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PHOSPHATE BINDER USE AND MORTALITY AMONG HEMODIALYSIS PATIENTS IN THE DOPPS: EVALUATION OF POSSIBLE CONFOUNDING BY NUTRITIONAL STATUS

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Abstract

Background—Poor nutritional status and both hyperphosphatemia and hypophosphatemia are associated with increased mortality in maintenance hemodialysis (MHD) patients. We assessed associations of PB prescription with survival and indicators of nutritional status among (MHD) patients.

Study Design—Prospective cohort study (DOPPS) 1996 to 2008.

Setting and Participants—23,898 MHD patients at 923 facilities in 12 countries.

Predictors—Patient-level PB prescription; and case-mix-adjusted facility percentage PB prescription using an instrumental-variable analysis.

Outcome—All-cause mortality.

Results—Overall, 88% of patients were prescribed PBs. The distributions of age, comorbidities and other characteristics showed small differences between facilities with higher and lower percentage PB prescription. Patient-level PB prescription was strongly associated at baseline with indicators of better nutrition, i.e., higher serum creatinine, albumin, normalized protein-catabolic rate, BMI and absence of cachectic appearance. Overall, patients prescribed PBs displayed 25% lower mortality (hazard ratio [HR] = 0.75, 95% confidence interval [CI] = 0.68–0.83) when adjusted for serum phosphorus and other covariates; further adjustment for nutritional indicators attenuated this association (HR = 0.88, 95% CI = 0.80–0.97). This inverse association, however, was observed only for patients with serum phosphorus > 3.5mg/dL. In the instrumental-variable analysis, case-mix-adjusted facility percentage PB prescription (range: 23–100%) was positively

associated with better nutritional status and inversely associated with mortality (HR for 10% more PB = 0.93, 95% CI = 0.89–0.96). Further adjustment for nutritional indicators reduced this association to HR = 0.95 (95% CI = 0.92–0.99).

Limitations—Results were based on PB prescription; PB and nutritional data were cross-sectional; dietary restriction was not assessed; observational design limits causal inference due to possible residual confounding.

Conclusions—Longer survival and better nutritional status were observed for MHD patients prescribed PBs and in facilities with greater percentage PB prescription. Understanding the mechanisms for explaining this effect and ruling out possible residual confounding require additional research.

INTRODUCTION

Poor nutritional status and both hyperphosphatemia and hypophosphatemia have been associated with increased mortality in maintenance hemodialysis (MHD) patients (1–5). To control hyperphosphatemia in these patients both low-phosphorus diet and phosphate binders (PBs) are used (6). The survival benefit of dietary restriction of phosphorus intake as compared with PBs to control hyperphosphatemia in MHD patients remains uncertain. One potential limitation of dietary phosphorus restriction is that it can be associated with reduced protein intake which may contribute to poor nutrition and increased mortality risk (7, 8). Controlling serum phosphorus with PBs for dialysis patients has the potential advantage of permitting a diet with less protein restriction, which may contribute to improved nutritional status and potentially prolong survival.

An observational study by Isakova et al (9) found longer survival for hemodialysis patients prescribed versus not prescribed PBs, even in subgroups with phosphorus concentrations within the range recommended both by the European Best Practice Guidelines (10) and the Kidney Disease Outcomes Quality Initiative (6). The results of this study suggest that PBs are associated with improved survival of MHD patients independent of their effects on serum phosphorus concentration. One plausible explanation to explain associations of PB use and survival is that patients who eat more are more likely to maintain a better nutritional status and are more likely to be prescribed a PB because of a higher tendency toward hyperphosphatemia.

Using a representative sample of hemodialysis patients from 12 countries enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS), the present study was developed to extend prior work on the association between PBs and survival among hemodialysis patients (9, 11). Our study assessed the association of PB prescription with mortality and indicators of nutritional status in MHD patients from the perspectives of patient-level PB prescription and facility-level percentage PB prescription. This latter facility practice based perspective was examined using an instrumental variable methodology to possibly reduce effects of unmeasured patient-level confounders. We also explored whether indicators of nutritional status could explain the inverse association between PB prescription and mortality in MHD patients.

METHODS

Data Source

Data were from phases I to III of the DOPPS, an international, prospective cohort study in 12 countries (12, 13). DOPPS is based on nationally representative samples of randomly selected dialysis facilities and patients. Within each participating facility, 20 to 40 patients were randomly selected, depending on facility size. Institutional review boards in each

country approved the study and informed patient consent was obtained in accordance with local requirements.

The main analyses were based on 23,898 adult patients with end-stage renal disease (ESRD) on hemodialysis for at least 90 days at DOPPS entry: DOPPS I (1996–2001, n=7,292 patients in 303 facilities from France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States), DOPPS II (2002–2004, n=8,512 patients in 320 facilities from the countries in DOPPS I, plus Australia, Belgium, Canada, New Zealand, and Sweden) and DOPPS III (2005–2008, n=8,094 patients in 300 facilities from the 12 countries in DOPPS II). In addition, a sensitivity mortality analysis was performed that included incident patients (n= 6,181) who initiated MHD within 30 days of study entry.

Outcomes and Predictors

All-cause mortality was the primary outcome. Time at risk was analyzed from study entry until the earliest of: end of study follow-up, kidney transplantation, or seven days following study departure for dialysis modality change or transfer to another dialysis facility. For the analysis of patient-level PB prescription, the primary predictor variable was PB prescription status (yes or no) at the start of follow-up. For analysis by facility PB prescription, the primary predictor variable was the case-mix adjusted percentage of MHD patients prescribed PBs at the start of follow-up in a prevalent cross-section of patients in each facility. Indicators of nutritional status (serum creatinine, serum albumin, normalized protein catabolic rate [nPCR], body mass index [BMI] and cachectic [i.e. undernourished or malnourished] appearance) and other covariates were the most recent data reported for the patient on or before the patient's date of study entry.

Statistical Analysis

Baseline patient characteristics (e.g., mean, median, or percentage) were calculated by patient-level PB prescription. Logistic regression was used to calculate the odds of PB prescription by patient characteristic with either minimal adjustments or extensive adjustments and applied generalized estimating equations to account for clustering at the facility level, assuming a compound symmetry covariance structure (14). The relationship of patient-level PB prescription with mortality was analyzed using Cox proportional hazards regression. To possibly reduce the impact of unmeasured patient-level confounders in mortality analyses, an instrumental variable (IV) approach was applied using the dialysis facility as the instrument. Two different IV methods, without and with adjustments for nutritional indicators, were used, and the results were compared for consistency. The first method was based on a generalization of the linear two-stage IV model to accommodate a non-linear second stage model. In the first stage, linear regression was used with PB prescription (yes/no) as the outcome, as a linear approximation to logistic regression, and with predictors including DOPPS facility indicator in addition to the following covariates: age, sex, black race, years on dialysis, coronary artery disease, congestive heart failure, hypertension, diabetes, peripheral artery disease, recurrent cellulitis/gangrene, neurologic disease, lung disease, gastrointestinal bleeding in prior 12 months, cancer, catheter use for vascular access, and baseline serum phosphorus. This first stage linear regression yields the case-mix adjusted facility percentage PB prescription as a fixed effect for each dialysis unit included in the analysis. In this first stage model using facilities as the instruments, a partial F statistic of 4.21 was observed, suggesting a weak instrument. Even when the instruments are weak, however, the potential bias for the treatment effect estimate from a two-stage least squares method is usually smaller than that obtained using conventional patient-level regression methods (15). In the second stage, Cox regression, without and with adjustments for nutritional indicators, was used to estimate the hazard ratio of patient-level mortality associated with the predicted case-mix adjusted facility percentage PB prescription obtained

from the first stage. All Cox models were stratified by region and study phase, and used the sandwich estimator to account for facility clustering effects (16).

The second IV method was based on limited information maximum likelihood (LIML) regression. LIML is considered more robust than the two-stage least squares IV method when instruments are weak (17), i.e., when the first stage partial F statistic for the instrument(s) is <10 (18). LIML uses linear models for both the first and second stage. We used one-year mortality as the second stage outcome, modeled as a dichotomous variable using linear regression as an approximation to logistic regression. This analysis assumes that vital status is known for all patients at the end of the one-year follow-up period. Facilities that dropped out of the study within the first six months were excluded, but patients who dropped out within the first year (about 10%) were assumed to be survivors. This convention may lead to under-estimation of death probabilities; the alternative of deleting these patients would lead to over-estimation of death probabilities. Covariates from the first IV method described above were included.

The proportional hazards assumption in Cox regression was confirmed graphically and by testing an interaction term between each covariate and log-transformed follow-up time. Missing data was imputed using IVEware, based on the sequential regression imputation method (19). Descriptive tables were based on a single imputation, whereas analytical results were based on combining results from five imputed data sets using Rubin's formula (19). Analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC). STROBE guidelines were followed for reporting observational studies for a cohort study (20).

RESULTS

Patient characteristics by phosphate binder prescription

Patient characteristics by PB prescription and odds ratios for PB prescription by patient characteristic are shown in Table 1 for the 23,898 MHD patients on hemodialysis for at least 90 days at study entry. Patients prescribed PBs represented 88.1% of the sample. Patients prescribed a PB had a lower prevalence of several comorbidities, and a profile consistent with better nutritional status for each of the five nutritional measures, i.e., lower frequency of cachexia and higher mean serum albumin, serum creatinine, BMI and nPCR level. These patterns were observed within each of the three study regions of North America, Japan, and Europe/Australia/New Zealand (Supplemental Table S1). After extensive adjustments some comorbidities (e.g., diabetes, cardiovascular disease, dementia, ascites) were only weakly or not significantly associated with PB prescription status. However, even after extensive adjustments for patient characteristics, PB prescription remained strongly and significantly (i.e. $p<0.05$) associated with each indicator of better nutritional status, i.e., lower likelihood of cachexia and greater odds of higher serum albumin, serum creatinine, BMI and nPCR level. Furthermore, patients prescribed a PB had a lower adjusted odds of being bothered by lack of appetite [14% lower for those prescribed Ca-based PB alone, (OR=0.86, 95% CI=0.78–0.95); 12% for sevelamer alone (OR=0.88, 95% CI=0.76–1.02); 20% for sevelamer plus Ca-based PB (OR=0.80, 95% CI=0.69–0.92)].

Variability in Phosphate Binder Prescription

Figure 1 shows distribution of the facility percentage of patients with PB prescription by DOPPS country and study phase. Median values of PB prescription varied modestly by country, showing a general trend towards slightly greater PB prescription over time in some countries. The distribution of prescription was skewed towards facilities prescribing PBs for the majority of their patients, with more than 90% of patients receiving PB prescription in

approximately half of the facilities. The percentage of patients prescribed PBs varied across the 923 dialysis facilities ranging from 31% to 82% in the lowest quartile and from 96% to 100% in the highest quartile.

Figure 2 shows the frequency of patients with PB prescription by serum phosphorus level. PB prescription was lower for patients with lower serum phosphorus levels. Among patients with serum phosphorus >5.5 mg/dL, a PB was prescribed for more than 89%. However, substantial PB prescription was observed even for patients with low serum phosphorus levels (79% PB prescription among patients with serum phosphorus $\leq$ 2.5 mg/dL). For patients prescribed PBs in DOPPS III (2005–2008), the types of PB prescribed included calcium- (Ca) containing PB only (46%), sevelamer PB only (16%), Ca-PB and sevelamer PB (21%), aluminum-containing PB only (6%), lanthanum-containing PB only (3%), and other PBs or other combinations of PBs (8%). (Data by type of PB are not shown.)

Nutritional indicators by patient-level PB prescription

As shown in Figure 3A–E, patients prescribed a PB displayed lower prevalence of cachexia and higher mean values of BMI, serum creatinine, nPCR and serum albumin across a wide range of serum phosphorus concentration levels. Table 2 shows the distribution of serum phosphorus and indicators of nutritional status by type of PB or combination of PB prescribed across all three DOPPS phases. Compared with patients not prescribed PB, those prescribed any type or combination of PB had significantly lower prevalence of cachectic appearance and higher mean values of serum phosphorus, serum albumin, serum creatinine, BMI and nPCR; each $p < 0.001$.

Facility-level PB prescription: relation to patient characteristics and nutritional status

Case-mix adjusted facility percentage PB prescription was calculated for each study site (minimum: 23%; median: 86%; interquartile range: 77%–91%). Across categories of the case-mix adjusted percentage of facility patients prescribed PBs (Table 3), only small differences were observed in patient characteristic prevalence and in selected facility characteristics (facility median treatment time, facility percentage of patients with spKt/V >1.2, serum hemoglobin >10 g/dL, or using an arteriovenous fistula).

Case-mix adjusted facility percentage PB prescription was also examined for odds of a patient having each nutritional indicator at or below the 25th percentile of the indicator's distribution (Figure 4). For serum creatinine, BMI, and nPCR, the odds of poorer nutritional status were higher in facilities with lower case-mix-adjusted percentage PB prescription.

Hazard of death by prescription of phosphate binder

Among 23,894 prevalent patients, 6,283 deaths were observed (median time-at-risk: 1.92 years). PB prescription was associated with a 25% lower death rate (adjusted hazard ratio [AHR]=0.75, 95% CI=0.68–0.83) in Cox models adjusted for numerous covariates, including achieved serum phosphorus level, but not for nutritional factors. A similar association was observed in a model excluding patients with dementia, cancer or who had been hospitalized in the previous three months (AHR=0.76, 95% CI=0.67–0.86, $p=0.002$). However, the strength of the association between PB prescription and mortality risk was reduced after adjusting for nutritional factors (AHR=0.88, 95% CI=0.80–0.97). Similar associations between PB prescription and lower mortality risk were observed in analyses comparing Ca-based PB with no PB prescription, and comparing sevelamer with no PB prescription. Also, in a Cox model adjusted for all covariates except for nutritional indicators, similar results were observed in a sensitivity analysis restricted to 6181 incident patients who had initiated MHD within 30 days of study. Among these incident patients, an

18.7% lower hazard of death was observed during the first year on MHD for those patients prescribed a PB at the time of study entry (AHR=0.81, 95% CI=0.71–0.93, $p=0.002$).

Figures 5A and 5B show the AHR of death for joint categories of PB prescription status and serum phosphorus concentration, without and with adjustment for nutritional indicators; the reference category is comprised of patients with serum phosphorus levels between 3.5 and 5.5 mg/dL who were prescribed PBs. Without adjusting for nutritional indicators, the mortality rate was consistently higher for patients not prescribed a PB (as compared with patients prescribed any PB) at all serum phosphorus concentrations ≥ 3.5 mg/dL (Figure 5A). The lowest mortality rate was observed for patients prescribed a PB and having a serum phosphorus level of 3.5–5.5 mg/dL. The differences in the AHR of patients not prescribed and those prescribed a PB with serum phosphorus ≥ 3.5 mg/dL (Figure 5A) were reduced after adjustments for nutritional indicators (Figure 5B). Supplementary Figure S1 illustrates the effect of PB on mortality across categories of nutritional indicators.

An instrumental variable analysis was applied to examine the relationship of mortality with PB prescription as a facility practice, represented as case-mix adjusted facility percentage PB prescription. The results indicate a 7% lower hazard of death for every 10-percentage points greater case-mix adjusted facility PB prescription, when adjusted for numerous covariates but not for nutritional indicators (AHR=0.93, 95% CI=0.89–0.96, $p<0.001$). The strength of the association was reduced after adjusting for nutritional indicators (AHR=0.95, 95% CI=0.92–0.99, $p=0.01$).

As a sensitivity analysis, LIML-regression models were used to assess the association between case-mix adjusted PB prescription and one-year survival (yes/no), and provided results consistent with those from the Cox-regression models. In the LIML regression, the one-year survival probability was significantly ($p<0.001$) higher in facilities with a higher percentage of patients prescribed PBs (difference per 10% greater case-mix-adjusted facility PB prescription=1.1%, 95% CI=0.5%–1.8%). The difference was reduced from 1.1% to 0.9% (difference=0.9%, 95% CI=0.3%–1.6%, $p=0.007$) after adjusting for nutritional indicators. The Cox regression model without adjustment for nutritional indicators showed an estimated 18% one-year mortality for those not prescribed PBs and 16.6% one-year mortality for those prescribed PBs (HR=0.92, 95% CI=0.87–0.96, $p<0.001$). The estimated unadjusted decrease in the mortality risk was 1.4% per each 10-percentage points greater case-mix adjusted facility PB prescription. This unadjusted decrease in the mortality risk associated with PB prescription estimated in the Cox regression model is comparable to the 1.1% reduction in the mortality risk estimated in the LIML model. After adjusting for nutritional indicators in the Cox regression model, the strength of the associations between PB prescription and one-year mortality was also reduced (AHR=0.94; 95% CI=0.90–0.99, $p=0.02$). The estimated decrease in the mortality risk after adjustment for nutritional indicators in the Cox regression model was 1.1% per each 10-percentage points greater case-mix adjusted facility PB prescription.

DISCUSSION

The results of this large international prospective cohort study indicate greater survival for MHD patients prescribed a PB and in facilities with a higher percentage of patients with a PB prescription. Sensitivity analyses suggest a similar survival benefit in prevalent and incident MHD patients. The longer first-year survival associated with PB prescription in incident MHD patients is consistent with results from a prospective cohort study by Isakova et al, both in their unmatched analysis (using data from 8,610 patients) and their propensity score matching analysis (using data from 6,372 patients) (9). Kovesdy et al recently reported a survival benefit with PB prescription in non-dialysis dependent male chronic kidney

disease patients (21). Winkelmayer et al observed lower mortality rates during the first year of dialysis in a 1996–97 cohort of incident US dialysis patients prescribed versus not prescribed PBs (11). However, this association was no longer statistically significant when analyzed by a propensity score methodology utilized to diminish differences in patient case-mix between the study groups [AHR=0.89, 95% CI=0.72–1.10]. The lack of statistical significance observed in the propensity matched analysis in the study by Winkelmayer et al., could reflect the smaller sample size of 1,600 subjects in that study compared with the 5-to-15 fold larger sample sizes in the Isakova et al. study (9) and in our current study, respectively.

Patients prescribed a PB had higher mean serum phosphorus concentrations. This has also been reported in previous studies (9, 11) and is likely due to the preferential prescription of PBs to patients with a serum phosphorus concentration above the recommended target, i.e. dosing by indication. By contrast, facility-based analyses often are more independent of treatment by indication bias, and in the present study facilities prescribing PBs for a larger fraction of patients displayed slightly lower mean serum phosphorus concentrations. This latter observation is consistent with the known action of PBs in reducing serum phosphorus levels in randomized clinical trials.

The simple nutritional indicators used in our study (serum albumin, serum creatinine, BMI, nPCR, and cachectic appearance) have been found to be associated with mortality risk; mediators of disease process, (such as inflammation and intakes of protein and calories), and change in body composition, in patients on MHD or peritoneal dialysis (2, 22–24). The association between PB prescription and better nutritional status as assessed by these five indicators was consistently seen within each of the three study regions (i.e., North America, Japan, and Europe/Australia/New Zealand) and across five categories of serum phosphorus (Figure 3). Furthermore, our results indicate that patients in facilities with high PB prescription display better control of hyperphosphatemia, better nutritional status, and lower mortality rate, even after adjusting for differences in achieved serum phosphorus levels, and numerous patient characteristics. Higher mean concentrations of serum creatinine, BMI and nPCR were seen in facilities prescribing PBs for nearly all patients compared with facilities prescribing PBs for a lower fraction of patients (e.g., for <82% of facility patients). Previously, we showed that lack of appetite was associated with poor nutritional status as assessed by serum albumin, nPCR, serum creatinine, BMI and cachectic appearance (1). The present study suggests that odds of lack of appetite are lower in patients prescribed PB. These findings support the possibility that the better nutritional status and the improved survival observed in patients prescribed PB may be partially due to their lower odds of lack of appetite.

It should be noted that prescription of PBs was associated with improved survival even for patients with serum phosphorus within the recommended range (i.e., 3.5–5.5 mg/dL). The difference was reduced after adjustment for nutritional indicators, supporting the hypothesis that the association between PB prescription and lower mortality risk is partially explained by a better nutritional status among those prescribed PBs. The facility-level analysis suggests that nearly 30% of the reduced hazard of all-cause death associated with greater percentage of patients prescribed PBs at the facility may be explained by better nutritional status of patients in facilities prescribing PBs for a larger fraction of patients. The observation of improved nutritional status of MHD patients with greater facility percentage PB prescription perhaps could be explained by a more liberalized diet which may require frequent use of PB to control hyperphosphatemia. This possibility is also consistent with a post-hoc analysis of the HEMO Study showing that an increased level of dietary phosphorus restriction was associated with poorer nutritional status and higher mortality risk (8).

Although approximately half of the dialysis units in this study prescribed PBs for at least 90% of their hemodialysis patients, the lowest quartile prescribed PBs for a substantially smaller fraction of patients, ranging from 23%–78%. This difference in facility PB prescription likely reflects in part, differences in provider preferences for PB prescription. Some facilities prescribe PBs based on a different serum phosphorus target than others.

Thanks to its randomized sampling design, the DOPPS findings may be viewed as generalizable to the broad MHD population in each participating country (12, 13). However, methodological limitations cannot be ignored. Because the study is observational it does not allow conclusions about cause-effect association between PB and mortality risk. It is possible that the better survival among patients with a PB prescription is partially due to unmeasured confounders. However, the facility-level PB prescription analysis based on IV methods used in the present study should have reduced the influence of unmeasured patient-level confounders. This IV approach relates outcomes to a facility practice of PB prescription rather than actual treatment received. It is worth noting that the IV model showed a fairly balanced distribution of patient characteristics among facilities with higher and lower PB prescription. The association of greater facility percentage PB prescription and lower mean serum phosphorus levels observed in the IV model is a finding consistent with the pharmacological effect of PB. The consistency of the results observed in the patient-based analysis and in the two IV methods should be viewed as additional evidence that PB is associated with a lower mortality risk in MHD patients (25, 26).

Another methodological limitation is that the assessment of the PB effect and the predictor covariates were based on baseline data, whereas adherence to medication use and PB prescription during follow-up were not assessed. There are data to indicate that a considerable proportion of MHD patients do not adhere to PB prescription (27, 28). Non-adherence to PB prescription as well as PB prescription for patients who did not have a prescription at baseline are likely to bias the association of PB with survival towards the null hypothesis. This suggests that the independent associations between PB prescription and improved survival observed in the present study could be even stronger if all patients prescribed PBs had in fact closely adhered to taking the PBs as prescribed. The study could not assess whether the higher mortality rate among patients not prescribed PBs was in fact due to a lower dietary protein intake in an attempt to control hyperphosphatemia by dietary restriction of phosphorus. This possibility should be viewed as an important question for future research. Studies are still needed to assess whether the positive relationship of PB prescription with MHD patient survival may also be due to direct effects of PBs on mediators of mineral metabolism, e.g., fetuin-A and FGF-23 (29, 30), although this is less likely as PBs are designed not to be absorbed, and as such should have minimal systemic effects.

In conclusion, the results of the current study provide new perspectives of the relationship between facility-level PB prescription and MHD patient outcomes. Patients in facilities with higher PB prescription display better control of hyperphosphatemia, better nutritional status, and longer survival. The association of case-mix adjusted facility PB prescription with greater survival was seen even after controlling for differences in achieved serum phosphorus levels and numerous patient characteristics. The results suggest that the improved patient survival in facilities with a higher percentage of patients prescribed a PB may be partially explained by the better nutritional status of their patients. The results are also consistent with the possibility that a greater prescription of PBs may be due to more liberal dietary intake, which may potentially contribute to improved survival in MHD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**% of facility patients
with PB Rx**

Figure 1.
Distribution of facility percentage of patients with phosphate binder (PB) prescription, by DOPPS country and study phase n=23,898 patients (923 facilities) in DOPPS I (1996–2001), DOPPS II (2002–2004), and DOPPS III (2005–2008). Abbreviations: ANZ=Australia and New Zealand, BE=Belgium, CA=Canada, FR=France, GE=Germany, IT=Italy, JPN=Japan, SP=Spain, SW=Sweden.

Figure 2.

Percentage of patients with phosphate binder (PB) prescription, by baseline serum phosphorus level. US to International Conversions: serum phosphorus in mg/dL to mmol/L, $\times 0.3229$.

Figure 3.

Nutritional indicator levels by phosphate binder prescription and serum phosphorus category. The results in Figures 3A to 3E are based on separate mixed linear regression models estimating the mean level of the indicated nutritional indicator within each serum phosphorus concentration depending on whether patients were prescribed a phosphate binder. The associations accounted for facility clustering effects and were adjusted for age, male, race, 13 summary comorbid conditions, region and study phase. BMI=body mass index; PB=phosphate binder, No PB=phosphate binder was not prescribed. US to International Conversions: serum albumin in g/dL to g/L, x10; serum creatinine in mg/dL to $\mu\text{mol/L}$, x88.4; serum phosphorus in mg/dL to mmol/L, x0.3229.

Figure 4.

Odds ratios of the associations of quintile of case-mix adjusted facility percentage of patients who received a prescription of phosphate binders with the odds of nutritional measures below the 25th percentile (n=23,952). US to International Conversions: serum albumin in g/dL to g/L, x10; serum creatinine in mg/dL to $\mu\text{mol/L}$, x88.4. Ref. = reference group. The results are based on data of 23,898 prevalent hemodialysis patients with ESRD duration at least 90 days from 923 facilities in DOPPS I–III (1996–2008). Case mix adjusted facility percentage of phosphate binder prescription was calculated from mixed linear regression adjusted for age, male gender, ESRD duration, 10 comorbid conditions, serum phosphorus, catheter use, serum calcium (albumin adjusted). Second stage logistic

regression models used the same adjustments as in the first stage, phase, and region and accounted for facility clustering.

Figure 5.

*Nutritional factors were normalized PCR, cachexia, serum albumin, creatinine, and body mass index. Adjusted hazard ratios and 95% confidence intervals of the association of all-cause mortality with patient-level phosphate binder prescription by serum phosphorus levels, without adjustment for nutritional indicators (Figure 5A) and with adjustment for nutritional indicators (Figure 5B). The analysis was based on data of 23,898 prevalent MHD patients with ESRD duration at least 90 days from 923 facilities in DOPPS I–III (1996–2008). US to International Conversions: serum phosphorus in mg/dL to mmol/L, $\times 0.3229$. Reference group was comprised of patients with serum phosphorus 3.5–5.5 mg/dL and with phosphate binder prescription. All models were adjusted for age, male gender, ESRD duration, residual kidney function, 13 comorbid conditions, serum phosphorus, catheter use, serum calcium (albumin adjusted), stratified by phase and region and accounted for facility clustering.

Table 1

Patient characteristics by phosphate binder prescription (n=23,898)

Characteristics	Phosphate Binder		Minimally Adjusted Odds Ratio ^a (95% CI) [*]	Extensively Adjusted Odds Ratio (95% CI) [†]
	Yes	No		
N (%)	21,061 (88.1%)	2,837 (11.9%)		
Age in years (mean±SD, per 10 years older)	61.4±14.6	65.6±14.1	0.76 (0.71, 0.82)	0.78 (0.73, 0.84)
Black (% , vs. non-black)	12.3	11.6	0.78 (0.64, 0.96)	0.76 (0.62, 0.93)
Black restricted to US (%)	37.7	37.3		
Hispanic restricted to US (%)	9.7	9.6		
Male (% , vs. female)	57.3	56.5	1.01 (0.93, 1.10)	1.02 (0.93, 1.11)
Presence of residual kidney function (% , vs. absence)	26.2	29.4	0.83 (0.75, 0.93)	0.86 (0.77, 0.96)
Years of ESRD (median, per 1 year longer)	3.4	2.6	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)
Comorbidities (% , vs. absence)				
Coronary Artery Disease	45.7	47.7	0.94 (0.85, 1.04)	0.96 (0.87, 1.06)
Cancer	10.8	12.2	0.99 (0.87, 1.14)	1.00 (0.87, 1.14)
Other Cardiovascular Disease	36.1	39.4	0.93 (0.85, 1.03)	0.93 (0.84, 1.03)
Cerebrovascular Disease	16.7	20.5	0.84 (0.76, 0.94)	0.93 (0.82, 1.04)
Congestive Heart Failure	32.9	33.3	0.96 (0.85, 1.07)	1.02 (0.90, 1.15)
Diabetes	34.9	37.7	0.86 (0.78, 0.95)	0.91 (0.82, 1.01)
Gastrointestinal Bleed	5.8	7.4	0.80 (0.67, 0.94)	0.84 (0.71, 0.99)
Hypertension	78.3	73.1	1.22 (1.09, 1.36)	1.31 (1.17, 1.47)
Lung Disease	10.9	11.4	0.95 (0.83, 1.10)	0.98 (0.85, 1.12)
Neurologic Disorder	10.2	14.7	0.64 (0.56, 0.73)	0.67 (0.58, 0.78)
Psychological Disorder	16.4	17.7	0.79 (0.69, 0.89)	0.84 (0.74, 0.96)
Peripheral Vascular Disease	25.6	27.3	0.91 (0.83, 1.01)	0.96 (0.85, 1.09)
Cellulitis, Skin Infection or Gangrene	8.2	8.4	0.87 (0.75, 1.01)	0.96 (0.81, 1.14)
Alcohol Abuse	2.9	3.9	0.60 (0.45, 0.81)	0.72 (0.52, 1.01)
Dementia	3.2	6.3	0.58 (0.47, 0.71)	0.82 (0.64, 1.05)
Ascites within the past 12 months	1.3	1.9	0.67 (0.46, 0.97)	0.75 (0.51, 1.09)
Hepatitis B or C	12	12	0.98 (0.86, 1.13)	0.92 (0.80, 1.06)
Vascular Access by Catheter (% , vs. other VA)	13.7	15	0.83 (0.72, 0.96)	0.89 (0.77, 1.03)
Hospitalization in the last 3 months (% , vs. none)	19	26.8	0.69 (0.62, 0.78)	0.74 (0.66, 0.84)
Prescription of Vitamin D and analogs (% , vs. none)	49.3	39.7	1.45 (1.29, 1.64)	1.44 (1.27, 1.62)
Hemoglobin in g/dL (mean±SD, per 1 g/dL higher)	11.2±1.6	10.9±1.7	1.07 (1.04, 1.12)	1.06 (1.03, 1.10)
Hemoglobin<9 g/dL (% , vs. 9)	8.1	12.8	0.73 (0.63, 0.86)	0.75 (0.64, 0.88)
SpKt/V (mean±SD, per 0.1 higher)	1.44±0.29	1.41±0.33	1.02 (0.99, 1.04)	1.01 (0.98, 1.03)
Serum phosphate in mg/dL (mean±SD, per 1 mg/dL higher)	5.6±1.8	5.2±1.8	1.17 (1.12, 1.21)	1.16 (1.11, 1.21)
Serum phosphate < 3.0 mg/dL (% , vs. 3)	4	7.2	0.59 (0.49, 0.71)	0.60 (0.49, 0.72)
Serum phosphate > 7.0 mg/dL (% , vs. 7)	18.1	13.5	1.39 (1.20, 1.60)	1.37 (1.19, 1.58)
Serum Calcium _{adj} in mg/dL (mean±SD, per 1 mg/dL higher)	9.5±0.89	9.4±0.97	1.12 (1.05, 1.19)	1.10 (1.03, 1.16)
PTH in pg/mL (median, per 100 pg/mL higher)	165	157.5	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)

Characteristics	Phosphate Binder		Minimally Adjusted Odds Ratio ^a (95% CI) [*]	Extensively Adjusted Odds Ratio (95% CI) [†]
	Yes	No		
N (%)	21,061 (88.1%)	2,837 (11.9%)		
Cachectic Appearance (% , vs. none)	8	13.7	0.54 (0.47, 0.63)	0.57 (0.50, 0.66)
Body Mass Index in kg/m ² (mean±SD, per 1 kg/m ² higher)	24.4±5.6	23.41±5.1	1.04 (1.02, 1.05)	1.04 (1.03, 1.06)
Body Mass Index <18.5 kg/m ² (% , vs. 18.5 kg/m ²)	10	15.2	0.65 (0.56, 0.74)	0.63 (0.55, 0.73)
Serum Albumin in g/dL (mean±SD)	3.8±0.5	3.7±0.5	1.59 (1.41, 1.80)	1.52 (1.35, 1.72)
Serum Albumin <3 g/dL (% , vs. 3 g/dL)	3.9	7.7	0.49 (0.41, 0.59)	0.53 (0.44, 0.63)
Serum Creatinine in mg/dL (mean±SD, per 1 mg/dL higher)	9.6±3.0	8.2±3.0	1.25 (1.21, 1.30)	1.27 (1.23, 1.32)
Serum Creatinine <8 mg/dL (% , vs. 8 mg/dL)	30.5	51.9	0.38 (0.34, 0.43)	0.38 (0.34, 0.42)
nPCR in g/kg/day (mean±SD, per 0.1 g/kg/day higher)	1.04±0.2	0.96±0.3	1.14 (1.12, 1.17)	1.13 (1.11, 1.16)
nPCR <1 g/kg/day (% , vs. 1 g/kg/day)	46.1	59.9	0.60 (0.54, 0.66)	0.62 (0.56, 0.69)

US to International Conversions: serum albumin in g/dL to g/L, x10; serum calcium in mg/dL to mmol/L, x0.2495; serum creatinine in mg/dL to μmol/L, x88.4; hemoglobin in g/dL to g/L, x10; PTH in pg/mL to ng/L, no conversion needed; serum phosphorus in mg/dL to mmol/L, x0.3229.

^aOdds ratios indicate likelihood of PB prescription for the given unit increase (continuous variables) or compared to the referent group (dichotomous variables).

^{*} The logistic models for the minimally adjusted odds ratios include geographic region, study phase, and age and accounting for facility clustering effects.

[†] The logistic models for the extensively adjusted odds ratios include geographic region, study phase, age, race, male, residual kidney function (yes/no), years with ESRD, and 13 summary comorbid conditions (coronary heart disease, cancer, other cardiovascular disease, cerebrovascular disease, congestive heart disease, diabetes mellitus, GI bleeding, hypertension, lung disease, neurological disorders, psychological disorders, peripheral vascular disease, and recurrent cellulitis/gangrene), and accounting for facility clustering effects.

Calcium_{alb} = albumin-corrected calcium; ESRD = End-stage renal disease; nPCR = normalized protein catabolic rate; PTH = parathyroid hormone; SpKt/V = single pool Kt/V.

Table 2
Serum phosphorus and indicators of nutritional status by type or combination of phosphate binder prescription

Type/Combination of Phosphate Binder Prescribed	Number of Patients	Serum Phosphorus (mean±SD)	Serum Albumin (mean±SD)	Serum Creatinine (mean±SD)	Body Mass Index (mean±SD)	Normalized PCR (mean±SD)	Cachectic Appearance (%)
None	2304	5.15±1.83	3.69±0.51	8.09±2.97	23.16±5.0 ₂	0.96±0.27	14.0
Ca-Based alone	13892	5.48±1.73	3.77±0.44	9.61±3.12	24.00±5.4 ₈	1.04±0.27	8.3
Sevelamer alone	1861	5.72±1.68	3.81±0.46	9.20±2.94	25.66±5.8 ₇	1.03±0.27	7.9
Sevelamer plus Ca-based	2547	5.81±1.70	3.80±0.43	9.88±2.96	25.56±6.0 ₀	1.08±0.26	6.8

Values represent data from DOPPS phases I, II, and III. Within each column, comparisons of each prescription type vs. "None", $p<0.001$.

US to International Conversions: serum albumin in g/dL to g/L, x10; serum creatinine in mg/dL to µmol/L, x88.4; serum phosphorus in mg/dL to mmol/L, x0.3229.

Table 3

Patient Characteristics by Quartile of Case-mix Adjusted Facility Percentage Phosphate Binder Prescription* (n=23,898)

	Prescription of phosphate binder				p for trend**
	78%	79 – <86%	86 – <91%	91%	
Number of Patients	6,353	6,145	5,787	5,613	
Patient characteristics					
Age	61.6	61.4	61.6	63.0	0.9
Male, %	57.1	56.8	58.7	56.2	0.08
Black, %	11.2	12.4	9.3	16.0	0.2
Years of ESRD, mean	5.5	5.3	5.4	4.6	0.3
Coronary artery disease, %	39.6	46.4	46.2	52.5	0.1
Congestive heart failure, %	26.1	32.2	33.1	41.1	0.003
Cerebrovascular disease, %	15.8	15.8	17.3	19.7	0.1
Other Cardiovascular disease, %	32.7	36.3	37.6	39.6	0.003
Hypertension, %	70.3	77.8	81.4	82.4	0.001
Diabetes, %	30.7	34.4	36.1	40.1	0.1
Peripheral arterial disease, %	21.8	24.7	26.7	30.7	0.02
Lung disease, %	8.4	10.2	10.7	14.8	0.01
Gastrointestinal Bleed in prior 12 mo, %	4.8	6.8	5.3	7.3	0.03
Neurologic disease, %	9.6	10.5	10.5	12.7	0.8
Psychological disorder, %	14.1	17.3	16.0	19.2	0.5
Cancer, %	10.1	10.7	11.1	12.5	0.7
Recurrent Cellulitis/gangrene, %	6.4	8.0	8.3	10.7	0.001
Catheter, %	11.0	13.0	12.3	19.5	0.8
Serum calcium (albumin-corrected), mg/dL	9.45	9.49	9.51	9.50	<0.001
Serum Phosphorus, mg/dL	5.70	5.62	5.50	5.40	<0.001
Facility Characteristics					
Facility median treatment time in minutes	232.9	230.2	235.3	231.6	0.2
Facility % of patients with spKt/V >1.2	73.2	78.1	78.6	81.2	0.002
Facility % of patients with Hgb >10 g/dL	70.8	74.3	81.0	85.6	<0.001
Facility % of patients with AVF	68.3	63.3	67.3	59.4	0.4

AVF=arteriovenous fistula; spKt/V=single pool Kt/V.

US to International Conversions: serum calcium in mg/dL to mmol/L, x0.2495; hemoglobin in g/dL to g/L, x10; serum phosphorus in mg/dL to mmol/L, x0.3229.

* Data of patients enrolled in the three DOPPS phases were used for the analysis. Case-mix adjusted facility percentage of phosphate binder (PB) prescription was estimated by a linear regression model with fixed effects for facility, adjusted for age, sex, race, years on dialysis, coronary artery disease, congestive heart failure, hypertension, diabetes, peripheral artery disease, recurrent cellulitis/gangrene, neurologic disease, lung disease, gastrointestinal bleeding in prior 12 months, cancer, catheter use for vascular access, and baseline serum phosphorus.

** Trend analysis was based on a linear regression model predicting levels of each patient characteristic in relationship to case-mix adjusted facility percentage PB prescription modeled as a continuous variable adjusting for geographic regions and study phase. Similar results for the trend analyses were obtained when case-mix adjusted PB prescription was modeled as ordinal variable.