cause mortality and CV mortality in HD patients on PPIs. Our findings are consistent with those of previous studies that also found increased hazards of CV disease and death with PPI use in other populations. Maggio *et al*. investigated the relationship between PPI use and study outcomes in patients 65 years or older who were discharged from acute care medical wards.[9] The authors concluded that high-dose PPI use was associated with increased 1-year mortality. Charlot *et al*. studied aspirin-treated patients with first-time myocardial infarction and found that treatment with PPIs was associated with an increased risk of adverse CV events.[10] Bell *et al*. observed that baseline PPI use was associated with all-cause mortality in 2 cohorts of institutionalized older persons.[11]

Table 4. Baseline characteristics in the propensity-matched cohort (n = 820)

Characteristic	No PPI (n = 410)	PPI (n = 410)	Standardized differences		P
			Before PSM	After PSM	
Demographics					
Age, yr	70 (56–76)	68 (59–77)	0.65	0.09	0.89
Gender, female	33.66%	38.05%	0.05	0.00	0.19
Dialysis vintage, mo	32.48 (17.18–70.75)	41.02 (21.1–76.35)	0.10	0.02	0.07
Diabetes mellitus	32.93%	36.10%	0.14	0.02	0.34
Charlson Comorbidity Index[a]	2 (2–3)	2 (2–3)	0.06	0.03	0.32
HD clinical parameters					
AVF	74.63%	71.71%	0.05	0.04	0.35
OL-HDF	57.56%	56.34%	0.10	0.04	0.75
Kt/v	1.92 ± 0.38	1.92 ± 0.39	0.14	0.08	0.90
Td, min	245.79 ± 11.39	246.6 ± 11.76	0.09	0.03	0.32
SBP pre-HD, mm Hg	134.98 ± 21.61	134.08 ± 22.51	0.03	0.01	0.56
AvROH	10.01 (4.78–14.42)	10.02 (4.09–14.81)	0.07	0.01	0.78
Laboratory values					
Albumin, g/dl	3.89 ± 0.35	3.85 ± 0.35	0.07	0.04	0.08
Hemoglobin, g/dl	11.74 ± 1.36	11.75 ± 1.4	0.13	0.03	0.96
CRP, mg/l	5.13 (1.9–12.95)	5.97 (2.11–12.25)	0.06	0.02	0.37
Magnesium, mg/dl	2.41 ± 0.37	2.37 ± 0.42	0.08	0.03	0.19
Calcium, mg/dl	9.04 ± 0.52	8.97 ± 0.54	0.32	0.02	0.07
VitD, ng/dl	15.7 (10.98–24)	15.35 (10–25.28)	0.07	0.05	0.75
Antithrombotic agents					
Vitamin K antagonists[b]	8.05%	9.51%	0.03	0.01	0.46
Platelet aggregation inhibitors excluding heparin[c]	37.32%	42.68%	0.12	0.02	0.12
Systemic corticosteroids	3.41%	3.66%	0.34	0.06	0.85

AVF, arteriovenous fistula; AvROH, average relative overhydration; CRP, C-reactive protein; HD, hemodialysis; OL-HDF, online hemodiafiltration; PPI, proton pump inhibitor; PSM, propensity score matching; SBP pre-HD, systolic blood pressure measured before hemodialysis session; Td, effective treatment time; VitD, 25-hydroxycolecalciferol.
[a]Charlson Comorbidity Index: excluding age and diabetes mellitus.
[b]Vitamin K antagonists: including acenocoumarol or warfarin.
[c]Platelet aggregation inhibitors excluding heparin: including clopidogrel or acetylsalicylic acid.

Two factors may be associated with the risk of death in HD patients: the high prevalence of CV disease[14,15] and the high use of PPIs. Bailie *et al*. investigated HD patients from 7 countries in the prospective observational Dialysis Outcomes and Practice Patterns Study and found that 0.8% to 26.9% were on PPI treatment, depending upon the country. In the present study, performed 16 years later using data collected at 40 HD facilities in Spain, 1776 of 2242 HD patients (79%) were on PPI therapy.[16] This is an extremely high percentage and should be kept in mind when considering medical management of HD patients. In fact, PPIs are very often prescribed outside of the approved indications.

PPIs are associated with an increased risk of vitamin and mineral deficiencies, including vitamin B_{12}, vitamin C, calcium, iron, and magnesium deficiencies, particularly in elderly and malnourished patients and in those on chronic HD and concomitant PPI therapy.[29] There are several case reports of hypomagnesemia detected in patients who use PPIs; their serum magnesium levels normalized once PPI treatment was stopped. Gau *et al*. showed that serum magnesium levels were lower in hospitalized patients who use PPIs versus those who did not use them.[30] Hypomagnesemia was reported to be linked to PPI use in HD patients.[31] Specifically, lower levels of serum magnesium were associated with a higher rate of PPI use in hypomagnesemic patients compared to normomagnesemic patients. The report concluded that hypomagnesemia might occur with PPI use in HD patients with dialysate magnesium levels of 0.5–0.375 mmol/l. In a systematic review that included a meta-analysis of 9 studies with a total of 115,455 patients, hypomagnesemia was more frequent in patients using PPIs (OR = 1.775), although there was significant heterogeneity among the included studies.[32] The U.S. Food and Drug administration has issued a warning that the prolonged use of PPIs may cause low serum magnesium levels, and recommends obtaining serum magnesium levels prior to prescribing PPI treatment in patients who are expected to use these drugs long term.[17]

The mechanism underlying hypomagnesemia that is associated with PPI use is still under investigation. PPIs may decrease intestinal magnesium absorption by interfering with both active absorption via transient receptor potential melastatin (TRPM) protein channels and with passive absorption through the paracellular pores.[33,34] PPIs may also affect the absorption of magnesium in the colon. The pH in the cecum is usually acidic due to the fermentation of carbohydrates, so PPI

inhibition of colonic proton pumps may increase the pH of the distal colon and indirectly decrease active magnesium absorption in the colon by TRPM6 and by passive paracellular transport.[35]

There are several possible mechanisms that could explain the relationship between PPIs and the risk of death. We speculate that hypomagnesemia could be considered for CV events and mortality. Low serum magnesium was associated with an increased risk of CHD mortality and sudden cardiac death in a prospective, population-based cohort study.[36] Hypomagnesemia was also significantly associated with an increased risk of mortality in HD patients.[37] In an FMC North American HD center, Lacson *et al*. found a clear increase in mortality rates in the 2 patient groups with the lowest serum magnesium levels (<0.65 and 0.65–0.8 mmol/l) compared to the group with the highest serum magnesium levels. There is sufficient evidence to indicate that hypomagnesemia significantly exacerbates the proarrhythmic effect of hypokalemia, particularly if it occurs in the presence of digoxin toxicity. Potassium and magnesium depletion are commonly concomitant and are associated with higher prevalence rates of ventricular arrhythmias.[38,39] Rapid changes in electrolyte levels that occur during HD, including low magnesium, low potassium, low calcium, and a pH shift from acidotic to alkaline conditions, create the perfect conditions for acute arrhythmia and sudden death or for subacute cardiac events. However our multivariate analysis did not identify magnesium levels as an independent all-cause mortality predictor.

Another factor that links PPIs to the risk of death relates to liver metabolism of clopidogrel and PPIs. This metabolic process may explain the reduction of efficacy of antithrombotics. Clinical studies of the risk of adverse CV events associated with the dual use of clopidogrel and PPIs show conflicting results.[40] Clopidogrel and PPIs are metabolized by the same hepatic isoenzyme, CYP2C19,[41] and PPIs might interfere with the conversion of clopidogrel to its active metabolite and thereby reduce its clinical benefit. However, PPIs also diminish the benefits of ticagrelor, a drug that does not require hepatic activation.[42] In our study, dual PPI and clopidogrel use was associated with a higher risk of all-cause mortality in the univariate and multivariate Cox regression analyses. This finding could be an example of reverse causality due to the observational nature of the study. A higher CV disease index could explain the higher rate of clopidogrel prescription. Nevertheless, in the PSM analysis, in which the compared groups did not differ according to clopidogrel therapy, PPI use was an independent factor for mortality.

Finally, another mechanism that connects PPIs and mortality relates to plasma asymmetrical dimethylarginine (ADMA) degradation. ADMA is an endogenous inhibitor of nitric oxide synthase, and elevated plasma ADMA is associated with increased risk of CV disease, likely because of its attenuation of the vasoprotective effects of endothelial nitric oxide synthase. Ghebremariam *et al*. found that PPIs elevate plasma ADMA levels and reduce nitric oxide levels and endothelium-dependent vasodilation in a murine model and in *ex vivo* human tissues.[43] PPIs increase ADMA levels because they bind to and inhibit the enzyme dimethylarginine dimethylaminohydrolase, which degrades ADMA. Notably, ADMA levels were found to predict renal disease progression and death in patients with moderate to severe renal insufficiency.[44] ADMA may be involved in the atherosclerosis process and may be an important factor in determining the risk of renal insufficiency.[45] As a consequence, PPI usage induces the dysregulation of vascular NOS, which may explain how PPIs increase long-term CV risk even in individuals who are not taking clopidogrel.

This study has several limitations. One limitation is the lack of information about duration of exposure to PPIs and therefore its intention-to-treat nature. In addition, the measurement of total magnesium may have overestimated the incidence of hypomagnesemia when significant hypoalbuminemia was present. Moreover, this could be more pronounced in the non-PPI patient group with low magnesium levels if this group had less opportunity to complete 6 months of follow-up. In this regard, a hypomagnesemia predictor analysis was not possible to perform using a full 6-month follow-up period for all the patients or further Cox regression models.

It should also be noted that only total serum magnesium was measured in this study, and because ionized magnesium is the active state in membrane and cell transport, cell polarization effects, and other mechanisms, the hypomagnesemia numbers may be biased.[46] Unmeasured confounders such as the residual renal function or other factors that are linked to poor prognosis in older patients, such as malnutrition, might also affect our results. Our only information about nutrition was the serum albumin level, which was significantly lower in patients on PPI treatment before PSM. It is also possible that PPI use is a marker of a frail population that has more comorbidities and polypharmacotherapy. Therefore, bias by indication cannot be wholly excluded. Moreover, in our study, non-incident PPI users were examined, and our analysis did not include a possible H2 blocker group as (negative) controls or consider the type of PPI, the duration of exposure, adherence, serum magnesium level before starting PPIs, or the proportion of patients with previous PPI use before enrollment. Despite previous PPI

use, some patients in the PPI group may consistently have had magnesium levels in the normal range during the study period.

On the other hand, our study of the interactions between PPI and hypomagnesemia in relation to mortality outcomes has several strengths, including the several adjustments performed in the different multivariate models and the use of PSM and robust findings that support our conclusion. However, despite the PSM apparently having resolved the imbalance between the 2 populations studied, we cannot exclude the possibility that it failed to produce 2 well-matched groups, and the analysis derived from this population could be affected by bias resulting from indication, reverse causality, or residual confounding phenomena. On the contrary, our data were derived from a large validated database that includes integrated clinical and biochemical data, which minimizes selection bias.

In conclusion, our results suggest that PPI use is associated with hypomagnesemia and with excess mortality risk in HD patients. Nevertheless our findings need to be confirmed in further randomized controlled trials analyzing the differences in mortality between patients who are new users in the drug and also by magnesium levels. In any case, balance between positive and possible negative effects should be considered before long-term exposure of HD patients to PPIs. In this population, the long-term use of PPIs may not often be warranted.

DISCLOSURE

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AUTHOR CONTRIBUTIONS

ALMdF acted as the principal investigator, conceptualized and designed the study, performed the literature review, drafted the initial paper, and approved the final paper as submitted. JV conceptualized and designed the study, supervised the review of the literature and the preparation of the paper, performed the statistical analysis, and approved the final paper as submitted. RR and JIM conceptualized and designed the study, performed the review of the literature, designed the figures, and approved the final paper as submitted. BC, SS, MS, JP, and PA substantially participated in the revision of the initial paper and approved the final paper as submitted.

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SUPPLEMENTARY MATERIAL

Table S1. Univariate and multivariate Cox regression analysis of all-cause mortality in the entire study population. Supplementary material is linked to the online version of the paper at www.kireports.org.

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