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Original Articles

Large variations in prescriptions of gastrointestinal medications in hemodialysis patients on three continents: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Abstract

Little is known about proton pump inhibitor (PPI) or H_2 receptor antagonist (HA) prescription patterns or regarding use of predictors in hemodialysis patients. Proton pump inhibitor and HA prescribing patterns were investigated in 8628 hemodialysis patients from seven countries enrolled in the prospective, observational Dialysis Outcomes and Practice Patterns Study. Logistic regression examined predictors associated with PPI and HA use, adjusting for age, sex, country, time with end-stage renal disease, medications, 14 comorbid conditions, and the association between the number of comorbid conditions and the prescription of gastrointestinal (GI) medications. In a cross-section from February 1, 2000, 3.4% to 36.9% of patients received an HA and 0.8% to 26.9% took a PPI, depending upon the country. From 1996 to 2001, the prescription of HAs declined while PPI use increased. Facility use of HAs and PPIs ranged from 0% to 94% of patients. H_2 receptor antagonist or PPI use was significantly and independently associated with age, narcotic use, corticosteroids, acetaminophen, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, coronary artery disease history, cardiovascular diseases other than hypertension or congestive heart failure, peripheral vascular disease, pulmonary disease, and GI bleed. Proton pump inhibitors or HAs were more likely to be prescribed in Italy, Spain, and the United Kingdom than in the United States. The odds of PPI prescription increased if serum phosphorus <5.5 mEq/L or serum albumin <3.5 g/dL. Prescription of GI medications was associated with many comorbidities and use of several medications. Extreme variability of prescription patterns suggests that there is no standard approach in treatment practices.

Key words: Hemodialysis, gastrointestinal medications, proton pump inhibitors, H_2 receptor antagonists, prescription patterns, DOPPS

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INTRODUCTION

Patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) often have gastrointestinal (GI)

complications, such as chronic bleeds, gastritis, ulcers, nausea, vomiting, gastroesophageal reflux disease, and stasis.[1–4] Many medications are widely prescribed for these indications in both the general population and in patients with kidney disease. Care should be taken with use of these agents in patients with ESRD because of inherent characteristics of the drugs and dialysis.[5–10] Despite the high prevalence of indications for GI medications in the dialysis population, relatively little is known about proton pump inhibitor (PPI) and H_2 receptor antagonist (HA) prescription patterns, apart from frequency of use. The 1998 annual report from the United States Renal Data System (USRDS), which described data collected in 1996, showed that 30% of patients sampled were prescribed either agent, but did not specify the exact proportions of the agents used.[11] More recently, data from two studies documented the prescription rates of GI medications in several individual dialysis centers. One of these studies, reporting data collected in 1998, found that 42.2% of patients were prescribed either PPIs or HAs, representing a substantial increase in prescription rates over that reported in the USRDS data.[12] The second study, citing data collected in 2001, indicated that 62.4% of patients were prescribed either agent, with a higher proportion prescribed to diabetic patients (67.5%) than to nondiabetic individuals (55.4%).[13]

The present investigation used data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) to provide a more detailed examination of the prescription practices of PPIs and HAs, including patient characteristics associated with GI medication prescription and predictors of HA and PPI use.

METHODS

Data sources

This study used a sample of prevalent hemodialysis patients from February 1, 2000 from DOPPS I, a cross-sectional, prospective, observational study involving a sample of adult hemodialysis patients randomly selected from representative dialysis facilities in France, Germany, Italy, Spain, the United Kingdom, Japan, and the United States. This data set has been previously described.[14,15] Patients' data in this sample were taken from the survey closest to February 1, 2000, within 120 days of the date. Briefly, the major goal of the DOPPS is to investigate the impact of hemodialysis practice patterns on patient outcomes. The primary study endpoints for DOPPS are mortality, hospitalization, vascular access outcomes, and quality of life. A stratified random sample of chronic dialysis facilities was selected to document variation in practice patterns and outcomes. Within each facility, a random sample of 20 to 40 hemodialysis patients was selected for participation in the DOPPS. Patients who were lost to follow-up (died or departed from the facility) were replaced by newly enrolled patients. Facilities in the United States (n=143) entered the study in 1997, Europe (n=100) in 1998, and Japan (n=65) in 1999.

Drug data were previously classified using a drug database system. This computerized system allowed drugs to be categorized down to the specific drug brand, dosage form, and strength while allowing categorization into one or several drug classes. All prescribed medications for the management of GI disorders were recorded for each patient, including name, dose, and frequency, at just one time in the study (upon entry). Prescribed medication names were reported at 4-month intervals. The actual consumption of prescribed medicines was not recorded.

Statistical methods

The main outcome variable of interest was the extent of PPI and HA use. Prevalence percentages were calculated from a cross-section taken on February 1, 2000 (n=8628), as all countries participating in DOPPS I had entered the study by this time. To estimate the overall proportions of patient GI medication use by country, sample weights from the initial cross-section were used to account for the differing proportion of patients sampled in each facility and for the differing numbers of facilities in each stratum. This weighting allowed our sample to represent all patients from a given country.

Logistic regression was used to examine predictors of patient characteristics associated with PPI and HA use. Patient characteristics examined included those used in previous DOPPS analyses, including age, gender, race, time with ESRD, other medication use (nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids, oral iron, acetaminophen, narcotics for pain relief, selective serotonin reuptake inhibitors, and tricyclic antidepressants), the year of the patient's enrollment in the study, country of residence, and 14 comorbid conditions (coronary artery disease [CAD], congestive heart failure [CHF], cardiac disease other than CAD or CHF, hypertension, diabetes, cerebrovascular disease, peripheral vascular disease [PVD], cancer [other than skin], HIV/AIDS, lung disease, neurologic disorders, psychiatric disease, GI bleed, and recurrent cellulitis/gangrene). As an alternative to entering an indicator for each of the 14 comorbid conditions, we also used the number of a patient's comorbid conditions as a proxy for degree of illness. For the logistic

regression models, generalized estimating equations were used to account for clustering at the facility level, assuming a compound symmetry covariance structure,[16] and sample weights were not used. All analyses were performed using the SAS statistical package, version 8.2 (SAS Institute, Cary, NC, U.S.A.).

RESULTS

Data for a total of 8628 prevalent patients from February 1, 2000 in 308 dialysis facilities were available for analysis. Table 1 shows the demographic data. A longitudinal analysis of the use of HAs, PPIs, and overall use of both HAs and PPIs over time by country is shown in Figure 1a,b, and the overall prescription trends are demonstrated in Figure 1c. There was a general trend over time toward a decrease in HA prescriptions in the United States mirrored by a general increase in the use of PPIs. The use of HAs was relatively constant over time in Japan and Europe. Over the same period, there was an increased use of PPIs in Europe, but not Japan. Thus, overall, there was a decreasing use of HAs with a concomitant increasing use of PPIs, resulting in a relatively continuous overall prescription rate of about 36% to 38% of patients. In a cross-sectional sample of patients taken from February 1, 2000, the proportion receiving a PPI varied greatly by country, ranging from 0.8% in Japan to 27.3% in the United Kingdom, for an overall average of 15%. The percentage receiving an HA also varied greatly by country, ranging from 3.4% in France to 36.9% in Italy for an overall average of 22.4% (Table 2). Patients were rarely prescribed both medications. Overall, omeprazole and ranitidine were the most commonly prescribed PPI and HA, respectively.

Table 1 Demographic and comorbid data

Characteristic	N	Mean (SD)
Age	8542	60.0 (14.7)
% Male	8577	56.9
% Black	8628	38.2
Years on dialysis	8518	4.9 (5.4)
% Glomerular disease	5832	11.0
% CAD	8628	36.0
% Cancer	8628	8.3
% Other cardiovascular disease	8628	33.2
% Cerebrovascular disease	8628	15.4
% CHF	8628	29.6
% Diabetes	8628	32.9
% GI bleeding	8628	6.9
% HIV/AIDS	8628	0.5
% Hypertension	8628	73.1
% Lung disease	8628	9.4
% Neurologic disease	8628	8.4
% Psychiatric disorder	8628	18.9
% PVD	8628	21.3
% Recurrent cellulitis	8628	7.5
% NSAID use	8455	5.3
% Steroid use	8455	4.9
% Oral Iron use	8455	41.3
% Acetaminophen use	8455	4.4
% Narcotic use	8455	9.5

Substantial variation existed among facilities in prescribing patterns for GI medications. Facility use of HAs and PPIs ranged from 0% to 94% of patients (Figure 2a,b). There was a very weak correlation between the prescription of PPIs and HAs within facilities (adjusted $r^2 = 0.1$).

Table 3 summarizes the variables predictive of HA and PPI prescription by demographics, comorbidities, countries, year enrolled, and medications coadministered.

Table 4 indicates the cross-sectional association of being prescribed an HA or a PPI, by surrogate markers of nutritional status. There were increased odds of being prescribed a PPI if serum albumin was <3.5 g/dL (adjusted odds ratio [AOR] = 1.41, $p<0.0001$), if serum phosphorus was <5.5 mEq/L (AOR = 1.26, $p<0.0001$), or if creatinine was <11 mg/dL (AOR = 1.20, $p=0.011$). Patients with transferrin saturation $<20\%$ had lower odds of being prescribed an HA (AOR = 0.86, $p=0.013$).

Using the presence of comorbidities as a marker for how ill a patient was showed that for each additional comorbidity, a patient had a 15% greater chance of taking either a PPI or an HA (AOR = 1.15, $p<0.0001$) (data not shown).

The distribution of patient time on dialysis among the February 1, 2000 cross-section of those taking PPIs or HAs is shown in Figure 3. A large proportion of patients on dialysis for a year or less were prescribed PPIs (53.8%) or HAs (35.7%), compared with those on dialysis for longer periods of time.

DISCUSSION

This is the first study to examine in detail the factors associated with PPI and HA prescription patterns in hemodialysis patients, and to compare the patterns between countries. There were several limitations to this study. First, the data reflect prescription, not actual consumption, of PPIs and HAs. The results may therefore be significantly influenced by patient adherence to a specific regimen, which in turn may be influenced by a variety of

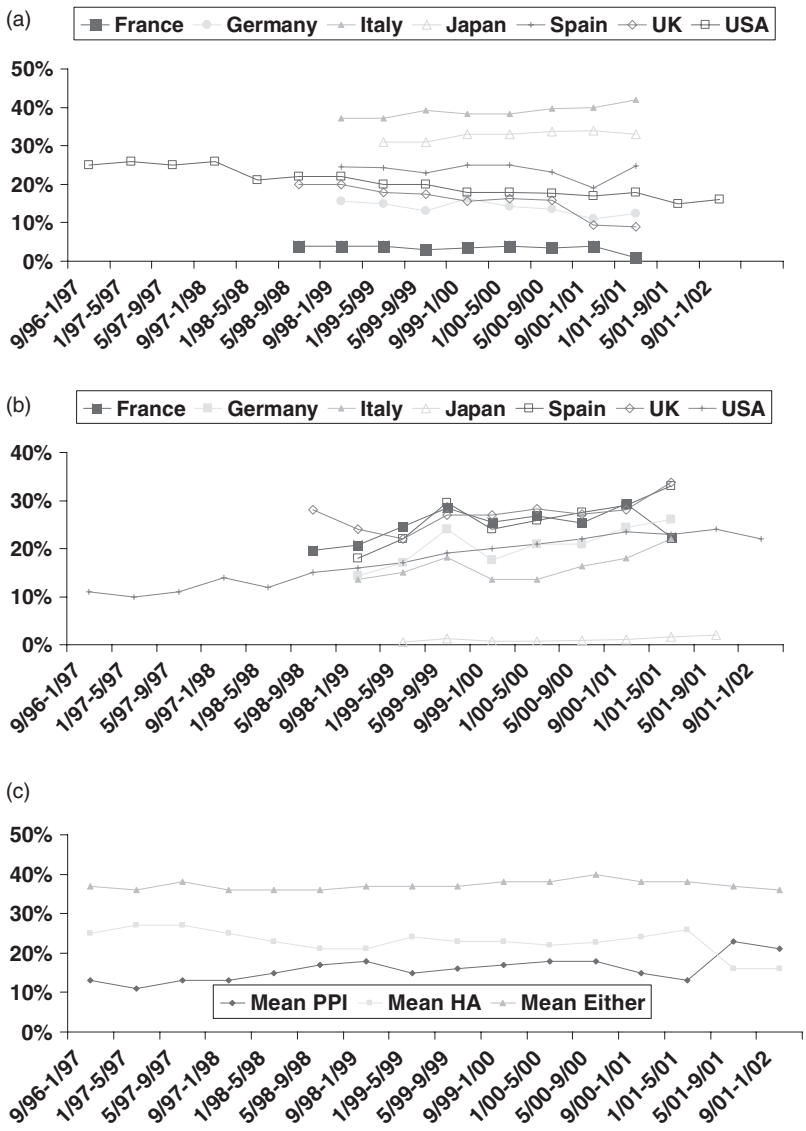

Figure 1 (a) Proportion taking HA over time by region. (b) Proportion taking PPI over time by region. (c) Overall prescription of HA and PPI. Note: Data for the United States have been collected since 1996, for Europe since 1998, and for Japan since 1999. HA = H_2 receptor antagonists, PPI = proton pump inhibitors.

factors including cost, health insurance coverage, adverse effects, and memory. Second, it is possible that some medications may have been misclassified by the system, owing to the differences (and similarities) in drug names from country to country. Finally, while this study collected data on over-the-counter medications that were prescribed, it is possible that some patients may have purchased different PPIs or HAs over the counter in different countries, which may not be reflected in the DOPPS data. The exact extent of the influence of these factors on the data is unknown.

There was a large variation in the extent of prescription of the different agents, both between countries and within different facilities. Spain had the greatest proportion of patients prescribed either a PPI or an HA (50.1%), followed by Italy (45.0%), the United Kingdom (37.7%), the United States (36.5%), Germany (35.1%), Japan (32.1%), and France (28.5%). While the prescription of HAs experienced an overall decline from 25% in 1996 to 16% in 2002, it was mirrored by an increase of a similar magnitude in the prescription of PPIs, which rose from 13% in 1996 to 21% in 2002. Presumably, these shifts are reflec-

Table 2 Percentage of patients prescribed H_2 receptor antagonists, proton pump inhibitors, or both[a] by country

	Percentage of patients						
Type of GI medication	France	Germany	Italy	Spain	UK	Japan	US
Sample size (n)	633	623	602	610	428	2188	2947
PPI (overall)	25.7	20.9	14.0	26.9	27.3	0.8	19.3
Lansoprazole	6	9	10	0	50	59	30
Omeprazole	89	74	72	98	49	12	69
Pantoprazole	5	17	18	2	0.5	0	0
Rabeprazole	0	0	0	0	0.5	29	1
HA (overall)	3.4	15.5	36.9	23.7	15.2	31.6	18.5
Cimetidine	5	4	0	15	2	14	9
Famotidine	15	17	1	4	0	51	45
Nizatidine	0	2	1	0	8	3	8
Ranitidine	80	77	98	81	90	26	38
PPI and HA (overall)	0.6	0.1	3.7	0.2	0.4	0.1	1.0

[a]Samples drawn from a February 1, 2000 cross-section in the DOPPS. Weighted to account for facility sampling fraction.
DOPPS, Dialysis Outcomes and Practice Patterns Study; HA = H_2 receptor antagonist; PPI = proton pump inhibitor.

tive of the more recent availability of PPIs. The situation in Japan may require some explanation, as only 0.8% of its patients were prescribed a PPI on June 1, 2000. Prior to 2000, normal prescription patterns in Japan limited the use of PPIs for gastric ulcers to 8 weeks. This limitation has since been removed, although the effect of this change on prescription frequency and duration is unclear.

Placing these findings into perspective to determine the actual amount of PPI or HA consumption by the general population at large is difficult. It is estimated that some 25% of the adult US population has heartburn on a regular basis, although the incidence may be less in non-western populations.[17,18] The proportion of these patients who self-medicate or who seek medical advice and are subsequently prescribed a PPI or an HA for this and other indications is presumably smaller, but the exact numbers are unclear. Our data suggest that in 2002, some 38% of hemodialysis patients were prescribed a PPI or an HA, suggesting that prescription rates in this population are several times greater than in the general population. Some trending data are available for patients in the general US population treated for gastroesophageal reflux disease. In one study that examined the relationship between PPI use and time trends for esophageal dilation, a trend similar to our study was observed, but of a much greater magnitude. Data obtained from a commercial source indicate that the number of prescriptions for HA in the United States (for all indications) increased from about 32 million per year in 1986, reaching a peak of about 55 million in 1995, and then fell to about 32 million again by 2001. Data for PPIs indicate that the number of prescriptions rose from about 10 million in 1995 to about 75 million in 2001. Proton pump inhibitor use first exceeded HA prescriptions in 1998.[19] A separate study examined outpatient Ohio Medicaid claims from 1994 to 1998 for patients with a diagnosis of gastroesophageal reflux disease.[20] Of over 5500 identified patients, there was a decreased frequency of HA use (from 72–47%) and an increased proportion of PPI prescription (from 17–43%) from 1994 to 1998, respectively. While it is not possible to infer the proportion of patients in the general population who are prescribed HAs or PPIs, the trends in both studies do, however, support our findings.

As has been previously observed with other medications,[21,22] there was considerable variation between facilities in the extent of prescription of these agents. The correlation between the prescription of PPIs and HAs within facilities was very weak (adjusted $r^2 = 0.1$), suggesting that clinicians were not necessarily substituting one agent for another. These data suggest that in some facilities clinicians may be less aware of the GI complications among dialysis patients, or are for some other reason less likely to prescribe agents for known problems. It is possible that because of the increasing number of clinical practice guidelines for many complications of CKD, attention has been focused away from other areas, even though clinical practice guidelines are available for the management of specific GI disorders in a variety of sources.[23–27]

There was a high prescription rate for both PPIs (53.8%) and HAs (35.7%) during the first year of dialysis, compared with rates for patients receiving dialysis for any period longer than a year. The reasons for this are, at best, speculative. It is possible that the data reflect the GI

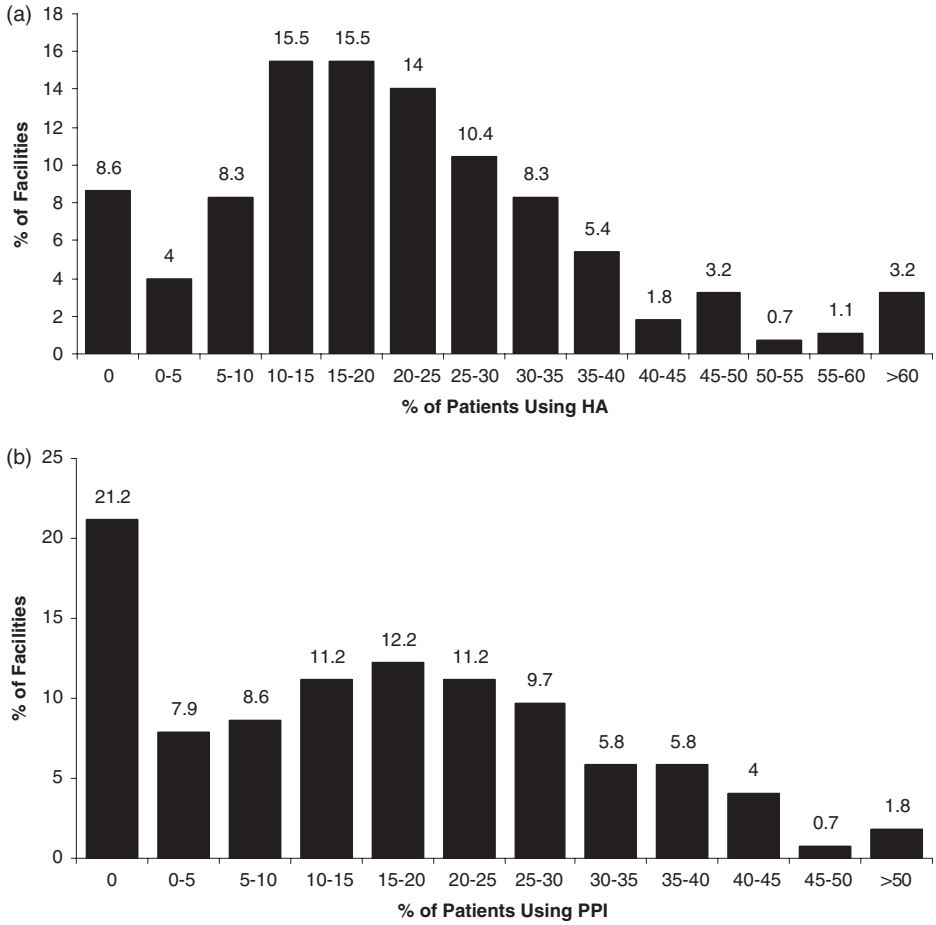

Figure 2 (a) H_2 receptor antagonists facility use distribution of proportion of patients with an HA prescription on February 1, 2000 (n=278). (b) PPI facility use distribution of proportion of patients with a PPI prescription on February 1, 2000 (n=278). HA=H_2 receptor antagonists; PPI=proton pump inhibitors.

medication prescription patterns during CKD Stage 4, when patients may have had a greater extent of GI uremic complications, which subsequently subsided over the course of the first dialysis year as they stabilized. It is also possible that the high prescription rates were held over from a predialysis period when at least some patients received oral corticosteroids as part of the treatment for progressive glomerular diseases, which was present in 11% of the overall population in this study. Indeed, there was a strong correlation between the prescription of GI medications and concomitant steroids in the population in this study (AOR=2.33).

There were strong associations between GI medication prescription and several comorbidities and concomitant medications. For example, predictors of GI medication prescription included CAD, other cardiovascular diseases (other than CAD, CHF, and hypertension), and peripheral vascular and pulmonary diseases, GI bleeds, as well as concomitant prescriptions for narcotic analgesics, corticosteroids, acetaminophen, NSAIDs, tricyclics, sevelamer, and SSRIs. Many of these are self-explanatory (such as GI bleeds, NSAIDs, and corticosteroids), because of the known influence of some medications on the GI tract. The association between GI medications and pain medications is unclear with regard to whether use of pain medications caused the side effects of GI distress or whether GI distress caused the need for GI medications and pain medications. This issue may be further complicated by the potential prophylactic use of GI medications by patients who take pain medications on an acute or chronic basis.

In this study, the prescription of GI medications was associated with a large number of comorbidities and the use of several concomitant medications. The extreme var-

Table 3 Variables associated with the use of H_2 receptor antagonists (HA) and proton pump inhibitors (PPI) (n=16,188)

	PPI		HA		Either or both	
Characteristic	AOR	p value	AOR	p value	AOR	p value
Age (per 5 years older)	1.00	0.611	1.04	<0.0001	1.02	<0.0001
Male (vs. female)	0.92	0.100	0.95	0.253	0.94	0.107
Black (vs. other race)	0.92	0.279	1.16	0.027	1.06	0.314
Comorbidities (yes vs. no)						
Coronary artery disease	1.34	<0.0001	1.10	0.052	1.20	<0.0001
Congestive heart failure	1.10	0.073	1.00	0.948	1.05	0.186
Other cardiovascular disease	1.15	0.013	1.15	0.002	1.16	0.0002
Hypertension	0.92	0.172	0.98	0.665	0.95	0.310
Cerebrovascular disease	1.16	0.016	1.05	0.331	1.10	0.028
PVD	1.36	<0.0001	1.06	0.233	1.18	<0.0001
Diabetes	1.07	0.232	0.99	0.830	1.03	0.476
Lung disease	1.13	0.081	1.27	0.0001	1.24	<0.0001
Cancer (other than skin)	1.12	0.124	0.99	0.872	1.05	0.384
HIV/AIDS	0.79	0.438	0.89	0.639	0.86	0.452
GI bleed	3.07	<0.0001	1.73	<0.0001	2.40	<0.0001
Neurological disorder	0.84	0.064	1.19	0.029	1.05	0.498
Psychiatric disease	1.18	0.006	1.06	0.273	1.12	0.018
Recurrent cellulitis/gangrene	0.88	0.178	1.00	0.969	0.97	0.621
Country (vs. US)						
France	1.50	0.004	0.18	<0.0001	0.77	0.043
Germany	1.42	0.102	1.03	0.894	1.16	0.379
Italy	1.64	0.042	3.24	<0.0001	2.45	<0.0001
Japan	0.05	<0.0001	2.38	<0.0001	1.18	0.112
Spain	1.99	<0.0001	1.92	0.0003	1.94	<0.0001
UK	2.00	<0.0001	1.41	0.050	1.69	0.0003
Year enrolled						
1996	0.49	<0.0001	1.82	<0.0001	0.93	0.364
1997	0.57	<0.0001	1.31	0.002	0.92	0.230
1998	0.83	0.012	1.09	0.394	0.92	0.295
1999	1.00	REF.	1.00	REF.	1.00	REF.
2000	1.20	0.026	0.97	0.691	1.08	0.250
2001	1.01	0.958	0.85	0.354	0.96	0.749
Vintage (per year on dialysis)	0.99	0.342	1.02	0.001	1.01	0.019
Medications						
Narcotics	1.48	<0.0001	1.36	<0.0001	1.43	<0.0001
Corticosteroids	2.52	<0.0001	1.77	<0.0001	2.33	<0.0001
Oral iron	0.96	0.450	1.11	0.028	1.04	0.346
Acetaminophen	1.28	0.036	1.21	0.078	1.22	0.035
NSAID	1.41	0.012	1.28	0.019	1.30	0.005
Tricyclic antidepressants	1.85	<0.0001	1.33	0.019	1.67	<0.0001
SSRI	1.97	<0.0001	1.82	<0.0001	2.02	<0.0001
Sevelamer[a]	0.65	0.026	0.73	0.113	0.69	0.008
HA	0.16	<0.0001	—	—	—	—
PPI	—	—	0.14	<0.0001	—	—
Depression (instead of psych disorders and SSRIs/tricyclics)	1.42	<0.0001	1.15	0.011	1.27	<0.0001

[a]Other phosphate binders (magnesium, calcium carbonate, calcium acetate, and aluminum hydroxide) were examined: there were no significant associations.

AOR=adjusted odds ratio; CAD=history of coronary artery disease; PVD=history of peripheral vascular disease; REF=reference; GI bleed=history of gastrointestinal bleed; other cardiovascular=history of cardiac disease other than CAD, CHF, or hypertension; narcotics/corticosteroids/acetaminophen/NSAID/tricyclic antidepressants/SSRI=patient concomitantly prescribed any of these medications.

Table 4 Adjusted odds ratio (AOR) of prescription of H_2 receptor antagonists and proton pump inhibitors by selected surrogate markers of nutritional status

	AOR			
Measure	HA vs. no HA	p value	PPI vs. no PPI	p value
TSAT < 20% (n = 8479)	0.86	0.013	0.96	0.512
Serum albumin < 3.5 g/dL (n = 12,194)	1.06	0.266	1.41	< 0.0001
Serum phosphorus < 5.5 mEq/L (n = 14,986)	1.01	0.881	1.26	< 0.0001
Serum creatinine < 11 mg/dL (n = 14,568)	0.97	0.6472	1.20	0.011

TSAT = transferrin saturation.

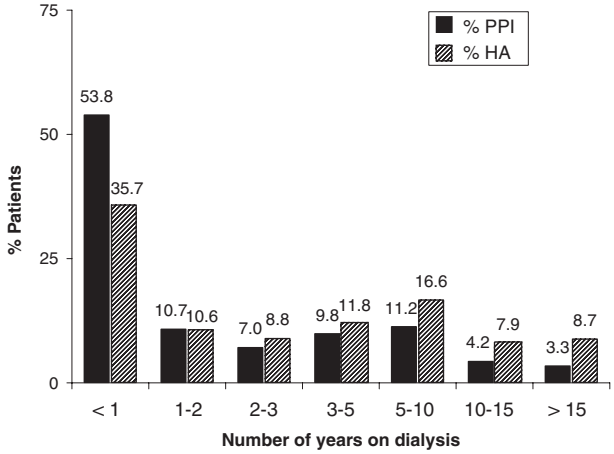

Figure 3 Patient time on dialysis, by PPI or HA. Cross-section on February 1, 2000 of those on PPIs (n = 1245) or HAs (n = 1795). HA = H_2 receptor antagonists; PPI = proton pump inhibitors.

iability of PPI and HA prescription patterns between facilities and between countries suggests that there is no standard approach in treatment practices. While the reasons for this are unclear, it may be prudent for clinicians to examine their procedures for investigation, assessment, and treatment of GI disease, and perhaps examine the clinical practice guidelines that have been developed for GI disorders in the general population.[23–27]

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