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Abstract

Background: Whether the benefits of phosphorus binders extend to those without end stage renal disease is uncertain. Among a large diverse non-dialysis chronic kidney disease (CKD) population with hyperphosphatemia, we sought to evaluate phosphorus binder use and compare mortality risk between patients prescribed and not prescribed binders. **Methods:** A retrospective cohort study within an integrated health system (January 1, 1998 – December 31, 2012) among CKD patients (age ≥18) was performed. Non-dialysis CKD patients with 2 separate estimated glomerular filtrate rate (eGFR) <30 mL/min/1.73 m^2 and serum phosphorus ≥5.0 mg/dL within 180 days of eGFR were included. Multivariable cox proportional hazards and inverse probability of treatment-weighted models were used to estimate mortality hazard ratios (HRs) for patients who received phosphorus binders compared to no binders. **Results:** Among 10,165 study patients, 2,733 subjects (27%) received phosphorus binders. Compared to the no-phosphorus–binder group, the binder group had mortality HRs (95% CI) of 0.86 (0.79–0.94) and 0.86 (0.80–0.93) using traditional multivariable and inverse probability of treatment-weighted models respectively. Sensitivity analyses removing patients who were prescribed binders >180 days after index date revealed no difference in mortality between those with binders and with no binders. **Conclusion:** Our findings from a real-world clinical environment revealed that 27% of hyperphosphatemic non-dialysis CKD patients were prescribed binders. They also had lower risk of mortality compared to those not prescribed phosphorus binders. However, the lower mortality risk was not observed when we accounted for immortal time bias. Whether phosphorus binder use in CKD improves survival remains to be determined.

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Background

Elevated serum phosphorus levels or hyperphosphatemia is a predictor of worsened cardiovascular and all-cause mortality outcomes among the end-stage renal disease (ESRD) population [1–5]. Treatment of hyperphosphatemia is commonly achieved through dietary

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restriction and administration of phosphorus-binding agents [6]. The use of these phosphorus binders in the dialysis population has been associated with improved outcomes and survival [7–9]. The benefits of binders have even been suggested to correct the pleiotropic condition and extend beyond the phosphorus-lowering effect [7–9].

The adverse outcomes associated with hyperphosphatemia are presumed to exist in the non-dialysis-dependent chronic kidney disease (CKD) population. To a lesser extent, hyperphosphatemia adversely affects the general population as well [10]. Elevations in serum phosphorus are not uncommon among the pre-dialysis CKD population where it is also associated with increased risk for cardiovascular and mortality outcomes [10–16]. Thus, strategies to improve phosphorus may lead to better outcomes and survival in non-dialysis CKD patients.

Few studies among non-dialysis-dependent CKD patients have demonstrated a survival advantage of phosphorus binder use [17, 18]. Admittedly these studies were derived from smaller specialized populations. Earlier treatment of hyperphosphatemia may be a better approach to CKD and transition to ESRD management. However, phosphorus binders are not FDA approved for use among the non-dialysis CKD population and very few are actually prescribed binders [19]. More studies on phosphorus binder use and outcomes among non-dialysis CKD patients would provide insights and pave the way for more definitive implementation strategies and recommendations for CKD-mineral bone disorders (CKD-MB) as a prelude to dialysis.

Using a large diverse population from a routine clinical practice environment, we sought to evaluate the rates of phosphorus binder use among non-dialysis CKD patients who had hyperphosphatemia. Among those CKD patients who were prescribed phosphorus binders compared to those not prescribed binders, we compared the risk for mortality and ESRD. Given the confounding by indication bias, we identified only patients who had elevated phosphorus measurements and performed instrumental variable analyses using propensity score adjusted and inverse probability of treatment-weighted modeling.

Methods

Study Population
A retrospective cohort study of Kaiser Permanente Southern California (KPSC) members was performed between January 1, 1998 and December 31, 2012. KPSC is a prepaid integrated health system (comprised of 14 medical centers and over 200 satellite clinics) that provides comprehensive care to over 4.2 million members throughout Southern California. As of December 31, 2012, there were over 2.5 million adult members within KPSC. The patient population is racially/ethnically and socioeconomically diverse, reflecting the general population of Southern California [20]. All KPSC members have similar benefits and access to healthcare services, clinic visits, procedures, and copays for medications. Complete healthcare encounters are tracked using a common electronic health record (EHR) from which all study information was extracted. The study was approved by the KPSC Institutional Review Board and exempted from informed consent.

The study population included individuals aged 18 years and older identified in the time period between January 1, 1998 and December 31, 2012. This cohort was followed until they experienced any outcome or for up to 2 years until the end of the observation period (December 31, 2014). In order to be included in this study, all individuals were required to have a minimum of 2 outpatient creatinine measurements 30 days or more apart that demonstrated an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 on both measurements. The eGFR was calculated using the CKD-Epidemiology Collaboration equation [21]. All subjects were required to have a minimum of 6 months of continuous membership in the health plan prior to the first creatinine measurement to reliably capture comorbidities. The date of the first eGFR <30 mL/min/1.73 m^2 measurement was used as the index date. All subjects were also required to have a phosphorus measurement of ≥5.0 mg/dL within 180 days of their first eGFR <30 mL/min/1.73 m^2 measurement. Individuals were excluded if they had any prior or active ESRD (treatment with hemodialysis or peritoneal dialysis, or renal transplantation) prior to the first eGFR <30 mL/min/1.73 m^2 measurement.

Phosphorus binder medication use was retrieved from KPSC pharmacy and analytic database. Prescription orders, pharmacy fills, and refills were tracked for KPSC members with pharmacy benefits. Individuals were determined to be on a phosphorus binder medication if it was prescribed and dispensed/sold by the pharmacy. Medications that were prescribed and sold for less than 30 days were not considered treated. The total number of phosphorus-binding medications was defined by the number of different phosphorus-binding medications prescribed to each individual. Phosphorus-binding medications were categorized as calcium-based binders (calcium acetetate or calcium carbonate) or non-calcium-based binders (sevelamer, lanthanum, or aluminum). Over-the-counter binders, namely, calcium carbonate were not reliably captured unless individual clinicians entered them in the HER as historical medicines.

Data Collection and Laboratory Measurements
All laboratory data, vital sign assessments, and diagnostic and procedure codes were collected in the EHR as part of routine clinical care encounters. Comorbidities, including hypertension (HTN), diabetes mellitus (DM), ischemic heart disease (IHD), congestive heart failure (CHF), and cerebrovascular disease were assessed based on inpatient and outpatient International Classification of Diseases (ICD) diagnoses coding. The Deyo adaption of the Charlson comorbidity index was determined using ICD diagnoses codes from inpatient and outpatient encounters as an overall measure of disease burden [22]. Serum phosphorus levels were measured using a standard colorimetric method with normal reference values of 2.7–4.5 mg/dL (Roche Diagnostics, Alameda, CA, USA). When available, laboratory values on serum albumin, he-

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moglobin, calcium, and parathyroid hormone were extracted. All laboratory measurements are performed and reported from an American College of Pathology/Clinical Laboratory Improvement Act-certified laboratory. Data on hospitalizations and diagnoses that occurred outside the healthcare system were available through administrative claims records.

Outcomes

The primary outcome evaluated was all-cause mortality. Mortality information for the cohort was obtained from internal health systems databases that combined 6 data sources including California State Death Master Files, California State Multiple Cause of Death Master Files, Social Security Administration Death Files, Death Master Files, KPSC Hospital and Emergency Department records, KPSC Membership System, KPSC Perinatal Data Mart, and Outside Claims Processing System. December 31, 2014 was used to censor follow-up. Individuals were followed until death, disenrollment from the health plan for up to 2 years from index date, or until the end of the study period (December 31, 2014).

The secondary outcome evaluated was incident ESRD. Incident ESRD was defined as treatment with dialysis (hemodialysis and peritoneal dialysis) or renal transplant. ESRD was identified from the EHR, procedure coding data, Medicare Form 2728, and information from the KPSC Renal Business Group. Each outcome was followed up separately.

Statistical Analyses

The characteristics of patients prescribed phosphorus binders were compared to those not prescribed binders. Student t test or non-parametric Kruskal–Wallis tests were used for comparison of continuous variables as appropriate, and chi-square test was used for comparison of categorical variables.

The rate of phosphorus binder use among the study cohort was determined. The primary analysis was to compare the risk of all-cause mortality among those prescribed phosphorus binders versus those not prescribed binders. Event rates were determined for both groups. Cox proportional hazards regression modeling was used to estimate hazard ratios (HRs) for mortality in those prescribed phosphorus binders versus not prescribed binders. Multivariable HRs were calculated with adjustment for potential confounders including age, gender, race/ethnicity, Charlson comorbidity index, eGFR, phosphorus level, hemoglobin level, albumin level, and preexisting comorbidities including HTN, DM, IHD, CHF, cerebrovascular disease, year of first eGFR measurement, and year of first phosphorus binder prescription. To further account for treatment bias, 2 additional models (propensity score covariate adjustment and propensity score inverse probability weighting method [IPTW]) were performed. Propensity scores were calculated to minimize potential selection bias and confounding by indication. Propensity scores were generated using logistic regression modeling, which included age, gender, race/ethnicity, Charlson comorbidity index, eGFR, phosphorus level, and preexisting comorbidities including HTN, DM, IHD, CHF, and cerebrovascular disease. In the second propensity score model, IPTW was used to balance baseline characteristics of the 2 populations. Phosphorus binder prescription subjects received a weight of 1/propensity score and the no binder subjects received a weight of 1/(1-propensity score). The standardized difference (SD) was used to determine the balance of covariates and confounders in the all-cause mortality and ESRD models.

To eliminate the potential immortal time bias, further sensitivity analyses were conducted where individuals who were prescribed binders more than 180 days after their first eGFR <30 mL/min/1.73 m^2 were excluded. Multivariable cox proportional hazards regression modeling was used to estimate HRs for mortality and ESRD in those prescribed phosphorus binders versus those not prescribed binders after exclusion of subjects who received phosphorus binders >180 days after their initial eGFR measurement.

All statistical analyses were generated using the SAS statistical software version 9.3 (SAS Institute, Cary, NC, USA). Results with $p < 0.05$ were considered statistically significant. An absolute SD <0.1 also indicated negligible differences between the 2 cohort groups.

Results

Cohort Characteristics

A total of 10,165 subjects were identified for inclusion in the study (Fig. 1). The mean age was 66 years, with 69% of the population age ≥60 years. Males accounted for 53% of the study population. The race/ethnicity composition of the population was 50% non-Hispanic white, 18% black, 24% Hispanic white, and 7% Asian (Table 1). The mean eGFR was 22 mL/min/1.73 m^2 with 80% in the range of 15–30 mL/min/1.73 m^2. The mean phosphorus was 5.6 mg/dL. The majority of the cohort (52%) had phosphorus levels between 5 and <6 mg/dL. HTN was identified in 69%, while DM was present in 44% of the study cohort. Mean hemoglobin was 11.4 g/dL and mean albumin was 3.0 g/dL (Table 1).

Phosphorus Binder Prescribed Population

Phosphorus binders were prescribed for 2,733 (26.9%) patients. The phosphorus binder cohort was comprised of 54% males with 57% age ≥60 years. The phosphorus binder cohort had 76% with eGFR between 15–30 and 49.6% with phosphorus levels between 5 and <6 mg/dL. Average phosphorus, albumin, calcium, and hemoglobin levels were 5.6 mg/dL, 3.0 g/dL, 8.9 mg/dL, and 11.0 g/dL, respectively. Among the binder population, 1,561 patients were prescribed calcium-based binders, 652 patients were prescribed non-calcium-based binders, and the remainder (520 patients) had prescriptions for both calcium-based and non-calcium-based binders (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000474959).

Compared with the no-phosphorus-binder group, the phosphorus-binder group had a lower rates of HTN (52 vs. 75%), DM (34 vs. 48%), CHF (19 vs. 32%), cerebrovascular disease (5 vs. 8%), and a lower Charlson comorbidity index score (2.7 vs. 4.0, $p < 0.001$).
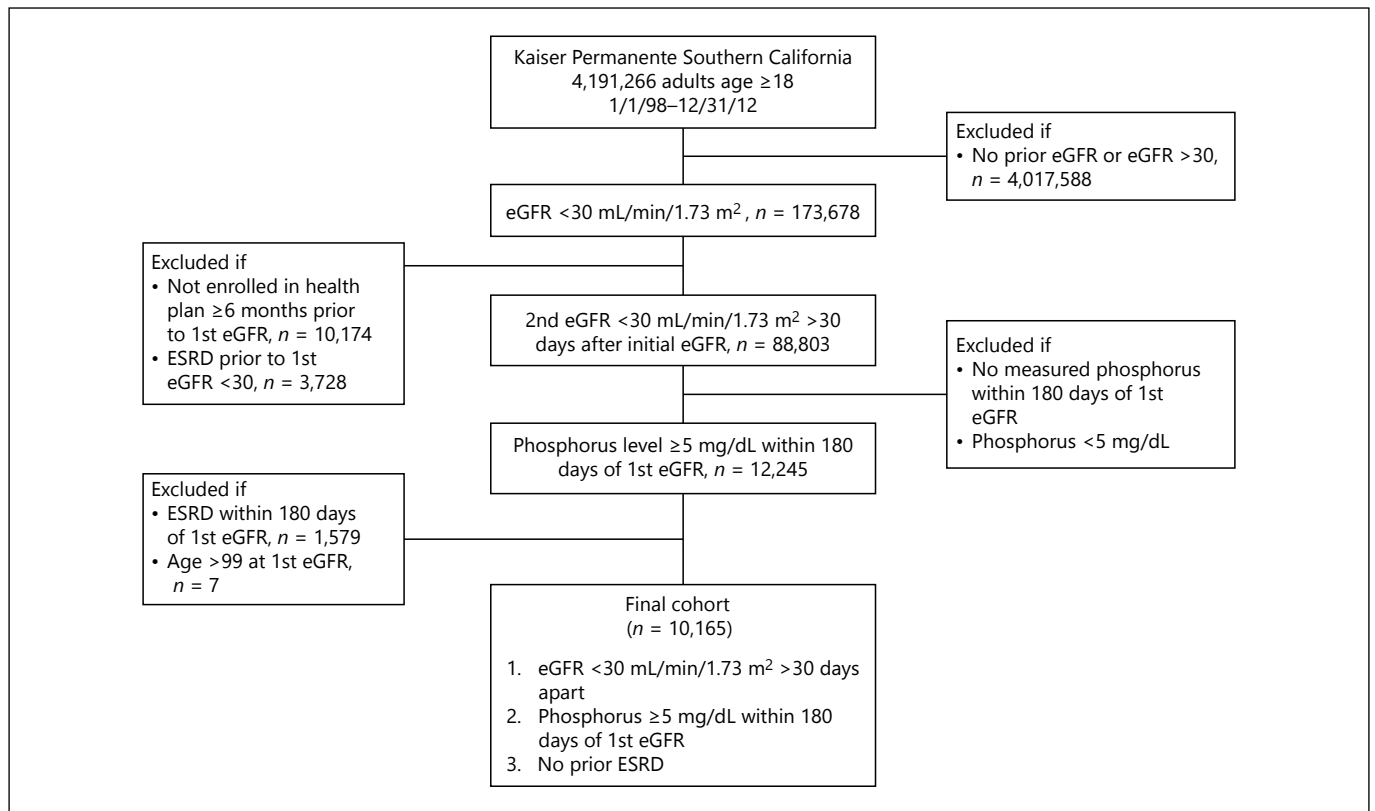
Kaiser Permanente Southern California
4,191,266 adults age ≥18
1/1/98–12/31/12

Excluded if
• No prior eGFR or eGFR >30,
  n = 4,017,588

eGFR <30 mL/min/1.73 m^2, n = 173,678

Excluded if
• Not enrolled in health
  plan ≥6 months prior
  to 1st eGFR, n = 10,174
• ESRD prior to 1st
  eGFR <30, n = 3,728

2nd eGFR <30 mL/min/1.73 m^2 >30
days after initial eGFR, n = 88,803

Excluded if
• No measured phosphorus
  within 180 days of 1st
  eGFR
• Phosphorus <5 mg/dL

Phosphorus level ≥5 mg/dL within 180
days of 1st eGFR, n = 12,245

Excluded if
• ESRD within 180 days
  of 1st eGFR, n = 1,579
• Age >99 at 1st eGFR,
  n = 7

Final cohort
(n = 10,165)

1. eGFR <30 mL/min/1.73 m^2 >30 days
   apart
2. Phosphorus ≥5 mg/dL within 180
   days of 1st eGFR
3. No prior ESRD

Fig. 1. During the period January 1, 1998 through December 31, 2012, 173,678 individuals with an eGFR <30 mL/min/1.73 m^2 were evaluated for inclusion into the study. Of these individuals, those with prior ESRD, those not enrolled in the health plan for 6 months prior to their 1st eGFR, and those without a phosphorus measurement ≥5 mg/dL within 180 days of their eGFR were all excluded. All subjects were required to have a 2nd eGFR <30 mL/min/1.73 m^2 >30 days after their initial eGFR measurement. A total of 10,165 patients met inclusion criteria and were included in study analyses. To eliminate the potential immortal time bias, individuals who were prescribed and sold a binder more than 180 days after their first eGFR <30 mL/min/1.73 m^2 (1,064 individuals) were excluded in a sensitivity analysis. A total of 9,101 patients were included in the sensitivity analysis.

Outcomes

Overall, 3,787 (37.3%) death events occurred among the study cohort (online suppl. Table 1). There were 800 (29.3%) deaths in the phosphorus-binder group and 2,987 (40.2%) in the no-binder group. The mean duration until a mortality outcome occurred was 1.4 years (525 days). A total of 1,223 patients transitioned to ESRD. When compared to the no-binder group, the phosphorus-binder group had a higher rate of incident ESRD (36.1 vs. 3.2%, $p < 0.001$).

Regressions

Compared to no-phosphorous binders, the phosphorus-binder group had a mortality HR (95% CI) of 0.86 (0.79–0.94; Table 2a). Every 0.5 mg/dL phosphorus elevation was associated with mortality HR of 1.17 (1.14–1.21), and every 5 mL/min/1.73 m^2 increase in eGFR was associated with mortality HR of 1.11 (1.09–1.14). Male gender, CHF, older age, and higher Charlson comorbidity index scores were also independently associated with increased HR for all-cause mortality . HTN (HR 0.81 [0.74–0.88]), DM (HR 0.64 [0.59–0.69]), coronary artery disease (HR 0.86 [0.79–0.93]), and albumin ≥4.0 g/dL (HR 0.70 [0.64–0.77]) had lower HR for all-cause mortality.

Compared to the no-phosphorus-binder group, phosphorus binder patients had an ESRD HR (95% CI) of 7.12 (6.09–8.32) after adjustment for age, gender, race/ethnicity, Charlson comorbidity index, eGFR, phosphorus level, hemoglobin level, albumin level, and preexisting comorbidities including HTN, DM, IHD, CHF, and cerebrovascular disease. Albumin ≥4 g/dL, calcium ≥8.5 mg/dL, hemoglobin ≥9 g/dL, and every 5 mL/min/1.73 m^2 increase in eGFR were all independently associated with lower HR for ESRD (Table 2b).

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Table 1. Characteristics of the study population

Characteristics	All CKD	Full cohort				After IPTW adjustment			
		CKD without binder	CKD with binder	p value	SD¹	CKD without binder	CKD with binder	p value	SD
n (%)	10,165 (100)	7,432 (73.1)	2,733 (26.9)			7,432 (73.1)	2,733 (26.9)		
Age, mean (SD)	66.2 (13.59)	67.9 (12.87)	61.8 (14.48)	<0.001					
Age ≥60 years, %	69.3	74.0	56.6	<0.001	−0.37	70.5	69.0	0.139	−0.03
Age/5 (increment 5 years), mean (SD)	13.2 (2.72)	13.6 (2.57)	12.4 (2.90)	<0.001	−0.44	13.3 (2.69)	13.3 (2.78)	<0.001	−0.02
Female, %	47.2	47.6	46.0	0.159	0.03	47.6	47.6	0.991	0.00
Race, %				<0.001	0.06			0.627	0.01
White	49.5	53.4	38.9						
Black	17.8	17.1	19.5			17.5	18.0		
Hispanic	24.4	21.6	31.8						
Asian/Pacific	6.7	6.3	7.8						
Other	1.7	1.6	2.0						
Diabetes mellitus, %	43.9	47.5	34.1	<0.001	−0.28	46.4	46.2	0.835	0.00
Hypertension, %	68.9	75.3	51.5	<0.001	−0.51	72.6	71.4	0.215	−0.03
Ischemic heart disease, %	26.8	30.9	15.7	<0.001	−0.37	27.9	27.8	0.959	0.00
Congestive heart failure, %	28.5	32.1	18.6	<0.001	−0.31	29.6	28.1	0.127	0.03
Cerebrovascular disease, %	7.2	8.1	4.5	<0.001	−0.15	7.3	6.8	0.389	−0.02
Charlson comorbidity score, mean (SD)	3.6 (2.97)	4.0 (2.87)	2.7 (3.03)	<0.001					
Charlson comorbidity score, %				<0.001	0.44			0.474	0.04
0–2	40.5	34.7	46.1			37.4	38.8		
3–4	25.2	27.8	18.2			26.6	25.9		
5–6	18.5	20.1	14.1			19.6	19.8		
≥7	15.8	17.4	11.6			16.4	15.5		
eGFR, mL/min/1.73 m², mean (SD)	21.6 (6.91)	21.9 (6.79)	20.9 (7.17)	<0.001	−0.14	21.5	21.6	<0.001	0.01
eGFR 0–14, %	20.3	18.9	24.3	<0.001	−0.13	19.5	20.2	0.424	−0.02
eGFR 15–30, %	79.7	81.1	75.7			80.5	79.8		
eGFR/5 (increment 5 units), mean (SD)	4.3 (1.38)	4.4 (1.36)	4.2 (1.43)	<0.001	−0.14	4.3 (1.39)	4.3 (1.41)	<0.001	0.01
Phosphorus, mg/dL, mean (SD)	5.6 (0.54)	5.6 (0.54)	5.6 (0.55)	<0.001	0.07	5.6 (0.55)	5.6 (0.53)	0.002	−0.02
Phosphorus 5 to <6 mg/dL, %	51.8	52.6	49.6	<0.001	0.06	51.4	51.6	0.843	−0.04
Phosphorus ≥6 mg/dL, %	48.2	47.4	50.4			48.6	48.4		
Phosphorus/0.5 (increment 0.5 units), mean (SD)	11.2 (1.08)	11.2 (1.08)	11.2 (1.10)	0.002	0.07	11.2 (1.09)	11.2 (1.06)	0.002	−0.02
Albumin, g/dL, mean (SD)	3.0 (0.88)	3.0 (0.88)	3.0 (0.86)	0.022					
Albumin ≥4 g/dL, %	18.2	19.7	14.1	<0.001	−0.15	19.3	19.5	0.822	0.01
Calcium, mg/dL, mean (SD)	9.0 (0.84)	9.0 (0.86)	8.9 (0.79)	<0.001					
Calcium ≥8.5 mg/dL, %	83.3	89.6	66.4	<0.001	−0.58	87.7	85.9	0.012	−0.06
Hemoglobin, g/dL, mean (SD)	11.4 (1.84)	11.4 (1.84)	11.0 (1.68)	<0.001					
Hemoglobin ≥9 g/dL, %	90.6	97.7	71.7	0.003	−0.79	93.2	90.9	0.797	−0.09

IPTW, inverse probability weighting method; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate. ¹SD, difference in means or proportions divided by SD; absolute standardized difference <0.1 indicates negligible differences between the 2 groups.

Table 2.

a Multivariable HRs for all-cause mortality

Variable	Adjusted HR (95% CI) for all-cause mortality	p value
Phosphorus binder prescription		
Any vs. none	0.86 (0.79–0.94)	<0.001
eGFR		
Increase in 5 units mL/min/1.73m^2	1.11 (1.09–1.14)	<0.001
Serum phosphorus		
Increase in 0.5 mg/dL	1.17 (1.14–1.21)	<0.001
Age		
Increase in 5 years	1.15 (1.13–1.17)	<0.001
Gender, male vs. female	1.11 (1.04–1.19)	<0.001
Race, non-black vs. black	0.88 (0.81–0.96)	<0.001
Preexisting HTN, yes vs. no	0.81 (0.74–0.88)	<0.001
Preexisting DM, yes vs. no	0.64 (0.59–0.69)	<0.001
Preexisting ischemic heart disease, yes vs. no	0.86 (0.79–0.93)	<0.001
Preexisting congestive heart failure, yes vs. no	1.09 (1.01–1.18)	0.032
Preexisting cerebrovascular disease, yes vs. no	1.06 (0.94–1.18)	0.340
Charlson comorbidity score		
3–4 vs. <3	1.54 (1.40–1.70)	<0.001
5–6 vs. <3	2.02 (1.81–2.25)	<0.001
≥7 vs. <3	3.42 (3.08–3.81)	<0.001
Albumin ≥4, yes vs. no	0.70 (0.64–0.77)	<0.001
Calcium ≥8.5, yes vs. no	0.94 (0.84–1.04)	0.201
Hemoglobin ≥9, yes vs. no	1.89 (1.57–2.27)	<0.001

b Multivariate HRs for ESRD

Variable	Adjusted HR (95% CI) for ESRD	p value
Phosphorus binder prescription		
Any vs. none	7.12 (6.09–8.32)	<0.001
eGFR		
Increase in 5 units mL/min/1.73 m^2	0.96 (0.92–1.00)	0.054
Serum phosphorus		
Increase in 0.5 mg/dL	0.91 (0.86–0.96)	0.001
Age		
Increase in 5 years	0.87 (0.85–0.89)	<0.001
Gender, male vs. female	1.30 (1.16–1.46)	<0.001
Race, non-black vs black	0.94 (0.82–1.08)	0.378
Preexisting HTN, yes vs. no	0.91 (0.76–1.08)	0.280
Preexisting DM, yes vs. no	1.37 (1.16–1.62)	<0.001
Preexisting ischemic heart disease, yes vs. no	0.74 (0.59–0.94)	0.012
Preexisting congestive heart failure, yes vs. no	0.85 (0.69–1.06)	0.152
Preexisting cerebrovascular disease, yes vs. no	0.74 (0.50–1.09)	0.127
Charlson comorbidity score		
3–4 vs. <3	1.03 (0.86–1.24)	0.723
5–6 vs. <3	0.86 (0.67–1.11)	0.250
≥7 vs. <3	0.78 (0.55–1.11)	0.171
Albumin ≥4, yes vs. no	0.57 (0.46–0.70)	<0.001
Calcium ≥8.5, yes vs. no	0.57 (0.47–0.68)	<0.001
Hemoglobin ≥9, yes vs. no	0.54 (0.44–0.66)	<0.001

ESRD, end-stage renal disease; CKD, chronic kidney disease; HR, hazard ratios; eGFR, estimated glomerular filtration rate; HTN, hypertension; DM, diabetes mellitus.

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Table 3. Sensitivity analysis of 9,101 subjects, removing those who received phosphorus binder >180 days after 1st eGFR. Multivariable HRs for all-cause mortality

Variable	Adjusted HR (95% CI) for all-cause mortality	p value
Phosphorus binder prescription		
Any vs. none	0.98 (0.90–1.07)	0.666
eGFR		
Increase in 5 units mL/min/1.73 m^2	1.12 (1.09–1.15)	<0.001
Serum phosphorus		
Increase in 0.5 mg/dL	1.16 (1.13–1.19)	<0.001
Age		
Increase in 5 years	1.14 (1.12–1.16)	<0.001
Gender, male vs. female	1.12 (1.05–1.20)	<0.001
Race, non-black vs. black	0.87 (0.80–0.95)	<0.001
Preexisting HTN, yes vs. no	0.79 (0.73–0.87)	<0.001
Preexisting DM, yes vs. no	0.64 (0.59–0.69)	<0.001
Preexisting ischemic heart disease, yes vs. no	0.86 (0.79–0.93)	<0.001
Preexisting congestive heart failure, yes vs. no	1.08 (1.00–1.17)	0.047
Preexisting cerebrovascular disease, yes vs. no	1.06 (0.95–1.19)	0.280
Charlson comorbidity score		
3–4 vs. <3	1.51 (1.37–1.66)	<0.001
5–6 vs. <3	1.98 (1.77–2.21)	<0.001
≥7 vs. <3	3.34 (3.00–3.72)	<0.001
Albumin ≥4, yes vs. no	0.69 (0.63–0.76)	<0.001
Calcium ≥8.5, yes vs. no	0.91 (0.82–1.01)	0.070
Hemoglobin ≥9, yes vs. no	1.70 (1.28–2.25)	<0.001

ESRD, end-stage renal disease; CKD, chronic kidney disease; HR, hazard ratios; eGFR, estimated glomerular filtration rate; HTN, hypertension; DM, diabetes mellitus.

Inverse Probability Weighting Method

With the exception of small residual differences in age, the characteristics among the phosphorus-binder and no-phosphorus-binder groups were matched in the IPTW adjusted cohorts (Tables 1 and 2). After adjustment for age, gender, race/ethnicity, Charlson comorbidity index, eGFR, phosphorus level, preexisting HTN, DM, IHD, CHF, and cerebrovascular disease, the IPTW-weighted model found that phosphorus binder use was associated with an HR of 0.86 (0.80–0.93) for all-cause mortality and an HR of 7.60 (6.61–8.73) for ESRD (online suppl. Table 2).

Sensitivity Analyses

To eliminate potential immortal time bias, individuals who were prescribed and sold a binder for more than 180 days after their first eGFR <30 mL/min/1.73 m^2 (1,064 individuals) were excluded in sensitivity analyses. A total of 9,101 individuals were identified for inclusion (Table 3). Among this sub-population, 1,669 (18.3%) patients had phosphorus binders prescribed. The mean eGFR was 22 mL/min/1.73 m^2 and the mean phosphorus

was 5.6 mg/dL. Compared to no-phosphorus binders, the phosphorus-binder group had a mortality HR (95% CI) of 0.98 (0.90–1.07) and an ESRD HR of 4.63 (3.85–5.56).

Discussion

Our study within a real-world clinical environment that comprised of 10,165 non-dialysis-dependent CKD (eGFR <30 mL/min) patients with elevated serum phosphorus levels found that 26.9% were prescribed phosphorus binders. We observed that those prescribed phosphorus binders had a 14% lower risk for all-cause mortality. The clinical information in our study was derived from a real-world clinical care environment with a large racially/ethnically diverse CKD population. Using the KPSC EHR, we were able to reliably capture health information including medication prescriptions, comorbidities, and outcomes. We attempted to address the selection and treatment bias with propensity score matched and inverse probability of treatment-weighted adjusted analyses,

which continued to demonstrate a mortality benefit of phosphorus binders. However, in further sensitivity analyses removing 1,064 individuals who received a phosphorus binder prescription >180 days after their initial eGFR, we did not observe any difference in 2-year mortality risk among patients prescribed phosphorus binders versus those who were not prescribed phosphorus binders. Our findings underscore the uncertainty in terms of the ideal CKD-MB management strategies in CKD.

The potential benefit of phosphorus binders in non-dialysis CKD has not been well described. There are fewer observations of binder use in non-dialysis CKD [4, 7–9, 17, 18, 23, 24]. Two studies including a randomized interventional trial among the CKD population have found a mortality benefit in those prescribed phosphorus binders [17, 18]. Among a predominantly male CKD population within the United States Veterans Administration health system, Kovesdy et al. [18] reported 39% lower mortality with phosphorus binders but noted no benefit from phosphorus binders on CKD progression. However, a recent meta-analysis of 77 studies, which included 12,562 adults with CKD, found no evidence that phosphate binders lowered mortality [24]. These findings were true for both calcium- and non-calcium-based phosphorus binders.

In our CKD cohort, we found that previously described risk factors including older age, CHF, higher phosphorus levels, higher Chalrson comorbidity index, and lower albumin levels were associated with higher mortality. Surprisingly, certain comorbidities including HTN, DM, and IHD were associated with lower mortality risk. This may speak to the fact that our CKD cohort included those with advanced CKD (eGFR <30). A survival bias may have occurred since most CKD patients with DM and/or HTN may have died rather than progressing to later stages of CKD [25]. As most CKD patients die than progress toward ESRD [25], our study population may reflect the sturdier patients with chronic conditions such as DM, HTN, and IHD who are more likely to have survived the earlier stages of CKD. In addition, those with higher comorbidity burden were more likely to be identified and more aggressively managed by clinicians.

The lower mortality risk observed in patients prescribed phosphorus binders occurred even after adjustment for differences in serum phosphorus levels. Elevated phosphorus levels are associated with increased cardiovascular, renal, and all-cause mortality outcomes in the hemodialysis, non-dialysis CKD, and even the general population [1–3, 10, 16]. Elevated phosphorus levels are thought to promote vascular injury, arterial calcifications, left ventricular hypertrophy, and nephrocalcinosis

[5, 26–30]. Certain phosphorus-binding agents have been shown to reduce total cholesterol, uric acid levels, and improve iron indexes [31–35]. Prior studies have shown that phosphorus-binding agents lower serum fibroblast growth factor-23 (FGF-23) levels and may improve outcomes by lowering FGF-23 levels even when phosphorus levels remain within the normal range [36–38].

We observed a seven-fold greater risk for ESRD among the phosphorus binder population compared to patients who received no phosphorus binders. The competing risk of death may explain the reason for lower ESRD in the no-binder group. When we evaluated combined outcomes of death and ESRD, the no-binder group had 313 combined events (per 1,000 patient years) of which 290 events were deaths and only 23 events were ESRD. This is in comparison to 469 combined events (per 1,000 patient years) among the binder group, where death accounted for 184 events and ESRD accounted for 278. Similarly, patients with higher eGFR in our study had lower HR for ESRD but that was offset by greater risk for death, which is consistent with the expected clinical course of patients with advanced CKD [25].

In our study, we used IPTW propensity score adjustment to match serum albumin, phosphorus levels, and calcium between the phosphorus binder and no-binder groups. Lower serum albumin is known to be a surrogate marker for nutritional status and is associated with increased mortality risk. We found that patients with albumin ≥4 gm/dL had improved survival. Prior studies have postulated that the association between phosphorus binders and lower mortality risk may be explained in part by better nutritional status in those who needed phosphorus binders [8]. Individuals who were not prescribed phosphorus binders may have had lower dietary phosphorus consumption compared to those who had binders prescribed. Binder patients may reflect those who were more likely to have a liberal diet and therefore improved nutritional status [8, 9, 16]. Conversely, dietary phosphorus restriction has been shown to be associated with poor nutritional status and greater mortality risk [8, 9, 39, 40]. The lower risk for mortality seen in the phosphorus binder cohort remained significant even after controlling for albumin.

The advanced non-dialysis CKD population is emerging as a focus of concern as they transition to ESRD. There remain many unanswered questions regarding the ideal transition management strategies to improve overall ESRD outcomes. Among 10,165 subjects with CKD and elevated phosphorus levels, 26.9% were noted to be prescribed phosphorus binders. Our sensitivity analyses, which excluded individuals who were prescribed phosphorus binders for

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more than 6 months after their eGFR measurement, found that only 18.3% were prescribed phosphorus binders. While phosphorus binders are FDA approved for use only among dialysis patients, the impact of phosphorus binder treatment among non-dialysis dependent CKD population remains largely unknown [16]. It also remains to be determined whether the different binder types have variations on outcomes as suggested by some studies [17, 41, 42].

Limitations

There are several potential limitations to our study that may confound the interpretation of our findings. Phosphorus binder use was determined by pharmacy prescription information, and we were unable to confirm or evaluate actual binder use among the study population. Phosphorus-related non-adherence is not uncommon and associated with poorer phosphorus control [43]. For the purposes of this study, we retrieved prescribed forms of phosphorus binder medications only. Over-the-counter binders including calcium carbonate were not reliably captured unless clinicians entered them as historical medicines. Due to multiple reasons including cost and the fact that phosphorus binders are not FDA approved in non-dialysis CKD, clinicians are often inclined to recommend over-the-counter calcium carbonate as first line for initial phosphorus elevations before escalating to prescription binders. Thus, patients may have been taking over-the-counter binders prior to prescription binders. This could make our immortal time bias assumptions even more conservative. Conversely, there may have been patients who were on over-the-counter binders that were categorized in the no-binder group. Given that our cohort was derived from a real-world practice environment, we could not account for the overall heterogeneity in treatment patterns by individual practitioners. Despite several modeling and propensity score matching analyses, we cannot fully eliminate treatment/selection bias and other unmeasured confounders, which may be relevant and influence outcomes. These include accounting for FGF-23 levels, as this measurement was not performed for nearly all our study population. Another example would be the lack of information on the timing of dialysis, since patients who were deemed sicker may have been initiated on dialysis earlier. Unfortunately, we did not have serial laboratory measurements on the study cohort during the follow-up period, including eGFR. The slope of eGFR prior to identification of the cohort and the eGFR at initiation of dialysis would have provided additional insights into potential differences in the 2 comparison populations. Lastly, we identified the study cohort from a 13-year window and evaluated outcomes for only a 2-year follow-up period in order to compare similar outcome risk across different periods. A longer-term follow-up period for outcomes may be needed to study the benefits of binders or conversely the harms of hyperphosphatemia. Along similar lines, we used the criteria of only a 30-day supply of binders to be categorized in the phosphorus binder population. A longer duration of binder exposure would provide a more reliable effect of binders.

Conclusion

Among an advanced CKD population with elevated serum phosphorus levels, we observed a 14% lower risk for mortality among those prescribed phosphorus binders. However, this lower risk was not observed in our sensitivity analyses that attempted to account for immortal time bias. Our study and findings raise the question of the role of phosphorus binders in non-dialysis CKD patients as they transition to ESRD.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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