Comparative Effectiveness of Calcium-Containing Phosphate Binders in Incident U.S. Dialysis Patients

Wolfgang C. Winkelmayer,†* *Jun Liu,** *and Bryan Kestenbaum*‡*

Summary

Background and objectives Few studies have assessed the association between phosphate binder use and hard outcomes in dialysis patients. Furthermore, the comparative effectiveness of calcium carbonate and acetate is untested. We studied the association between use versus nonuse of calcium-containing phosphate binders (CCPBs) and mortality from any cause. We also tested whether mortality differed among users of individual CCPBs.

Design, setting, participants, & measurements A nationally representative prospective cohort of incident U.S. dialysis patients (1996 to 1997), assembled before the availability of sevelamer and lanthanum, was used. Use of each CCPB was ascertained from chart abstraction records. A large number of sociodemographic, clinical, and laboratory characteristics were available for confounding control in multivariate and propensity score-matched Cox regression models.

Results Among 3603 incident dialysis patients, 77.5% used a CCPB, whereas 22.5% did not. Baseline use of CCPB was associated with an adjusted 19% lower mortality rate among CCPB users compared with nonusers. With successful matching of 800 exposed and nonexposed individuals on their exposure propensity score, however, CCPB users and nonusers had similar mortality. No mortality differences were observed between calcium acetate and calcium carbonate users in crude, adjusted, or propensity-matched analyses.

Conclusions No association was found between CCPB use and 1-year mortality in incident dialysis patients; choice of calcium carbonate versus acetate was also not associated with this outcome. Randomized trials are necessary to understand whether the prevailing practice of phosphate-binding therapy actually reduces adverse clinical outcomes.

Clin J Am Soc Nephrol 6: 175–183, 2011. doi: 10.2215/CJN.05060610

*Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Division of Nephrology, Stanford University School of Medicine, Palo Alto, California; and ‡Division of Nephrology, University of Washington, Seattle, Washington

Correspondence: Dr. Wolfgang C. Winkelmayer, Division of Nephrology, Stanford University School of Medicine, 780 Welch Road, Suite 106, Palo Alto, CA 94304. Phone: 650-723-2387; Fax: 650-721-1443; E-mail: wcw1@stanford.edu

Introduction

Disturbances in bone mineral metabolism are omnipresent in chronic dialysis patients, and their evaluation and treatment comprise a substantial portion of current ESRD care (1). Most patients undergoing chronic dialysis have hyperphosphatemia, which is associated with vascular calcification, cardiovascular events, and death (2–5). Phosphate binders significantly lower serum phosphate concentrations in short-term clinical trials (6–9) and were approved for use in chronic dialysis patients on this basis. Despite consistent associations of phosphate excess with adverse clinical outcomes, only a single study to date has tried to evaluate the assumption that pharmacologically lowering serum phosphate concentrations can improve the health of patients with ESRD (10). In this observational study, phosphate binder use within the first 3 months of hemodialysis was associated with approximately 30% lower 1-year mortality after adjustment for relevant confounding factors (10). Residual confounding by indication remains a possible explanation for this finding and some have suggested that placebo-controlled randomized trials are necessary to definitively prove the benefit of treatment (11). Medical history includes many instances of drugs that were approved based on their ability to alter a surrogate biomarker, but later found to be clinically ineffective or even harmful. However, placebo-controlled randomized trials of phosphate binders that evaluate clinical endpoints have not been conducted, and to our knowledge, none are currently underway. Instead, recent research has focused on the choice of phosphate binder type, a question that generally relates to the marketing of these products (12).

Questions of comparative effectiveness and safety of phosphate binders as well as other drugs used for the treatment of patients undergoing maintenance dialysis have recently surfaced to the top of the clinical and scientific debate in the United States. As of January 2011, all dialysis services including laboratory studies, intravenous medications, and certain dialysis-relevant oral medications will be bundled into a single payment for patients insured by Medicare. It can be expected that a system that previously fostered overuse will suddenly give way to one that incents providers to reduce resources directed toward medications covered by this capitation payment, including

phosphate binders. The Centers for Medicare and Medicaid Services (CMS) have assembled technical expert panels to establish and help implement quality measures, including some that specifically focus on bone mineral metabolism. The evidence supporting these measures is unfortunately thin, but even worse is the evidence that supports treatment decisions among medications that can be used to treat a certain aspect of care such as bone mineral metabolism. Providers who were previously willing to prescribe more expensive phosphate binders such as sevelamer or lanthanum may suddenly re-evaluate the literature and discover their fondness of cheaper compounds such as calcium-containing phosphate binders.

The widespread use of phosphate binders in chronic dialysis patients, the absence of meaningful clinical outcome data, and the expected changes in physician behavior motivate the comprehensive investigation of risks and benefits of these drugs using the best available methods. Comparative effectiveness and safety studies (observational studies of medication use) can assess clinical outcomes of medication use in "real-world" patient populations that are not restricted by stringent inclusion criteria and monitoring procedures of clinical trials. No studies thus far have investigated the association between calcium-containing phosphate binders (CCPB) and hard study outcomes or conducted intraclass comparisons among CCPBs. We tested two related hypotheses: primarily, we evaluated the association of use *versus* nonuse of calcium-based phosphate binders with survival, and secondarily, compared outcomes of calcium carbonate *versus* calcium acetate in a prospective cohort of incident dialysis patients.

Materials and Methods

Study Population

Data were obtained from the United States Renal Data System (USRDS), which collects detailed information for patients receiving chronic renal replacement therapy in the United States. We used data from the Dialysis Morbidity and Mortality Study (DMMS) Wave 2, a nationally representative cohort study of 4024 patients who initiated chronic dialysis in 1996 to 1997. Peritoneal dialysis patients were oversampled in DMMS Wave 2 to comprise approximately 50% of the cohort. Patients were excluded from DMMS Wave 2 if they were younger than 18 years, were receiving home hemodialysis, or were previously transplanted. Patients were enrolled into the DMMS at approximately 60 days after start of dialysis, which is also when all patient information was ascertained. We further excluded patients if they did not have a USRDS identifier, or if they were not truly incident dialysis patients, as evident from receipt of maintenance dialysis or a kidney transplant before the DMMS Wave 2 enrollment period. We also excluded patients in whom all 15 medication fields were empty. For this study, we used the 2004 USRDS standard analysis files. No personally identifiable data were used in any of the analyses and the study was approved by the Institutional Review Boards of Brigham and Women's Hospital and Stanford University School of Medicine.

Exposure

The exposure of interest was the use of a CCPB. Newer phosphate-binding agents sevelamer and lanthanum were not used in 1996 to 1997. Dialysis center personnel recorded up to 15 medications per patient using medical record data from dialysis centers and direct patient interview. We abstracted all medication fields, translated these entries into a database of consistent generic substance names, and compared these names to a list of known phosphorus binders. We sought to identify CCPBs in general and specific type of CCPB (carbonate *versus* acetate).

Outcome

The outcome of interest was 1-year mortality from any cause as reported by the USRDS. The USRDS obtains dates of death from the Centers for Medicare and Medicaid Services (CMS) Form 2746, which is completed by the primary nephrologist after the death of any dialysis patient. We chose to evaluate primarily 1-year mortality because phosphate binder data were available only at baseline, potentially misclassifying phosphate binder use over time due to crossover. We also explored whether our findings would be sensitive to duration of follow-up, up to 5 years.

Other Patient Characteristics

For each patient, we identified demographic and socioeconomic characteristics: age at first dialysis, sex, race (white, black, Asian, Native American, other), Hispanic ethnicity (yes *versus* no), education, marital status, and whether they lived alone. We identified the presence of comorbidities abstracted from patient records in DMMS Wave 2: diabetes, hypertension, coronary heart disease, congestive heart failure, peripheral artery disease or amputation, cerebrovascular disease, chronic obstructive pulmonary disease, history of cardiac arrest, and malignancy. We also identified prevalent use of other medications by comparing listed medications to known brand and generic drug names, including statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and β-blockers. The USRDS determines dialysis modality (hemodialysis, peritoneal dialysis) at dialysis day 60. Dialysis personnel abstracted systolic and diastolic BP and laboratory measurements from each patient's medical records. Laboratory data include serum concentrations of phosphorus, calcium, parathyroid hormone, albumin, total cholesterol, and triglycerides.

Follow-up

Patients were considered at risk on the study day, which was the day that study personnel abstracted the study information into the study forms (intended to be day 60 after initiation of dialysis), until the first

occurrence of death, loss to follow-up, or the completion of 1 year of follow-up.

Statistical Analyses

We compared characteristics of patients who used CCPBs with those who did not using the *t* test and χ^2 test. We used Cox regression models to estimate the association between CCPB use *versus* nonuse and the instantaneous hazard of mortality from any cause after adjustment for potential confounding variables. We built nested Cox models in a gradual fashion from univariate models to fully adjusted multivariate models and show results from several intermediate modeling steps. We use the Wald test to determine *P* values and 95% confidence intervals for model covariates. We also calculated each patient's exposure propensity score, based on all available information, and selected a cohort of tightly (within a propensity score of <0.001) matched exposed and unexposed pairs.

In all multivariate Cox regression models, we tested for violations of the proportionality assumption using interactions with follow-up time. We also tested for effect modification by all available baseline characteristics.

Using the same study plan, we compared patients using calcium carbonate to those using calcium acetate. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Cohort Selection

Of the 4024 patients who initiated renal replacement therapy in 1996 to 1997, there were 3930 with a unique and valid USRDS identifier. We excluded 254 patients who were not truly incident as reflected in past dialysis or transplantation claims within USRDS, and 73 patients who could not be matched to the USRDS patient's file, which contains follow-up information for these patients. After exclusions, 3603 patients were available for analysis.

Calcium-Containing Phosphate Binder Use and All-Cause Mortality

Patients who used a CCPB at baseline were younger, and less likely to have prevalent comorbid conditions, compared with nonusers (Table 1). Specifically, CCPB users had a lower prevalence of coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery vascular disease, and diabetes. Users of CCPB also had higher serum phosphate concentrations and higher systolic BP. Race, sex, primary cause of ESRD, and dialysis modality were similar across the two groups. Propensity matching resulted in 800 pairs of exposed and unexposed patients whose individual characteristics and mean propensity scores were exquisitely similar (Table 1).

During 1 year of observation, 541 patients died (15.0%). Before adjustment, CCPB users had a 38% (95% CI: 27% to 48%) lower risk of mortality. This association was attenuated by adjustment for comorbidity and other covariates (Table 2). After full adjustment CCPB was associated with a 19% (95% CI: 4% to 34%) lower risk of death. In the propensity matched cohort, we observed further attenuation, and the association was no longer significant (hazard ratio [HR] = 0.89; 95% confidence interval [CI]: 0.72 to 1.10). No effect modification was found in formal testing, in particular, by age, dialysis modality, or presence of comorbidities. The findings were also not sensitive to follow-up time.

Calcium Carbonate *versus* Calcium Acetate Use

Of the 2794 users of CCPBs, 122 patients either were reported to be using both calcium carbonate and acetate or could not be clearly allocated to one of these two exposure groups (*e.g.*, the medication entry listed "calcium"). Of the remaining 2672 CCPB users, 1443 (54%) used only calcium carbonate and 1229 (46%) used only calcium acetate. Baseline characteristics of calcium carbonate calcium acetate users were similar (Table 3); however, calcium acetate users were more likely to be receiving peritoneal dialysis, were more likely to be male, and had modestly higher serum phosphate concentrations. Propensity matching removed these minor imbalances completely (Table 3). In univariate, multivariate, or propensity-matched models, there were no differences in 1-year mortality among calcium acetate compared with calcium carbonate users (Table 4; HR = 1.02; 95% CI: 0.83 to 1.25).

Discussion

We used a large random sample of all new dialysis patients in the United States who started renal replacement therapy in 1996 and 1997 to study important comparative effectiveness questions pertinent to calcium-containing phosphate binders. We chose to use this cohort because patients were prospectively characterized and enrolled in an era that preceded the introduction of sevelamer and lanthanum into clinical practice. In summary, after matching on exposure propensity score, which balanced the observed patient characteristics, we did not observe any difference in 1-year mortality risk among chronic dialysis patients who were prescribed a calcium-containing phosphate binder compared with those without such therapy. We then found no differences in mortality among users of calcium acetate *versus* calcium carbonate, the most widely used phosphate binders during that time period. Our analyses took advantage of a detailed assessment of oral medications in that study, data usually unavailable in large dialysis cohorts at the time. Our findings inform clinical decisions that will arise as bundling of Medicare payment for dialysis services will be implemented in the U.S. in 2011, which will further expand to include oral prescription drugs that are specific to dialysis patients by 2014. This reimbursement change will incent physicians to search for more cost-effective strategies to treat patients with ESRD.

Higher serum phosphate concentrations are consistently associated with premature death in observa-

Table 1. Characteristics of users and nonusers of calcium-containing phosphate binders

	Full Cohort			Propensity Score–Matched Cohort		
	Users (n = 2794)	Nonusers (n = 809)	P	Users (n = 800)	Nonusers (n = 800)	P
Age	58.0 (±15.7)	61.1 (±15.2)	<0.001	61.2 (±15.2)	61.0 (±15.2)	0.84
Women	46.1	49.3	0.11	50.4	49.3	
Race						
white	66.4	65.4		64.1	65.5	
black	27.5	30.2		31.0	30.0	
Asian	3.8	2.4		3.0	2.4	
Native American	1.0	1.2		0.8	1.3	
other	1.4	0.9	0.20	1.1	0.9	0.72
Hispanic ethnicity	11.6	10.8	0.52	10.9	10.8	0.94
Education (n = 3,224)						
<high school	32.7	37.3		36.0	37.3	
high school graduate	34.4	32.9		31.7	33.1	
some college	17.4	15.4		15.5	15.4	
college graduate	15.5	14.5	0.14	16.8	14.3	0.61
Marital status						
married	54.7	54.6		54.0	54.9	
not married	15.8	13.0		13.2	13.1	
divorced/separated	29.5	32.4	0.08	32.8	32.0	0.94
Living						
not alone	78.6	75.8		78.8	76.6	
alone	16.5	14.1		12.7	14.3	
other	4.9	10.1	<0.001	8.5	9.1	0.58
Hemodialysis *versus* peritoneal dialysis	55.0	58.5	0.20	57.9	58.1	0.71
Suspected native kidney disease						
glomerulonephritis	9.1	5.7		6.0	5.8	
diabetes	42.1	44.5		45.1	44.1	
hypertension	25.7	27.2		27.1	27.3	
other	22.2	22.6	0.02	21.8	22.9	0.95
Comorbid conditions						
coronary artery disease	35.4	42.8	<0.001	44.4	42.5	0.45
congestive heart failure	35.0	42.5	<0.001	44.1	42.4	0.48
chronic obstructive lung disease	7.3	9.0	0.11	9.0	9.0	1.00
cerebrovascular disease	8.6	13.5	<0.001	13.0	13.3	0.88
history of cardiac arrest	1.9	1.4	0.35	1.8	1.9	0.85
hypertension	70.0	70.5	0.79	70.1	70.6	0.83
diabetes	47.8	51.8	0.04	51.4	51.5	0.96
HIV	1.3	1.5	0.61	1.1	1.5	0.51
malignancy	8.1	8.8	0.53	7.6	8.8	0.41
peripheral artery vascular disease	16.5	20.3	0.01	19.3	20.0	0.71
Systolic BP (n = 3531)	147 (±21)	145 (±22)	0.02	145 (±21)	145 (±22)	0.62
Diastolic BP (n = 3530)	80 (±12)	78 (±12)	<0.001	78 (±12)	78 (±12)	0.53
Laboratory measurements						
phosphate (n = 3442)	5.6 (±1.8)	5.3 (±1.7)	<0.001	5.3 (±1.7)	5.3 (±1.7)	0.90
calcium (n = 3450)	8.6 (±1.1)	8.7 (±0.9)	0.21	8.7 (±0.9)	8.7 (±1.0)	0.54

Table 1. (Continued)

	Full Cohort			Propensity Score–Matched Cohort		
	Users (n = 2794)	Nonusers (n = 809)	P	Users (n = 800)	Nonusers (n = 800)	P
parathyroid hormone (n = 2838)	316.4 (±347)	307 (±398)	0.61	302 (±322)	310 (±400)	0.71
parathyroid hormone (n = 2838) (percentiles)	25%: 102 50%: 218 75%: 417	25%: 86 50%: 184 75%: 393		25%: 90 50%: 192 75%: 408	25%: 89 50%: 189 75%: 395	
triglycerides (n = 2798)	199 (±131)	201 (±122)	0.70	205 (±150)	201 (±122)	0.60
Other medication use						
statins	10.8	10.0	0.50	12.8	10.1	0.10
ACE/ARBs	26.9	24.7	0.22	25.8	25.0	0.73
beta blockers	20.5	18.3	0.16	17.1	18.5	0.47
Propensity score				0.75 (±0.08)	0.75 (±0.08)	0.95

All data are presented in column percent or in mean (± standard deviation) unless indicated otherwise.

Table 2. Relative 1-year mortality rate between users and nonusers of calcium-containing phosphate binders

	Hazard Ratio[a]	95% CI	P
Univariate	0.62	0.52 to 0.73	<0.001
Adjusted for demographic variables (age, gender, race, ethnicity)	0.68	0.57 to 0.80	<0.001
Additionally adjusted for marital status, living situation, educational level, comorbidities,[b] and baseline dialysis modality	0.75	0.63 to 0.89	0.001
Additionally adjusted for blood pressure and laboratory measurements[b]	0.81	0.68 to 0.96	0.01
Additionally adjusted for use of other medications[b]	0.81	0.68 to 0.96	0.02
Propensity score–matched cohort (n = 1600)	0.89	0.72 to 1.10	0.28

[a]Nonusers constituted the reference group.

[b]Comorbidities include coronary heart disease, congestive heart failure, chronic obstructive lung disease, cerebrovascular disease, history of cardiac arrest, hypertension, diabetes, HIV positivity, malignancy, and peripheral artery vascular disease. Laboratory measurements include serum phosphate, calcium, parathyroid hormone, albumin, total cholesterol, and triglyceride concentrations. Other medications include statins, angiotensin-conversion enzyme inhibitors, angiotensin-receptor blockers, and beta blockers.

tional cohort studies of chronic dialysis patients (2–5). These associations are independent of traditional cardiovascular risk factors, strengthen in a dose-dependent fashion with higher serum phosphate concentrations, and are corroborated by biologic evidence for phosphate as a novel vascular toxin. *In vitro*, exogenous phosphate transforms cultured human smooth muscle tissue into osteoblast-like cells with calcification of extracellular matrix proteins (13). In chronic dialysis patients, higher serum phosphate concentrations are associated with coronary artery and aortic calcification (14). Whereas calcium carbonate was shown to reduce serum phosphorus in the seminal study of Slatopolsky *et al.*, it became evident that such treatment raised serum calcium concentrations (6). The authors speculated that long-term treatment with calcium carbonate might lead to increased calcification, which was later corroborated by Goodman *et al.* (14) Thus, it is important to determine whether lowering phosphorus by means of CCPBs yields net benefits or risks. The critical missing link is a demonstration that lowering serum phosphate concentrations translates into decreased rates of mortality and cardiovascular events. However, a number of barriers prevent this final essential step. First, CCPBs and other currently used phosphate binders rarely control serum phosphate con-

Table 3. Characteristics of calcium carbonate and calcium acetate users

	Full Cohort			Propensity Score–Matched Cohort		
	Calcium Carbonate (n = 1443)	Calcium Acetate (n = 1229)	P	Calcium Carbonate (n = 1139)	Calcium Acetate (n = 1139)	P
Age	58.1 (±15.5)	58.1 (±15.8)	0.96	58.1 (±15.6)	58.3 (±15.8)	0.77
Women	47.9	43.9	0.04	46.1	45.4	
Race						
white	65.3	68.0		67.9	67.3	
black	28.8	26.0		26.6	26.7	
Asian	3.6	3.6		3.3	3.7	
Native American	1.4	0.6		1.2	0.6	
other	0	0.1	0.04	1.0	1.7	0.34
Hispanic ethnicity	11.2	11.7	0.65	11.7	11.3	0.79
Education (263 missing)						
<high school	31.1	34.6		33.0	32.8	
high school grad	34.5	34.6		34.1	35.3	
some college	18.0	16.4		17.8	17.1	
college graduate	16.4	14.1	0.20	15.0	14.8	0.94
Marital status						
married	56.0	53.7		55.1	54.7	
not married	15.6	15.9		15.1	15.3	
divorced/separated	28.4	30.4	0.45	29.8	30.0	0.98
Living						
not alone	78.6	78.8		79.0	78.7	
alone	16.5	16.4		16.1	16.4	
other	4.9	4.9	0.99	4.9	4.9	0.97
Hemodialysis *versus* peritoneal dialysis	52.2	57.4	0.03	56.5	56.0	0.77
Suspected native kidney disease						
glomerulonephritis	9.1	9.2		9.2	8.9	
diabetes	42.4	43.5		43.3	43.3	
hypertension	26.3	25.2		25.9	25.9	
other	22.2	22.1	0.92	21.9	21.6	0.99
Comorbid conditions						
coronary artery disease	34.7	36.4	0.37	35.7	36.1	0.79
congestive heart failure	33.8	36.1	0.21	35.6	35.7	0.93
chronic obstructive lung disease	6.7	8.1	0.19	7.6	7.3	0.81
cerebrovascular disease	8.7	8.2	0.64	8.9	8.4	0.71
history of cardiac arrest	1.7	1.2	0.34	1.4	1.3	0.86
hypertension	70.3	69.8	0.80	69.9	69.9	1.00
diabetes	47.6	47.4	0.93	47.8	47.8	1.00
HIV	1.2	1.3	0.77	1.1	1.1	0.84
malignancy	8.0	8.1	0.87	8.1	8.3	0.88
peripheral artery vascular disease	16.1	17.4	0.33	16.9	17.6	0.70
Systolic BP (n = 2627)	147 (±20)	148 (±21)	0.25	147 (±20)	147 (±21)	0.93
Diastolic BP (n = 2627)	80 (±12)	80 (±12)	0.31	80 (±11)	80 (±12)	0.95
Laboratory measurements						
phosphate (n = 2569)	5.5 (±1.8)	5.7 (±1.9)	0.01	5.6 (±1.8)	5.6 (±1.8)	0.73
calcium (n = 2574)	8.6 (±1.1)	8.7 (±1.0)	0.09	8.7 (±1.0)	8.7 (±1.0)	0.39

Table 3. (Continued)

	Full Cohort			Propensity Score–Matched Cohort		
	Calcium Carbonate (n = 1443)	Calcium Acetate (n = 1229)	P	Calcium Carbonate (n = 1139)	Calcium Acetate (n = 1139)	P
parathyroid hormone (n = 2143)	318 (±370)	314 (±313)	0.80	311 (±311)	313 (±304)	0.86
parathyroid hormone (n = 2143)	25%: 101	25%: 103		25%: 103	25%: 102	
	50%: 218	50%: 214		50%: 220	50%: 217	
	75%: 410	75%: 428		75%: 409	75%: 428	
total cholesterol (n = 2456)	195 (±54)	193 (±53)	0.45	194 (±55)	193 (±52)	0.84
triglycerides (n = 2080)	195 (±129)	203 (±134)	0.15	195 (±125)	198 (±121)	0.64
Other medication use						
statins	10.9	10.9	0.98	10.5	10.8	0.84
ACE/ARBs	27.4	26.4	0.56	25.9	26.9	0.60
beta blockers	20.7	20.8	0.95	20.2	21.3	0.50
Propensity score				0.46 (±0.06)	0.46 (±0.06)	0.95

All data are presented in column percent or in mean (± standard deviation) unless indicated otherwise.

Table 4. Relative mortality rate between calcium acetate and calcium carbonate users

	Hazard Ratio[a]	95% CI	P
Univariate	1.07	0.88 to 1.30	0.48
Adjusted for demographic variables (age, gender, race, ethnicity)	1.07	0.89 to 1.30	0.47
Additionally adjusted for marital status, living situation, educational level, comorbidities,[b] and baseline dialysis modality	1.02	0.84 to 1.24	0.84
Additionally adjusted for BP and laboratory measurements[b]	1.01	0.83 to 1.23	0.94
Additionally adjusted for use of other medications[b]	1.02	0.84 to 1.24	0.84
Propensity score–matched cohort (n = 2278)	1.02	0.83 to 1.25	0.86

[a]Calcium carbonate users constituted the reference group.

[b]Comorbidities include coronary heart disease, congestive heart failure, chronic obstructive lung disease, cerebrovascular disease, history of cardiac arrest, hypertension, diabetes, HIV positivity, malignancy, and peripheral artery vascular disease. Laboratory measurements include serum phosphate, calcium, parathyroid hormone, albumin, total cholesterol, and triglyceride concentrations. Other medications include statins, angiotensin-conversion enzyme inhibitors, angiotensin-receptor blockers, and beta blockers.

centrations to the normal range. This problem may be compounded by recent observations suggesting possible toxicity of even high-normal serum phosphate concentrations in nondialysis patients with chronic kidney disease (15,16). An increase in dialysis dose or dialysis pattern (*i.e.*, daily dialysis) may be needed to normalize the serum phosphate concentration, but this approach could not distinguish whether phosphate lowering or greater dialysis intensity were responsible for potential health benefits. Second, there is limited enthusiasm from industry for sponsoring clinical trials of a medication that is already perceived to be necessary by practicing physicians and has achieved high penetrance in the chronic dialysis population.

The absence of a significant reduction in 1-year mortality in our study seems at odds with the recent observation by Isakova *et al.*, who found a 30% reduction in mortality in a more recent cohort of incident hemodialysis patients (10). Several factors may contribute to the discrepancy of their and our findings. Whereas Isakova's study captured information on vitamin D therapy and vascular access (unavailable in

our study), our study had detailed information on several socioeconomic factors such as educational level, marital status, patients' living situations (living alone), and the presence of reported comorbid conditions. Several comorbidities, especially those of a cardiovascular nature, were determinants of access to treatment in our study (Table 1); information on these important confounders was not available in Isakova's cohort. Another difference between the studies is our inclusion of patients receiving peritoneal dialysis, which constituted approximately half of our cohort; Isakova only studied patients receiving hemodialysis.

Our study cohort was assembled at a time when phosphate binder choice was mostly restricted to CCBP, and no major marketing efforts were promoting these medications. By contrast, Isakova's study used patients who initiated hemodialysis in 2004 and 2005, an era when sevelamer had already captured almost half of the prescription phosphate binder market in the United States and was marketed heavily toward both providers and patients. It is possible that such marketing changes physician prescribing behavior and that the differences in (observed and unobserved) characteristics among treated and untreated patients changed over time, thus changing the dynamics of unobserved confounding.

What unifies both studies is the clear indication that treatment with phosphate binders was not random, but rather correlated with prognostic factors. Users of phosphate binders in both studies were systematically younger and healthier on observed characteristics, rendering the possibility likely that unobserved characteristics were also imbalanced. Both studies showed strong attenuation of the crude associations between phosphate binder use and mortality after adjustment (HR: 0.58 → 0.71 in Isakova *et al.*; HR: 0.62 → 0.81 in our study), illustrating that accounting for unobserved characteristics in both studies could further reduce these associations toward unity. Propensity matching, a powerful method to assemble comparison groups that are highly comparable, yielded further reduction of the estimated associations (to HR: 0.75 in Isakova *et al.* and HR: 0.89 in ours), which in addition was no longer significant in our study. This marked shift in the estimated association has to be interpreted in that patients with particularly poor prognosis in the nonuser group could not be matched to a treated individual, indicating that the more favorable association in the full cohort was driven by a subgroup of untreated patients that was incomparable to those receiving CCBP treatment (17). Another difference between these two studies is the fact that Isakova *et al.* studied patients exposed to any phosphate binder, which included patients receiving a CCPB, a non-CCPB, or both (10). Some may be tempted to conclude that this may be the reason for the discrepant findings between their and our study. We do not think that such a conclusion is warranted, especially in light of a negative randomized clinical trial comparing CCPB with sevelamer, (18) and that the explanations provided above are more plausible reasons for the discrepancy in study results.

In our second hypothesis, we could not detect survival differences comparing calcium carbonate to calcium acetate. The hazard ratio was essentially at unity and baseline characteristics in the full cohort were rather balanced between the treatment groups, which reduces the likelihood of the existence of influential unobserved confounders. This lack of difference is even more remarkable because calcium acetate has been shown to possess enhanced binding to phosphate in the small intestine, where dietary phosphate is absorbed (19). If effectiveness of a treatment strategy based on using calcium carbonate indeed equaled one using calcium acetate instead, important economic implications arise. The cost of over-the-counter calcium is a fraction of the costs of brand or generic calcium acetate, and providers may see an opportunity to increase the efficiency of their practice in light of the pressures to contain costs in a fully capitated payment system.

These considerations need to be weighed against the limitations of the present study. Medications were abstracted by clinic personnel, with the possibility of erroneous or missing data entry. The most important limitation is the potential for residual confounding by indication, such that CCPB users possessed other healthy characteristics or behaviors that were responsible for their improved survival. The decision to start any medication represents not only the indication for that medication but also subtle characteristics of the physician-patient relationship. We found that CCPBs were more likely to be prescribed to younger patients who had fewer comorbid diseases. Adjustment for age and comorbidity attenuated the association of CCPB with survival to some extent, but associations persisted. It remains possible that factors not measured in this study could also be linked with CCPB use and survival. The dosage of CCPBs was not available. This limitation may hinder interpretation of the comparison of calcium acetate with calcium carbonate because the latter may be more calcemic at equivalent dosages. Our comparative study was not designed to compare effective doses, however, but rather to understand the downstream consequences of a practice built on using calcium carbonate *versus* another one using calcium acetate. We cannot exclude the possibilities of medication noncompliance or crossover, such that CCPB users stopped binder use and/or CCPB nonusers started it. We selected a conservative ("intention-to-treat") analytic strategy that yields relative risk estimates that are closer to 1.0 in the presence of crossover and limited the observation period to 1 year to increase the accuracy of medication classification. The current study cannot comment on whether non-calcium–containing phosphate binders are effective and safe in hemodialysis patients or whether those should replace CCPBs.

In summary, we found similar mortality among chronic dialysis patients who were prescribed a calcium-based phosphate binder with those who did not.

Death was also not predicted by baseline calcium carbonate *versus* acetate use. These data are among the first to our knowledge to examine phosphate binder use in relation to a meaningful clinical outcome in chronic dialysis patients. Whether the observed associations are causal is uncertain and can only be determined by a large and well-conducted trial. In light of the treatment uncertainty and the expected economic pressures on clinical decisions in 2011, it would seem mandatory and ethical to conduct such trials. In the interim, there is no conclusive support in favor of lowering phosphorus in dialysis patients using oral binder medications. If a provider were compelled to use such a therapy, however, there is currently no hard endpoint evidence in favor of using calcium acetate, sevelamer, or lanthanum instead of the least expensive treatment option, over-the-counter calcium carbonate.

Acknowledgments

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the U.S. government. The manuscript has undergone review for privacy content by the National Institutes for Diabetes and Digestive and Kidney Diseases and received clearance on June 10, 2010.

Disclosures

In the last 3 years, Dr. Winkelmayer has received investigator-initiated research support from Amgen and Fibrogen and has served as a consultant/advisor for AMAG Pharmaceuticals, Amgen, Astellas/Fibrogen, Fresenius/Vifor, and Hexal/Sandoz. Dr. Liu has no conflicts of interest to report. Dr. Kestenbaum has received investigator-initiated research support from Amgen.

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Received: June 9, 2010 **Accepted:** September 7, 2010

Published online ahead of print. Publication date available at www.cjasn.org.