




## ORIGINAL ARTICLE

# European hemodialysis patient satisfaction with phosphate binders is associated with serum phosphorus levels: the Dialysis Outcomes and Practice Patterns Study

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## ABSTRACT

**Background.** Hemodialysis (HD) patients are commonly prescribed phosphate binders (PBs) to manage serum phosphorus levels, as hyperphosphatemia is strongly associated with poorer survival. Nonadherence with the PB prescription is associated with elevated serum phosphorus levels. We studied associations between patient satisfaction with their PB and serum phosphorus levels and mortality rates.

**Methods.** Adult HD patients in Germany, Italy, Spain and the UK in the Dialysis Outcomes and Practice Patterns Study were administered a survey instrument in late 2017. Patients were asked about their satisfaction with their PBs, as measured through three questions (difficulty, inconvenience and dissatisfaction) on a 5-point Likert scale, with each dichotomized into average worst versus good responses. These were used as predictors in linear regression models of continuous serum phosphorus levels and in Cox proportional hazards models of mortality, with adjustments for demographics, comorbidities and laboratory values.

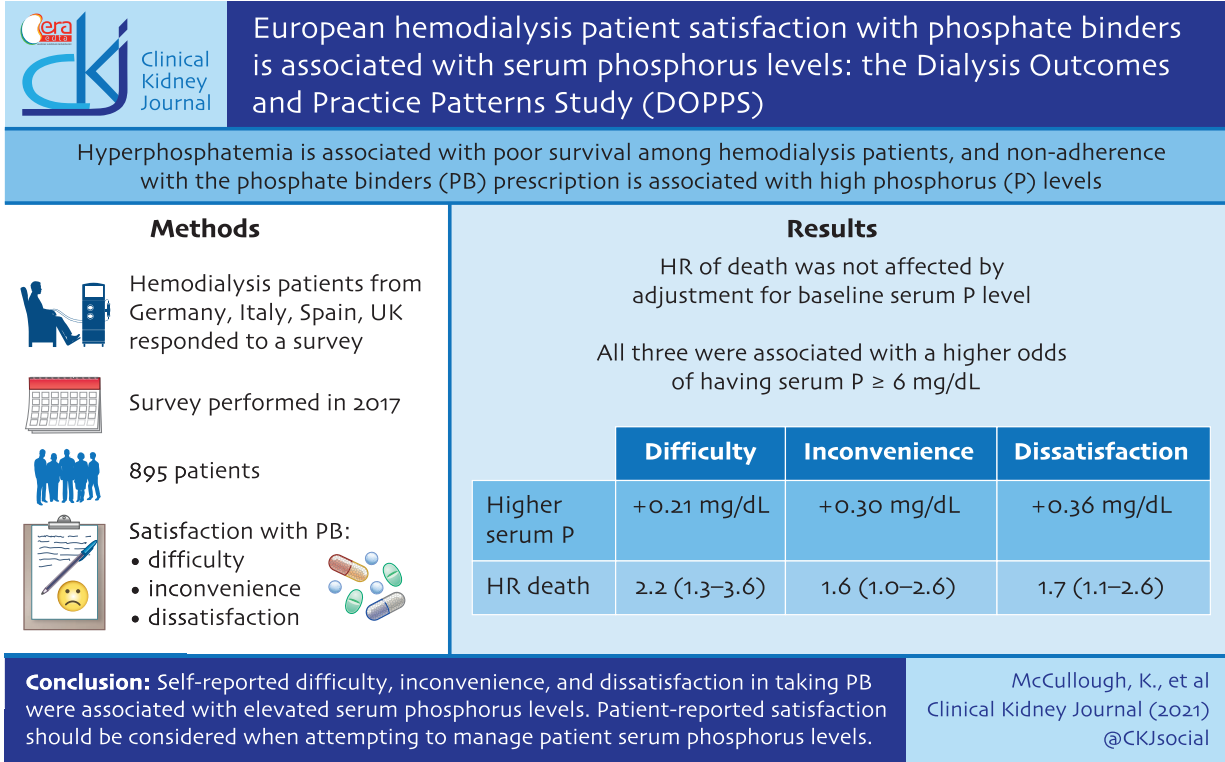
**Results.** Patients having greater difficulty, inconvenience and dissatisfaction with their PB had higher serum phosphorus levels in adjusted models {+0.21 mg/dL [95% confidence interval (CI) ±0.23], +0.30 (±0.21) and 0.36 (±0.22), respectively}, and higher odds of having serum phosphorus levels ≥6.0 mg/dL. Measures of dissatisfaction were also associated with an

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## GRAPHICAL ABSTRACT



elevated risk of mortality, with adjusted hazard ratios of 2.2 (95% CI 1.3–3.6), 1.6 (1.0–2.6) and 1.7 (1.1–2.7), respectively; this association was not strongly affected by adjustment for baseline serum phosphorous level.

**Conclusions.** Self-reported difficulty, inconvenience and dissatisfaction in taking one's prescribed PBs were associated with elevated serum phosphorus levels and serum phosphorus levels above clinically meaningful thresholds. While the mechanism for the association with mortality is unclear, patient-reported satisfaction should be considered when attempting to manage patient serum phosphorus levels.

**Keywords:** hemodialysis, mortality, patient adherence, patient-reported outcomes, patient satisfaction, phosphate binders, serum phosphorus

## INTRODUCTION

Approximately 80% of hemodialysis (HD) patients are prescribed phosphate binders (PBs) to manage serum phosphorus levels, as hyperphosphatemia is associated with an increased risk of mortality among HD patients [1]. A substantial fraction of patients has reported challenges with self-management, such as adherence issues, when taking prescribed PBs, with nonadherence associated with elevated serum phosphorus levels ( $\geq 5.5$  mg/dL) [2]. PB use has been linked with lower mortality risk among patients with serum phosphorus levels  $>3.5$  mg/dL [3]. Previous studies have found that PB pill burden is associated with lower adherence [4, 5]. Other aspects of patient satisfaction with their PB may also influence adherence. High serum phosphorus levels among HD patients have been linked with patient symptoms such as bone and joint pain and itchy skin in some studies [6, 7] but not others [8–10]. Patient issues with taking their PB may be an important link in the patient adherence causal chain,

ultimately affecting clinical outcomes. This is illustrated in the following simplified causal chain diagram:

Patient PB satisfaction  $\rightarrow$  adherence  $\rightarrow$  phosphate control  $\rightarrow$  outcomes (mortality, symptoms)

Our primary objective was to investigate the association between measures of patient satisfaction with PBs and phosphate control after adjustment for patient factors (demographics and comorbid factors). We assessed this association among all patients and within patient subgroups (e.g. patients with varying pill burdens, patient age groups and country). We also investigated the association between measures of patient PB satisfaction and mortality.

## MATERIALS AND METHODS

The Dialysis Outcomes and Practice Patterns Study (DOPPS; www.dopps.org) is an international prospective cohort study of

Table 1. STROBE diagram of patient inclusion/exclusion

Inclusion criteria	Included, n	Excluded, n
Total patients in these Phase 6 countries	2233	
Patients with ePQ	1733	500 <sup>a</sup>
Patients with nonmissing age	1716	17
Patients with ePQ who specify they took a PB	951	367 missing data <sup>b</sup> , 398 'no'
Has prescription data on renal medications	916	35
ePQ filled out before last date of follow-up	901	15
Nonmissing serum phosphorus data	895	6
Patients used in analyses	895	

Thirty-nine patients had ePQ responses but no interval summary (IS) data. These were kept, with the assumption that the IS data were missing at random.

<sup>a</sup>150 of these patients left the study before the first ePQ was distributed.

<sup>b</sup>Among patients who did not respond as to whether they were taking a PB, only 7 of the 367 responded to other questions. We omitted all patients without a response on this.

Seventy-four patients skipped at least one adherence measure question. The questions most often skipped were 2 (problems remembering) and 4 (worse when taking), with 42 patients skipping each of these questions. The questions least often skipped were 1 (ever forget) and 5 (misses when away), with 29 and 31 patients skipping these questions, respectively.

patients  $\geq 18$  years of age receiving in-center HD for treatment of end-stage kidney disease. The analyses were based on 895 HD patients among those randomly selected to participate in Phase 6 of the DOPPS (2016–18) from national samples of dialysis facilities in Germany, Italy, Spain and the UK who completed an electronic patient questionnaire (ePQ) survey in 2017 and met other study inclusion criteria [see Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) inclusions/exclusions; Table 1]. This ePQ survey was developed to assess a patient's self-reported use, adherence and perspectives regarding the PB prescribed for managing serum phosphorus levels. The ePQ survey was offered to 2233 patients and completed by 1733 patients; 838 of these patients were excluded from analyses for the reasons identified in Table 1 (e.g. for not being on a PB at the time of survey completion), resulting in a total of 895 patients included in the current analyses. Missing data among patients in this group were handled using multiple imputation (SAS MI procedure using fully conditional specification methods, 30 imputations; SAS Institute, Cary, NC, USA) and Supplementary data, Table S1 shows that patients excluded (e.g. due to not filling out the questionnaire) were on average 2.4 years older and more likely to have comorbid conditions.

The data underlying this article cannot be shared publicly due to privacy concerns for the individuals who participated in the study. The data will be shared upon reasonable request to the DOPPS project (see <https://www.dopps.org/PartnerwithUs.aspx> for more information). National and/or local ethics committee study approval and written informed consent from patients were obtained in carrying out this study.

### Patient-reported PB issues

Information on patient satisfaction with taking their PBs was collected through the following three questions:

- How easy or difficult is it to take your PBs in its given form? (1 = very easy, 5 = very difficult).
- How convenient or inconvenient is it to take your PBs as instructed? (1 = very convenient, 5 = very inconvenient).
- Taking all things into account, how satisfied or dissatisfied are you with your PBs? (1 = very satisfied, 5 = very dissatisfied).

Distributions of these responses by country are shown in Supplementary data, Table S2. Similarly, patient adherence with their PB prescription was measured as a summary of eight questions (see Supplementary data, Table S3a and b). For some

analyses, these patient-reported PB issues were dichotomized, allowing comparisons between average to very difficult/inconvenient/dissatisfied responses regarding PBs versus very or moderately easy/convenient/satisfied responses. Patient adherence to their PB was also dichotomized at the median score for some analyses.

### Analyses of serum phosphorus control as the outcome

Linear regression models were used to assess adjusted associations between patient satisfaction with their PB and serum phosphorus levels as a continuous outcome. As sensitivity analyses, logistic models were used to assess associations between patient satisfaction with their PB and patients having a concurrent serum phosphorus level above various thresholds ( $\geq 6.0$ ,  $\geq 6.5$  and  $\geq 7.0$  mg/dL). In sensitivity analyses, patients with low serum phosphorus levels ( $< 2.5$ ,  $< 3.0$  or  $< 3.5$  mg/dL) were excluded from the analyses due to prior studies indicating that these patients have poorer survival, possibly due to malnutrition/cachexia [3, 11], and raising the question whether these patients should be prescribed a PB due to such nutritional issues. These analyses were cross-sectional, as laboratory values were from the most recent available value prior to a patient completing the patient satisfaction survey. Sequential adjustment was used in all analyses, with models adjusted for country, then demographics and comorbidities [age, years on dialysis, sex, body mass index and 13 comorbid conditions (coronary artery disease, cancer, other cardiovascular diseases, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurological disease, psychiatric disorder, peripheral vascular disease and recurrent cellulitis)], then treatment factors (PB type, number of medications and PB pill burden) and serum albumin. Our models incorporated an empirical repeated-measures variance estimate (with an exchangeable correlation structure) to account for within-facility clustering.

### Analyses of patient survival

Cox proportional hazards survival models were used to assess adjusted associations between patient satisfaction with their PB and patient survival from the time of ePQ survey completion to the first of death, transplantation, dialysis modality switch, sufficient recovery to discontinue dialysis, 7 days after the patient's transfer to another dialysis facility or the end of DOPPS Phase 6 follow-up. There was a median of 0.7 years/patient of follow-up

for mortality analyses (interquartile range 0.5–0.8) of follow-up for mortality analyses. Adjustments and sensitivity analyses excluding patients with low serum phosphorus levels were handled as described in the analyses of serum phosphorus control. In addition, to assess the degree to which the association between patient satisfaction with their PB and survival was operating through serum phosphorus control, serum phosphorus level was added as a final adjustment in the models to determine its effect on the estimates. Our survival models used a robust sandwich variance estimator to account for within-facility clustering.

## RESULTS

### Patient satisfaction with their PB and other patient-reported factors

Responses to the three questions about patients' satisfaction with their PB had a standardized Cronbach's  $\alpha$  of 0.85 (see [Supplementary data, Table S4](#)). This measure of internal consistency suggests that responses to these questions are in sufficient agreement to regard them as one group [12]. Adding our summary nonadherence measure based on eight questions reduced the Cronbach's  $\alpha$  to 0.80. When these four questions were tested with other patient-reported factors, the Cronbach's  $\alpha$  score dropped to 0.56–0.66, which is below most standard thresholds for acceptability [13]. The eight questions regarding adherence had a standardized Cronbach's  $\alpha$  of 0.89, indicating good agreement between them.

### Description of the patient study population

[Table 2](#) shows country comparisons of case-mix factors and measures of patient satisfaction with their PB. Most factors were distributed similarly among the countries. However, Germany had more patients with very high serum phosphorus levels ( $\geq 7.0$  mg/dL). [Table 3](#) shows the characteristics of patients who had positive (very or moderately easy/convenient/satisfied) responses to each of the three PB satisfaction questions versus patients who did not have positive responses. Patients who had positive responses tended to be older, averaging 65.3–66.1 years depending on which PB satisfaction question was answered positively, compared with 62.3–63.7 years for patients who did not respond positively. Few of the other factors listed had consistent associations with the above measures of patient satisfaction with their PB.

We investigated skipped treatments to see if this factor, being one type of treatment nonadherence, was predictive of PB nonadherence or patient satisfaction with their PB. Skipped treatments were positively associated with increased PB nonadherence and greater difficulty, albeit with  $P \geq 0.29$ , possibly because skipped treatments were rare in this population within the countries represented.

### Patient nonadherence and dissatisfaction with their PB are associated with serum phosphorus levels

Patient nonadherence and dissatisfaction with their PB were both associated with higher serum phosphorus levels, even after adjustment for patient characteristics ([Figure 1](#)). Serum phosphorus levels were 0.21 mg/dL higher ( $P = 0.07$ ) for patients who found their PB difficult, 0.30 mg/dL higher ( $P = 0.004$ ) for patients who found their PB inconvenient, 0.36 mg/dL higher ( $P = 0.002$ ) for patients who were dissatisfied with their PB and 0.47 mg/dL higher ( $P < 0.0001$ ) for patients who reported

nonadherence in taking their PB. This figure also shows the results of sensitivity analyses excluding patients with low serum phosphorus levels ( $< 2.5$ ,  $< 3.0$  and  $< 3.5$  mg/dL), in case these patients were fundamentally different (e.g. due to nutritional issues). These analyses produced similar estimates, usually within 0.06 mg/dL. The associations between measures of patient dissatisfaction with their PB and elevated serum phosphorus levels were universally positive.

Patient dissatisfaction measures with their PB were also associated with serum phosphorus levels at or above thresholds of 6.0, 6.5 and 7.0 mg/dL ([Supplementary data, Figures S1–S3](#): difficulty, inconvenience and dissatisfaction). While the direction of the association was consistent across every threshold of serum phosphorus level, the P-values for the fully adjusted models across the various thresholds and when patients with low serum phosphorus were excluded ranged from 0.006 to 0.34 for difficulty, from 0.01 to 0.52 for inconvenience and from 0.03 to 0.51 for dissatisfaction. The magnitudes of the odds ratios were generally largest at or above a threshold of 6.0 mg/dL.

Adjustment for patient demographics, case mix and PB type does not have a large effect on either the linear or the logistic serum phosphorus associations ([Figure 1](#); [Supplementary data, Figures S1–S4](#)).

Patient satisfaction with their PB was associated with serum phosphorus levels in consistent directions across subgroups by age, sex, comorbidity, education and country ([Figure 2](#)). The smaller numbers resulted in less precise estimates having wide confidence intervals. Three of the 21 interactions tested had P-values  $\leq 0.05$  (difficulty  $\times$  age, with  $P = 0.05$ ; inconvenience  $\times$  CAD, with  $P = 0.05$ ; and dissatisfaction  $\times$  CAD, with  $P = 0.01$ ), but after Benjamini–Hochberg correction for multiple comparisons, all P-values for interactions were  $> 0.20$ , indicating that the association between patient satisfaction with their PB and serum phosphorus levels was independent of these factors.

### Patient nonadherence and dissatisfaction with their PB are associated with higher mortality rates

Negative responses to any of the questions about patient satisfaction with their PB were associated with higher risks of mortality ([Figure 3](#)). The P-values ranged from 0.003 to 0.12. The associations were nearly as strong when serum phosphorus levels were accounted for, implying that the primary causal pathway is not through the serum phosphorus level. The associations were similar when adjusting only for country; when adjusting for country, demographics and comorbidities; and when type of PB, serum albumin, number of nonrenal medications and total pill burden were added to the model ([Supplementary data, Figure S5](#)).

## DISCUSSION

This study showed that patients' responses to questions about their difficulty, inconvenience and dissatisfaction in taking their PB, as well as their adherence to their PB prescription, were associated with elevated serum phosphorus levels and with serum phosphorus levels above clinically meaningful thresholds ([Figure 1](#)).

While some of these associations are individually statistically significant and others are not, the pattern is consistently positive. Dissatisfaction and nonadherence had slightly stronger associations than difficulty and inconvenience. Adjusting for potential confounders, varying the upper threshold and excluding patients with very low serum phosphorus levels had

Table 2. Case-mix factors and patient-reported PB issues by country

Factors	Germany	Italy	Spain	UK
Patients, n	258	165	282	190
Demographics				
Age (years), median (IQR)	67 (53–76)	70 (56–78)	68 (57–78)	66 (53–74)
Male, %	66	63	60	65
Education (<12 years), %	54	41	45	15
Education (≥12 years), %	17	51	39	16
Unknown education, %	29	8	16	68
Years on dialysis, median (IQR)	3.4 (1.6–6.2)	2.5 (1.1–6.9)	2.8 (0.8–6.3)	1.3 (0.4–4.4)
Comorbid factors, %				
Cancer	16	13	17	12
Cerebrovascular	11	11	15	12
Congestive heart disease	14	15	24	10
Coronary heart disease	38	23	22	24
Diabetes	33	33	42	36
Hypertension	95	83	91	65
Lung disease	16	17	15	7
Neurological disease	12	11	9	8
Psychiatric disorder	16	13	17	6
GI bleed	6	4	4	1
Laboratory values				
Serum phosphorus (mg/dL), median (IQR)	5.7 (4.6–6.8)	4.8 (4.1–5.7)	4.7 (3.7–5.7)	5.1 (4.3–6.1)
Serum phosphorus <2.5, %	0	1	4	2
Serum phosphorus 2.5–3.4, %	5	8	14	6
Serum phosphorus 3.5–5.4, %	40	59	51	50
Serum phosphorus 5.5–5.9, %	13	13	9	15
Serum phosphorus 6.0–6.4, %	14	9	8	9
Serum phosphorus 6.5–6.9, %	6	2	4	7
Serum phosphorus ≥7.0, %	22	6	10	11
Serum albumin (mg/dL), median (IQR)	3.9 (3.6–4.2)	3.7 (3.4–4.1)	3.9 (3.6–4.1)	3.9 (3.6–4.2)
ePQ responses				
Summary adherence measure, median (IQR)	9 (8–13)	10 (8–14)	10 (8–14)	11 (8–13)
Difficulty with PB (n), median (IQR)	2 (2–2)	2 (2–3)	2 (2–2)	2 (1–3)
Difficulty with PB (avg-worst <sup>a</sup> ), %	24	29	22	27
Convenience of PB, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	2 (1–3)
Convenience of PB (avg-worst <sup>a</sup> ), %	34	27	27	27
Satisfaction with PB, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	2 (1–3)
Satisfaction with PB (avg-worst <sup>a</sup> ), %	25	34	36	27
Other medication data, %				
PB taken				
Sucroferric oxyhydroxide	3	3	12	1
Sevelamer	43	55	51	24
Calcium-based	29	24	25	46
Lanthanide	17	11	25	13
Any PB	84	82	88	80
Patient-reported PB pills/day, median (IQR)	9.5 (7–13)	6 (4–8)	8 (5–10)	8 (5–10)
Number of nonrenal medications, median (IQR)	7 (6–9)	6 (5–8)	6 (5–8)	6 (5–8)
Clinical outcomes				
No. of deaths (rate/year)	19 (0.12)	15 (0.16)	30 (0.17)	20 (0.16)
No. of patients with hospitalization: total (rate/year)	49 (0.35)	8 (0.09)	14 (0.08)	42 (0.41)
Total follow-up (years)	163	96	176	122

<sup>a</sup>'avg-worst' indicates responses of 3–5, indicating responses of average to very difficult/inconvenient/dissatisfied versus responses of very or moderately easy/convenient/satisfied.

GI, gastrointestinal; IQR, interquartile range.

some effect on these associations, but the direction and magnitude were similar (Supplementary data, Figures S1–S4).

Nonadherence, difficulty, inconvenience or dissatisfaction in taking one's PB was associated with higher mortality risk (Figure 2). This association also remained positive after varying levels of adjustment and after excluding patients having low serum phosphorus levels (Supplementary data, Figure S5). Controlling for actual serum phosphorus levels reduced the

strength of these mortality associations by a relatively small amount, implying that most of the causal pathway between these patient-reported factors and subsequent mortality is not through the level of serum phosphorus control.

The mechanism(s) through which lower patient satisfaction is linked with increased mortality risk is currently unknown. It might be expected that patients who are less adherent in their PB usage might be less adherent in other aspects of their



Table 3. Case-mix factors by satisfaction indicator with PB

	Nonadherence		Difficult		Inconvenient		Dissatisfaction	
	Good	Worse	Good	Avg-worst	Good	Avg-worst	Good	Avg-worst
Germany, %	29	24	28	24	26	29	29	21
Italy, %	19	20	18	24	20	18	19	21
Spain, %	32	33	34	29	33	32	29	39
UK, %	19	23	20	24	21	21	22	18
Age (years), mean (SD)	67.1 (13.4)	62.3 (15.4)	65.3 (14.1)	63.6 (15.8)	65.4 (13.7)	63.7 (16.6)	66.1 (13.8)	62.3 (15.9)
Time on dialysis (years), mean (SD)	4.7 (5.9)	5.0 (7.0)	4.9 (6.6)	4.6 (6.0)	4.9 (6.4)	4.7 (6.4)	5.0 (6.6)	4.4 (6.1)
Male, %	62	63	64	58	61	65	61	66
BMI, mean (SD)	26.8 (5.4)	26.8 (5.7)	26.8 (5.5)	27.0 (5.6)	26.7 (5.3)	27.2 (6.0)	26.7 (5.4)	27.1 (5.8)
CAD, %	30	22	27	25	27	26	27	25
Other cardiovascular, %	32	25	29	29	29	29	30	25
Cerebrovascular, %	12	13	13	12	13	12	13	12
CHF, %	19	12	16	14	17	13	16	15
Diabetes, %	41	33	37	37	37	37	39	33
Cancer, %	15	14	14	16	15	14	14	15
GI bleeding, %	3	3	3	2	4	2	3	4
Hypertension, %	86	84	86	85	86	84	86	84
Lung disease, %	13	15	14	14	14	15	14	14
Neurological disease, %	9	10	9	12	9	10	10	8
Psychiatric disorder, %	12	16	13	17	13	16	13	16
PVD, %	26	19	23	24	22	26	22	24
Recurrent cellulitis, %	9	8	8	11	8	10	8	9
Any skipped dialysis sessions/month, %	2	3	2	4	3	3	3	3
Sucroferric oxygen, %	4	7	5	7	5	8	5	8
Sevelamer, %	43	43	43	44	43	44	43	43
Calcium-based PB, %	31	30	33	23	32	28	32	29
Lanthanide, %	15	22	17	23	17	21	19	18
Serum albumin (g/dL), mean (SD)	3.8 (0.4)	3.8 (0.5)	3.8 (0.4)	3.8 (0.5)	3.8 (0.4)	3.8 (0.5)	3.8 (0.4)	3.8 (0.5)
Prescribed nonrenal meds, n (%)	8.3 (3.8)	8.0 (3.7)	8.2 (3.7)	8.1 (3.9)	8.3 (3.7)	7.9 (3.9)	8.4 (3.7)	7.7 (3.9)
Total pills, n (%)	6.9 (2.6)	7.0 (2.8)	6.9 (2.6)	7.0 (2.9)	6.8 (2.6)	7.2 (2.9)	7.0 (2.7)	6.8 (2.8)
Nonadherence, %	0	100	39	68	36	73	34	74
Difficulty taking, %	15	36	0	100	11	58	10	57
Inconvenient, %	15	45	16	68	0	100	10	69
Dissatisfaction, %	15	50	18	73	14	75	0	100

For patient-reported PB satisfaction questions: 'good' = very easy or easy, very convenient or convenient or all very satisfied or satisfied, depending on the question. 'Avg-worst' = average, difficult or very difficult; average, inconvenient or very inconvenient; average, dissatisfied or very dissatisfied. For non-adherence, 'good' = scores of 8–10 and 'worse' = scores of 11–24.

BMI, body mass index; CHF, congestive heart failure; PVD, peripheral vascular disease; SD, standard deviation.

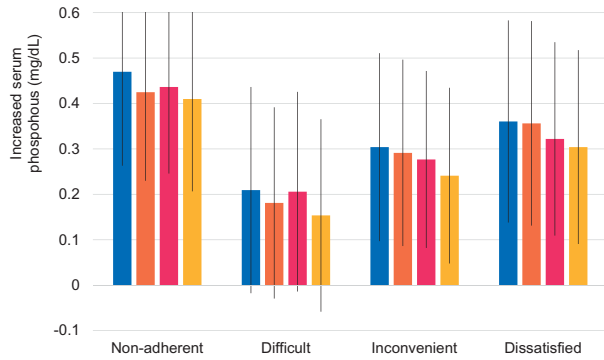
dialysis care, but one such measure, namely skipped HD treatments, was not substantially associated with these PB measures (Table 3). However, patients who reported measures of dissatisfaction with their PBs also reported worse effects and symptoms of kidney disease (Supplementary data, Table S5), even though these patients tended to be younger (Table 3).

Patients expressing dissatisfaction and nonadherence with their PB were generally younger (Table 3). This is consistent with other studies showing that younger patients are less adherent to PBs and to dietary phosphate intake recommendations [14]. Younger dialysis patients may also be less adherent to other aspects of dialysis treatment [15, 16]. Identifying the reasons why younger patients have particular adherence issues may lead to improved outcomes.

The findings regarding patient dissatisfaction with taking PBs may reflect other patient issues with their own, separate impacts on outcomes. While the Cronbach's  $\alpha$  results indicated that patient satisfaction with PBs differs from other patient-reported outcomes, which does not mean that these measures

are uncorrelated. We show this to be the case regarding substantial association of patient dissatisfaction with burden of kidney disease despite a lower Cronbach's  $\alpha$  correlation score. Additionally, being dissatisfied and nonadherent in taking PBs may be manifestations of broader difficulties coping with kidney disease or other underlying issues. Discussions regarding these issues coupled with shared decision-making regarding HD care may reduce dissatisfaction and alleviate some of the burden of kidney disease [17]. Also, the extent to which HD patients feel burdened by their kidney disease can affect the efficacy of a prescribed treatment. These related issues of patient satisfaction with a given treatment, adherence to the treatment and burdens of kidney disease should be included as key considerations when designing clinical trials and when assessing the efficacy of a drug in real-world settings.

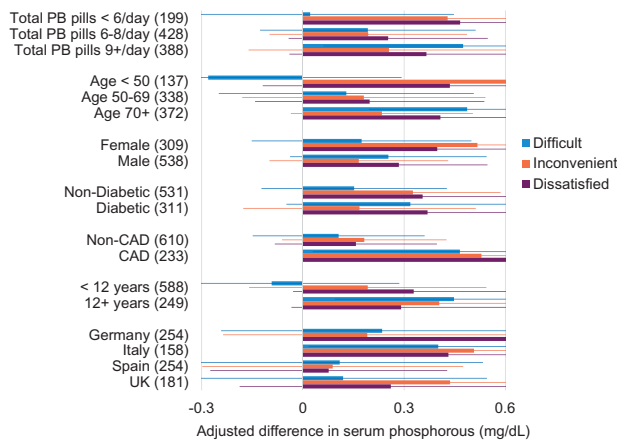
Patients who reported levels of nonadherence with their PB above the median were more likely to report difficulty (36% versus 15%), inconvenience (45% versus 15%) and dissatisfaction (50% versus 15%) with their PB (Table 3). Patient-reported



Different models excluded patients with serum phosphorous levels below threshold:

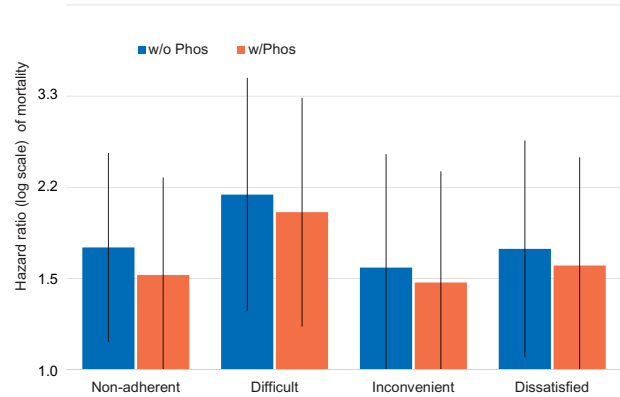
■ No exclusion ■ Excluded <2.5 mg/dL ■ Excluded <3.0 mg/dL ■ Excluded <3.5 mg/dL

**FIGURE 1:** Patient-reported PB issues as predictors of higher serum phosphorus levels in adjusted models, with various exclusions for patients with very low serum phosphorus levels. Patients with serum phosphorus levels below the threshold identified (no threshold, <2.5, <3.0 and <3.5 mg/dL) were excluded from each separate model run. Responses indicating difficulty, inconvenience or dissatisfaction measured as avg-worst versus good (see Table 3 definitions). Results are from linear models on serum phosphorous (mg/dL) adjusted for country indicators (Germany, Italy, Spain and UK), age, time on dialysis at study start, sex, body mass index, 13 comorbid conditions, the type of PB (sucroferic oxyhydroxide, sevelamer, calcium-based and lanthanide), serum albumin, number of nonrenal medications taken and total pills indicated by the patient on their ePQ. P-values for responses indicating difficulty were 0.07, 0.09, 0.07 and 0.16 for no exclusion, exclusion of <2.5 mg/dL, exclusion of <3.0 mg/dL and exclusion of <3.5 mg/dL, respectively. Similarly, P-values for responses indicating inconvenience were 0.004, 0.005, 0.005 and 0.015 and P-values for responses indicating dissatisfaction were 0.0015, 0.0019, 0.003 and 0.005. P-values for non-adherence were <0.0001 for all four models.



**FIGURE 2:** Forest plot of adjusted association between PB satisfaction and serum phosphorus (mg/dL). Excludes patients with serum phosphorous levels <3.0 mg/dL. Linear models on serum phosphorous (mg/dL) were adjusted for country indicators (Germany, Italy, Spain and UK), age, time on dialysis at study start, sex, body mass index, 13 comorbid conditions, the type of PB (sucroferic oxyhydroxide, sevelamer, calcium-based and lanthanide), serum albumin, number of nonrenal medications taken and total pills indicated by the patient on their ePQ.

dissatisfaction with their PB was strongly predictive of nonadherence, even after adjustment for case mix. There did not seem to be a specific component aspect of nonadherence that was substantially better predicted by any particular measure of patient satisfaction with their PB (Supplementary data, Figure S6).



**FIGURE 3:** Patient-reported PB satisfaction as predictors of mortality (progressive adjustment). Excludes patients with serum phosphorus levels <3.0 mg/dL. 'w/Phos' means that serum phosphorus level was added to the model as a linear term. Difficulty, inconvenience and dissatisfaction measured as average worst versus good (see Table 3 definitions). Cox proportional hazards models on mortality were adjusted for country indicators (Germany, Italy, Spain and UK), age, time on dialysis at study start, sex, body mass index, 13 comorbid conditions, the type of PB (sucroferic oxyhydroxide, sevelamer, calcium-based and lanthanide), serum albumin, number of nonrenal medications taken and total pills indicated by the patient on their ePQ. P-values for responses indicating difficulty with their PB were 0.003 and 0.007 for the models without and with adjustment for serum phosphorous, respectively. Similarly, P-values for responses indicating inconvenience were 0.08 and 0.12, P-values for responses indicating dissatisfaction were 0.03 and 0.06 and P-values for responses indicating nonadherence were 0.01 and 0.06.

Analyses of interactions between predictive factors, in this case, whether the association between patient-reported factors such as adherence, difficulty, inconvenience or dissatisfaction varies by patient group, require more statistical power than analyses of main effects. While there was variation among the subgroups, most of this variation stemmed from small numbers of high-phosphorus cases among patients within smaller subgroups.

A few factors may be of interest and warrant future investigation. The associations between patient-reported factors and serum phosphorus level were generally weaker in Spain than in the other countries, even though Spain had a higher percentage of respondents who were dissatisfied with their PBs. This may point to cultural differences either in patient actions or in their responses to the questions.

### Caveats/limitations

As with any observational study, there is the possibility of unmeasured confounders, and the analyses were limited to patients who responded to the survey. There was a limited follow-up for mortality analyses after the survey was administered. Laboratory values (including serum phosphorus) were taken before the survey was administered. Dichotomization of patient satisfaction with PB responses may have obscured informative differences between different levels of response to each question.

### SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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## CONFLICT OF INTEREST STATEMENT

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## APPENDIX

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