Phosphorus Binders and Survival on Hemodialysis

Tamara Isakova,* Orlando M. Gutiérrez,[†] Yuchiao Chang,[‡] Anand Shah,* Hector Tamez,*
Kelsey Smith,[†] Ravi Thadhani,* and Myles Wolf[†]

*Renal Unit, [‡]Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston,
Massachusetts; and [†]Division of Nephrology and Hypertension, University of Miami Miller School of Medicine,
Miami, Florida

ABSTRACT

Although hyperphosphatemia is a risk factor for mortality, there are limited data on whether therapy with phosphorus binders affects survival. We analyzed a prospective cohort study of 10,044 incident hemodialysis patients using Cox proportional hazards analyses to compare 1-yr all-cause mortality among patients who were or were not treated with phosphorus binders. We performed intention-to-treat analyses to compare patients who began treatment with phosphorus binders during the first 90 d after initiating hemodialysis ($n = 3555$) with those who remained untreated during that period ($n = 5055$). We also performed as-treated analyses that modeled phosphorus binder treatment as a time-dependent exposure. We compared survival in a subcohort of treated ($n = 3186$) and untreated ($n = 3186$) patients matched by their baseline serum phosphate levels and propensity score of receiving phosphorus binders during the first 90 d. One-year mortality was 191 deaths/1000 patient-years at risk. Treatment with phosphorus binders was independently associated with decreased mortality compared with no treatment in the intention-to-treat, as-treated, and matched analyses. The results were independent of baseline and follow-up serum phosphate levels and persisted in analyses that excluded deaths during the first 90 d of hemodialysis. In summary, treatment with phosphorus binders is independently associated with improved survival among incident hemodialysis patients. Although confirmatory studies are needed in the dialysis setting, future placebo-controlled, randomized trials of phosphorus binders might focus on predialysis patients with chronic kidney disease and normal serum phosphate levels.

Hyperphosphatemia is among the most common metabolic complications of ESRD.[1,2] Large observational studies have identified hyperphosphatemia as an independent risk factor for cardiovascular disease and mortality on dialysis,[1–5] and subsequent studies found that subtle increases in serum phosphate levels within the normal range are also associated with increased risk for death in predialysis and even non–kidney disease populations.[6–8] On the basis of these results, current national practice guidelines advocate more aggressive treatment of hyperphosphatemia to lower serum phosphate targets than in the past.[9] Restricting dietary phosphorus intake is recommended, but because it is difficult to maintain and can exacerbate protein malnutrition, administration of dietary phosphorus binders to block intestinal phosphorus absorption is the cornerstone of therapy for hyperphosphatemia. Indeed, the majority of dialysis patients are eventually prescribed phosphorus binders with an estimated annual cost that is expected to exceed $1 billion worldwide.[10]

The evidence linking hyperphosphatemia with adverse outcomes suggests that lowering serum phosphate levels in individual dialysis patients will

improve their clinical outcomes, but no interventional or even observational studies have examined the impact of serum phosphate reduction on survival. Furthermore, all of the phosphorus binders used in clinical practice were approved by the Food and Drug Administration on the basis of their efficacy in lowering serum phosphate levels in short-term studies of dialysis patients.[11–14] No placebo-controlled studies have examined the impact of treatment with phosphorus binders on hard clinical end points, including survival. Indeed, although several studies aimed to determine which specific phosphorus binder is best for dialysis patients,[15,16] there are no data on whether any phosphorus binder treatment *versus* none alters clinical outcomes. We analyzed a prospective cohort study of incident hemodialysis patients to test the hypothesis that therapy with any phosphorus binder *versus* none is associated with a survival benefit.

RESULTS

Baseline Characteristics

Comparisons of baseline characteristics of patients who were treated *versus* those who were untreated with phosphorus binders during the first 90 d after initiating outpatient hemodialysis are presented in Table 1. In the unmatched cohort, treated patients were younger; had higher BP, body mass index, serum phosphate, parathyroid hormone (PTH), and creatinine levels; and were more likely to have a fistula for vascular access. There were no differences in gender; race; or albumin, creatinine, or hemoglobin levels. With the exception of small residual differences in age, all other differences in baseline characteristics among treated and untreated patients were eliminated in the propensity score–matched cohort (Table 1).

Phosphorus Binders and Outcomes

The 1-yr mortality rate was 191 deaths/1000 patient-years at risk in the unmatched cohort. The phosphorus binder–treated group had a significantly lower mortality rate than the untreated group in the unmatched cohort (136 *versus* 235 deaths/1000 patient-years at risk; relative risk 0.58; 95% confidence interval [CI] 0.52 to 0.66; $P < 0.0001$).

The results of the univariate and multivariable-adjusted survival analyses are presented in Table 2. In both the intention-to-treat and the as-treated analyses, phosphorus binders were independently associated with a significant survival benefit, the magnitude of which ranged between 18 and 30% in multivariable models and were unaltered by further adjustment for administration of intravenous active vitamin D during the follow-up period or in facility-specific stratified analyses. The results were qualitatively unchanged in a prespecified

Table 1. Baseline characteristics of patients who were treated with phosphorus binders *versus* those who were untreated in the overall unmatched cohort and the propensity score–matched cohort[a]

Characteristic	Unmatched Cohort			Propensity Score–Matched Cohort		
	Treated (n = 3555)	Untreated (n = 5055)	P	Treated (n = 3186)	Untreated (n = 3186)	P
Age (yr; mean [SD])	60 (16)	65 (15)	<0.0001	61 (16)	62 (15)	0.01
Female (%)	45.4	45.6	0.89	46.7	45.1	0.21
Race/ethnicity (%)						
black	32.7	31.7	0.31	33.4	33.1	0.83
Hispanic	12.2	13.8	0.03	12.0	12.7	0.36
Cause of renal failure (%)						
diabetes	42.7	44.0	0.01	43.1	43.7	0.98
hypertension	35.7	35.1		35.7	35.0	
glomerulonephritis	10.4	8.5		10.1	10.0	
other	11.3	12.4		11.1	11.2	
Systolic BP (mmHg; mean [SD])	146 (22)	143 (23)	<0.0001	146 (22)	146 (23)	0.63
BMI (kg/m²; mean [SD])	28 (8)	27 (9)	<0.0001	28 (8)	28 (9)	0.41
Initial vascular access (%)						
fistula	26.7	22.6	<0.0001	26.9	25.5	0.39
graft	10.1	11.3		10.6	10.8	
catheter	58.9	62.8		58.5	60.1	
Laboratory tests (mean [SD])						
albumin (g/dl)	3.5 (0.5)	3.4 (0.5)	0.14	3.5 (0.5)	3.5 (0.5)	0.36
creatinine (mg/dl)	6.8 (2.8)	5.9 (2.6)	<0.0001	6.6 (2.8)	6.5 (2.6)	0.09
calcium (mg/dl)	8.4 (0.9)	8.4 (0.8)	0.30	8.4 (0.9)	8.4 (0.9)	0.59
phosphate (mg/dl)	5.0 (1.7)	4.5 (1.4)	<0.0001	4.8 (1.6)	4.8 (1.5)	0.15
PTH (pg/ml; median [IQR])	223 (123 to 384)	195 (105 to 331)	0.009	216 (119 to 375)	210 (115 to 355)	0.13
hemoglobin (g/dl)	10.3 (1.4)	10.4 (1.4)	0.003	10.3 (1.4)	10.3 (1.4)	0.84
Vitamin D therapy (% treated at initiation)	11.8	11.1	0.33	11.8	12.0	0.82

[a]The treated group included patients who began treatment during the first 90 d on hemodialysis, whereas the untreated group included those who were not treated during the first 90 d. IQR, interquartile range. BMI, body mass index.

Table 2. HRs for mortality comparing patients who were treated with phosphorus binders (n = 3555) with those who were untreated (n = 5055)

Parameter	HR	95% CI	P
Intention-to-treat analyses[a]			
no adjustment	0.58	0.52 to 0.66	<0.0001
multivariable-adjusted[b]	0.70	0.62 to 0.79	<0.0001
vitamin D–adjusted[c]	0.70	0.62 to 0.79	<0.0001
facility-specific SMR–stratified[d]	0.71	0.62 to 0.81	<0.0001
As-treated analyses[e]			
no adjustment	0.70	0.61 to 0.78	<0.0001
multivariable-adjusted[b]	0.82	0.72 to 0.93	0.001
vitamin D–adjusted[c]	0.82	0.72 to 0.93	0.002
facility-specific SMR–stratified[d]	0.71	0.63 to 0.81	<0.0001

[a]The treated group included patients who began treatment during the first 90 d on hemodialysis, whereas the untreated group included those who were not treated during the first 90 d.
[b]Adjusted for age; gender; race; ethnicity; cause of renal failure; systolic BP; BMI; SMR (standardized mortality rate); initial vascular access; coronary artery disease; congestive heart failure; laboratory variables including albumin, creatinine, calcium, phosphate, PTH, and hemoglobin; and vitamin D therapy at baseline.
[c]Multivariable-adjusted for all factors listed in [b] and time-dependent treatment with intravenous active vitamin D during the follow-up period.
[d]Multivariable-adjusted for the factors listed in [b] and stratified according to facility-specific SMR.
[e]Phosphorus binder therapy was modeled as a time-dependent covariate.

analysis that excluded patients who died during the first 90 d after initiating hemodialysis (hazard ratio [HR] 0.82; 95% CI 0.70 to 0.95; P = 0.01) and in analyses that incrementally excluded patients who died during consecutive 15-d intervals between days 0 and 90 (HR ranging between 0.74 and 0.85; all P < 0.05).

In analogous models, no significant survival effect was associated with aspirin (HR 0.98; 95% CI 0.78 to 1.23; P = 0.86) or angiotensin-converting enzyme inhibitors (HR 0.84; 95% CI 0.68 to 1.04; P = 0.11), whereas the association between phosphorus binders and survival persisted unchanged in a model that adjusted for these comparator medications (HR 0.71; 95% CI 0.60 to 0.85; P < 0.0001). Phosphorus binder therapy was associated with a significant survival benefit in many but not all strata, whereas lack of treatment was favored in no stratum (Figure 1). Formal testing for interaction revealed effect modification only by Hispanic ethnicity (P = 0.01), which was associated with a greater benefit from binders than non-Hispanic ethnicity. The multivariable-adjusted benefit of phosphorus binders was somewhat greater for cardiovascular-specific mortality (HR 0.67; 95% CI 0.57 to 0.79; P < 0.0001) than for death from other causes (HR 0.73; 95% CI 0.60 to 0.89; P = 0.002), but there was significant overlap in the CIs.

Propensity Score Matching

Phosphorus binder treatment was associated with a significant survival advantage in the propensity score–matched cohort (HR 0.75; 95% CI 0.66 to 0.87; P < 0.0001; Figure 2A); the results were unchanged when adjusted for the residual difference in age (Table 3). In addition, phosphorus binder treatment was associated with a significant survival advantage in

each quartile of baseline serum phosphate except the lowest (Figure 2, B through E; Table 3). Furthermore, the magnitude of the point estimate of phosphorus binders was minimally attenuated when the results were further adjusted for follow-up serum phosphate levels (Table 3).
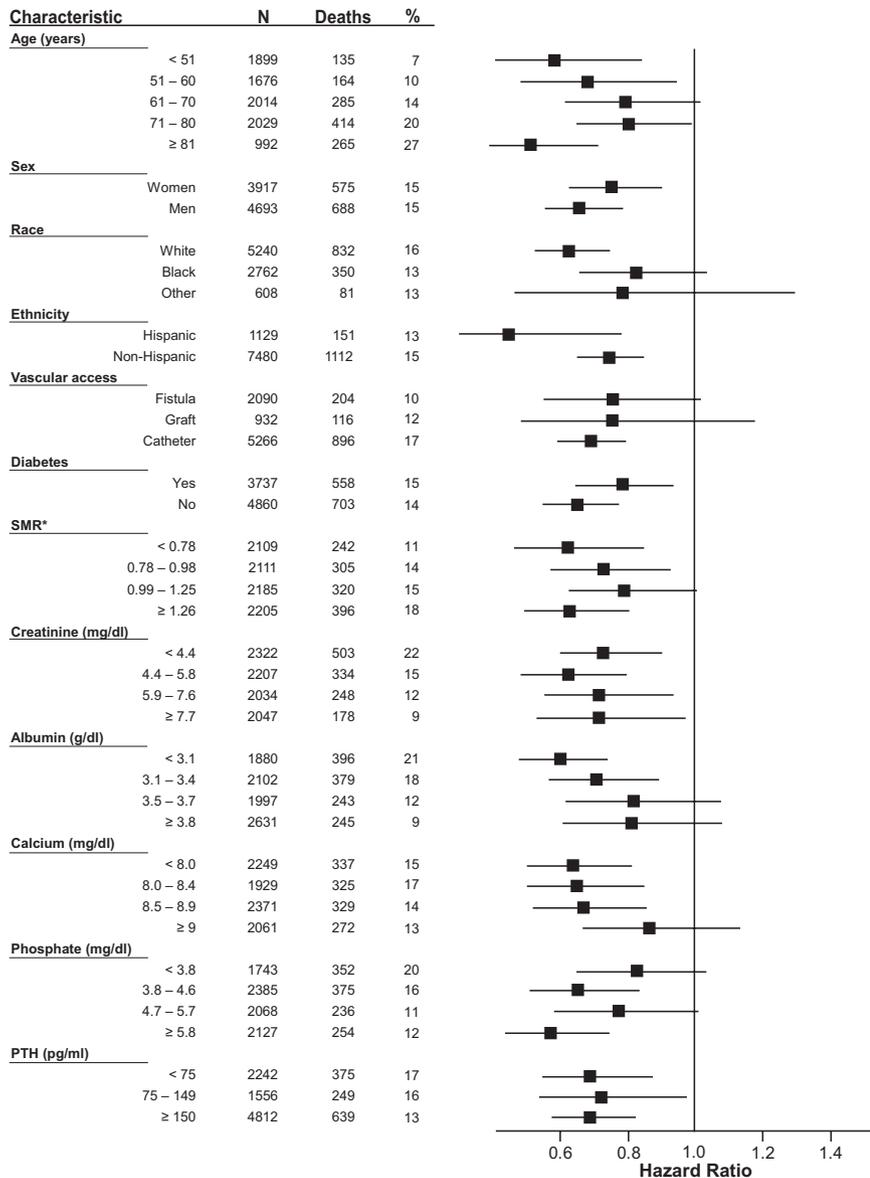
Treatment before Hemodialysis Initiation

Finally, we examined the outcomes of the 1434 patients who had begun treatment with phosphorus binders before the initiation of hemodialysis and were excluded from the previous analyses. These patients demonstrated a significant survival advantage compared with the 5055 patients who were untreated in the first 90 d (the control group in previous analyses; HR 0.74; 95% CI 0.61 to 0.88; P = 0.0008), and even when compared with all 8610 patients used in the intention-to-treat analyses (HR 0.83; 95% CI 0.70 to 0.98; P = 0.03), which included the 3555 who were treated during the first 90 d.

DISCUSSION

In this 1-yr prospective observational study of incident hemodialysis patients, treatment with phosphorus binders was associated with a significant survival advantage compared with no treatment. The benefit of phosphorus binders was independent of established risk factors, consistent across a variety of subgroups, and robust to different analytic strategies. Interestingly, we observed a survival benefit of phosphorus binders in each of the three upper quartiles of baseline serum phosphate, a group that spanned many patients for whom therapy is not currently recommended because their phosphate levels were not above the target range for dialysis patients.[9] Furthermore, although phosphorus binders are approved for lowering serum phosphate levels, the survival benefit of therapy was only minimally attenuated when adjusted for follow-up phosphate levels. Collectively, these results suggest potential benefits of phosphorus binders beyond reduction of serum phosphate levels that, if verified by other studies, would justify further exploration into potential mechanisms and perhaps support a broader role for phosphorus binder therapy in patients with chronic kidney disease.

Elevated serum phosphate levels are independently associated with mortality in hemodialysis, predialysis, and non–kidney disease populations.[1–7] Although the mechanisms are incompletely understood, hyperphosphatemia is linked to nonatherosclerotic arterial calcification, increased arterial stiffness, and left ventricular hypertrophy, each of which is an independent risk factor for death.[17–21] Calcium acetate and carbonate are phosphorus binders that are widely used to treat hyperphosphatemia on dialysis, but some experts have questioned their long-term safety because excessive calcium loading may exacerbate arterial calcification.[3] As a result, a number of studies explored differences in outcomes according to whether patients were treated with calcium- or newer non–calcium-based binders. Although the results of these studies

Characteristic	N	Deaths	%
Age (years)			
< 51	1899	135	7
51 – 60	1676	164	10
61 – 70	2014	285	14
71 – 80	2029	414	20
≥ 81	992	265	27
Sex			
Women	3917	575	15
Men	4693	688	15
Race			
White	5240	832	16
Black	2762	350	13
Other	608	81	13
Ethnicity			
Hispanic	1129	151	13
Non-Hispanic	7480	1112	15
Vascular access			
Fistula	2090	204	10
Graft	932	116	12
Catheter	5266	896	17
Diabetes			
Yes	3737	558	15
No	4860	703	14
SMR*			
< 0.78	2109	242	11
0.78 – 0.98	2111	305	14
0.99 – 1.25	2185	320	15
≥ 1.26	2205	396	18
Creatinine (mg/dl)			
< 4.4	2322	503	22
4.4 – 5.8	2207	334	15
5.9 – 7.6	2034	248	12
≥ 7.7	2047	178	9
Albumin (g/dl)			
< 3.1	1880	396	21
3.1 – 3.4	2102	379	18
3.5 – 3.7	1997	243	12
≥ 3.8	2631	245	9
Calcium (mg/dl)			
< 8.0	2249	337	15
8.0 – 8.4	1929	325	17
8.5 – 8.9	2371	329	14
≥ 9	2061	272	13
Phosphate (mg/dl)			
< 3.8	1743	352	20
3.8 – 4.6	2385	375	16
4.7 – 5.7	2068	236	11
≥ 5.8	2127	254	12
PTH (pg/ml)			
< 75	2242	375	17
75 – 149	1556	249	16
≥ 150	4812	639	13

Figure 1. Stratified HRs for mortality in the unmatched subcohort (*n* = 8610) comparing patients who began treatment with phosphorus binders during the first 90 d on hemodialysis *versus* those who were not treated during the first 90 d. Models within individual strata were adjusted for all other covariates, including age; gender; race; ethnicity; cause of renal failure; systolic BP; body mass index; standardized mortality rate; initial vascular access; coronary artery disease; congestive heart failure; laboratory variables including albumin, creatinine, calcium, phosphate, PTH, and hemoglobin; and vitamin D therapy at baseline. Percentages represent the proportion of deaths within each stratum, squares represent the HR point estimates, and horizontal lines represent 95% CIs. Point estimates to the left of unity (vertical line) favor a survival benefit of phosphorus binders.

have been mostly inconsistent with some but not all suggesting differences in cardiovascular surrogates and mortality according to specific binder classes,[22–25] until now, no studies examined the more fundamental question of whether treatment with any phosphorus binders *versus* none affects survival.

Lowering serum phosphate levels is an obvious mechanism through which phosphorus binders might be associated with a survival advantage, but the benefit we observed was independent of baseline and follow-up serum phosphate levels, suggesting additional protective mechanisms. An intriguing possibility is the effect of phosphorus binders on circulating levels of fibroblast growth factor 23 (FGF-23). FGF-23 is a hormone that regulates serum phosphate levels by modulating urinary phosphate excretion and 1,25-dihydroxyvitamin D synthesis in the kidney.[26] Patients with chronic kidney disease develop progressive increases in FGF-23 levels that often reach 100-fold above normal once they initiate dialysis.[27] Although increased FGF-23 levels are thought to represent a compensatory mechanism to maintain normophosphatemia in the face of declining nephron mass, increased FGF-23 levels were independently associated with increased risk for mortality in a dosage-dependent manner in a recent prospective study of incident hemodialysis patients.[27] Importantly, the association between increased FGF-23 levels and mortality was independent of serum phosphate levels, paralleling the results in this study. Given that phosphorus binders lower FGF-23 levels,[28,29] it is interesting to speculate that the benefit of binders that we observed might be mediated by attenuating potential toxicity of markedly increased FGF-23 levels in patients with only mild or even no increase in serum phosphate levels.

Serum phosphate levels increase with duration of dialysis.[1] Thus, a strength of this study was the large sample of incident hemodialysis patients that enabled us to study those with relatively low serum phosphate levels, many of whom were and were not treated with phosphorus binders. Had we studied prevalent patients, higher serum phosphate levels would have resulted in fewer untreated patients and increased the likelihood of selection bias. Furthermore, combining incident and prevalent patients would have introduced immortal time bias[30] given that prevalent patients would have had greater opportunity to survive long enough to receive phosphorus binders than incident patients because early mortality on dialysis is common.[31] Another benefit of the large sample of incident patients with detailed covariate data was the ability to perform well-powered propensity score–matched analyses, which minimize selection bias and confounding by indication by matching treated and untreated patients on their probability of being treated as a
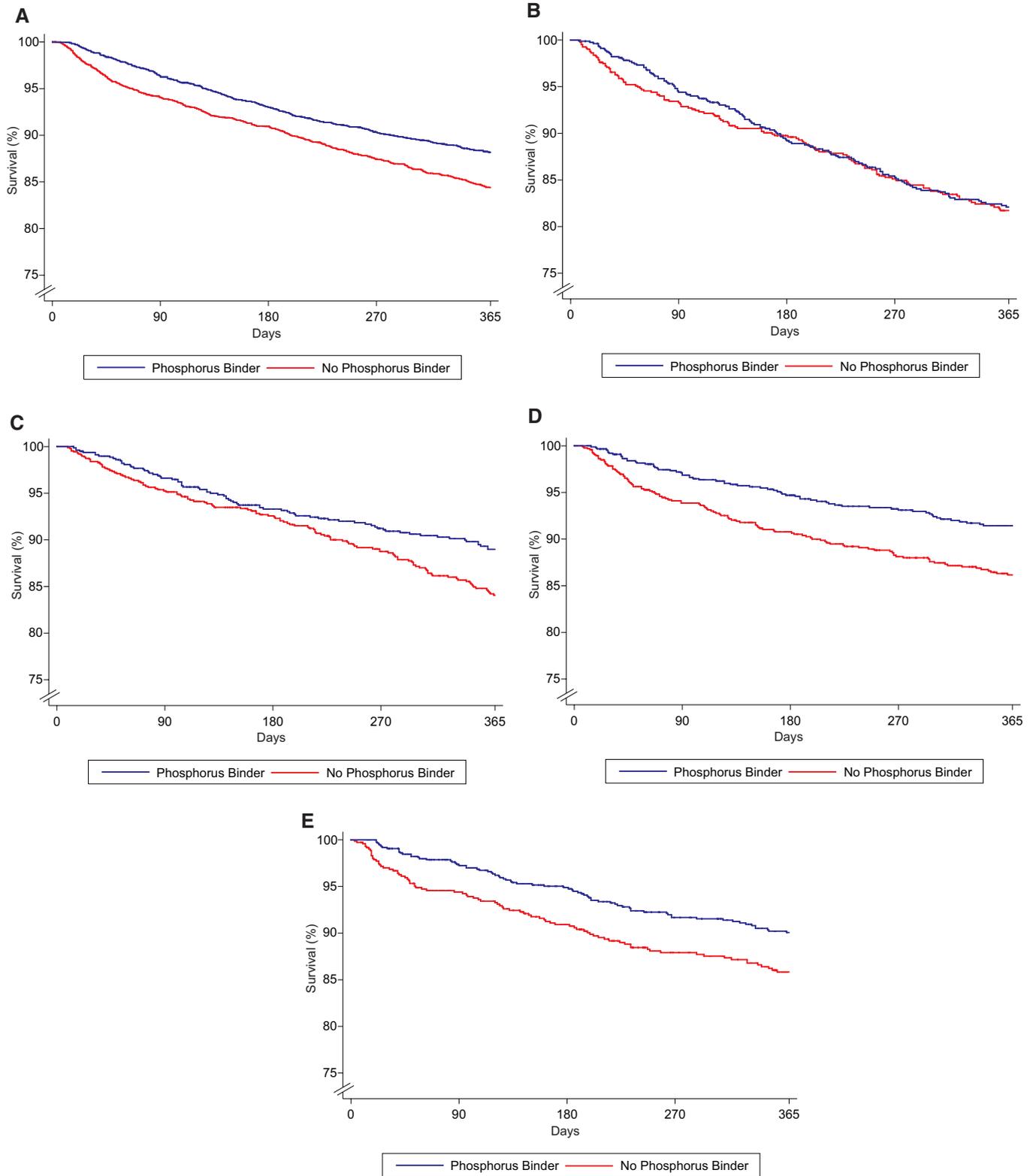
Figure 2. (A through E) Survival of treated and untreated patients in the overall propensity score–matched cohort (A) and according to quartiles of baseline serum phosphate: <3.7 mg/dl (B), 3.7 to 4.5 mg/dl (C), 4.6 to 5.5 mg/dl (D), and ≥5.6 mg/dl (E).

function of their baseline characteristics.[32] The effect of phosphorus binders on survival was consistent in these analyses, which suggests that the results were unlikely to be due to selec-

tion bias. We must be cautious, however, because, unlike randomized trials, propensity score matching can balance only known confounders; we cannot exclude residual confounding

Table 3. HRs for mortality in the serum phosphate and propensity score–matched subcohort comparing patients who were treated with phosphorus binders (n = 3186) with those who were untreated (n = 3186)

Parameter	HR	95% CI	P
Entire subcohort[a]			
no adjustment	0.75	0.66 to 0.87	<0.0001
age-adjusted	0.78	0.68 to 0.89	0.0003
time varying serum phosphate[c]	0.78	0.68 to 0.90	0.0004
Phosphate quartiles (mg/dl)			
<3.7	0.90	0.71 to 1.15	0.40
3.7 to 4.5	0.72	0.54 to 0.97	0.03
4.6 to 5.5	0.70	0.52 to 0.94	0.02
≥5.6	0.63	0.47 to 0.84	0.002

[a]The treated group included patients who began treatment during the first 90 d on hemodialysis, whereas the untreated group included those who were not treated during the first 90 d.
[c]Adjusted for age and follow-up serum phosphate levels.

by unmeasured confounders. Indeed, although our study design and multiple analytical approaches aimed to approximate a randomized trial, no single analysis could eliminate all potential sources of bias as an actual trial would. Thus, we must rely on the totality of the results and their qualitative consistency across different analytical strategies as the primary finding of this observational study.

This study has additional limitations. Phosphorus binder use was ascertained on the basis of its prescription, and although the percentage of patients who were prescribed these agents before and within 90 d of initiating dialysis was consistent with previous reports,[33] we did not have direct measures of compliance, such as pill counts, and we were unable to study dosage of therapy; however, noncompliance in the treated group and underascertainment of binder use in the untreated group would tend to bias the results to the null because the treated group would include patients who were actually untreated and the untreated group would include some patients who were. Furthermore, a benefit of binders was detectable regardless of treatment status with other oral and intravenous medications, suggesting that differential ascertainment did not account for the results. Second, there was a relatively high rate of censoring. Although this did not differ by binder treatment group and informative censoring is unlikely, there may have been potential differences between the comparison groups after loss of follow-up. Third, the duration of follow-up was relatively short, which may be a limitation because clinical outcomes related to certain binder types might be modified by duration of treatment beyond the first year.[24] Finally, like other large dialysis cohorts, we did not have information on dietary phosphorus intake, which would have been especially important to explore the observation that Hispanic patients derived a greater survival advantage than non-Hispanic patients. Further studies are needed to determine whether differences in phosphorus intake modify the survival benefit of phosphate binders and whether the effect in Hispanic patients is reproducible or an artifact of multiple subgroup analyses.

Our findings may have important clinical implications. The incidence of ESRD requiring dialysis is steadily growing while mortality rates on dialysis remain high.[34] Our results suggest that phosphorus binders are one therapeutic intervention that may improve outcomes, especially among patients who do not have severe hyperphosphatemia and may not be routinely treated. We acknowledge that, ideally, randomized trials rather than observational studies should drive changes in clinical practice; however, conducting a placebo-controlled, randomized trial of phosphorus binders on dialysis could be especially challenging. Current national practice guidelines for dialysis patients recommend that serum phosphate levels be maintained between 3.5 and 5.5 mg/dl.[9] This guideline is widely accepted by clinicians because of the body of evidence linking phosphorus excess and adverse outcomes; therefore, randomly assigning patients with hyperphosphatemia to placebo would likely be viewed as unethical. Indeed, this is an important reason that most outcomes studies of binders focused on comparisons of different binder classes rather than any *versus* none. Furthermore, whereas dialysis patients with normal serum phosphate levels could be randomly assigned, most patients in the placebo group would soon develop hyperphosphatemia that would necessitate crossover to the treatment arm or withdrawal from the trial, substantially limiting power. Although replacing mortality with a surrogate marker as the end point might offset attrition in the placebo arm (final assessments of surrogates could be done immediately before crossover or withdrawal), it is unclear which surrogate markers, if any, would reliably track with mortality, a problem highlighted by the disparate results of recent trials comparing specific binder classes.[22–25]

In contrast, a placebo-controlled, randomized trial would be most feasible in the very population in whom the greatest public health impact of phosphorus binders may be derived: patients with predialysis chronic kidney disease and normal serum phosphate levels. These patients number in the millions in the United States alone,[35] have alarmingly high mortality rates,[36] and have abnormal phosphate metabolism marked by high FGF-23 levels[26]; however, because >90% of these patients maintain normal serum phosphate levels,[26] they are rarely treated with phosphorus binders on the basis of current indications. A randomized trial of binders *versus* placebo to decrease mortality in patients with stages 3 and 4 chronic kidney disease and normal serum phosphate levels is feasible, would validate or cast doubt on the results of this study, and, if positive, would dramatically alter the treatment of patients with kidney disease worldwide.

CONCISE METHODS

Study Population
Accelerated Mortality on Renal Replacement (ArMORR) is a prospective cohort study of 10,044 patients who initiated long-term hemodialysis at any of 1056 US hemodialysis centers operated by Frese-

nius Medical Care, North America (Lexington, MA) between July 2004 and June 2005. Data were collected prospectively by individual patients' practitioners at the point of care and included demographics; comorbidities; medications such as phosphorus binders, activated vitamin D, and cardiovascular drugs; routine laboratory results performed by a central laboratory (Spectra East, Rockland, NJ); and outcomes. Longitudinal follow-up was continued through patients' first year on hemodialysis.

Home medications were ascertained at baseline and monthly thereafter through patients' verbal report; new prescriptions of dialysis-related medications such as phosphorus binders and activated vitamin D were entered into the database at the time of prescription. For data quality assurance, patients brought their pill bottles to the facility to verify the accuracy of the medication list in the database on a quarterly basis. Laboratory results obtained at the initiation of hemodialysis included albumin, creatinine, calcium, phosphate, and hemoglobin, which were measured using standard multisample automated analyzers, and PTH, which was measured using Nichols Bio-intact assay of full-length 1-84 PTH. The study was approved by the institutional review board of the Massachusetts General Hospital, which waived the need for informed consent because all clinical data were stripped of personal identifiers before transfer to the investigators.

Outcomes and Exposures

The primary outcome was all-cause mortality during the first year of hemodialysis, confirmed by mandatory discharge diagnosis reports from individual hemodialysis centers. We also examined cardiovascular and noncardiovascular mortality using *International Classification of Diseases, Ninth Revision* mortality codes, as done previously.[37] The primary exposure was any therapy with dietary phosphorus binders. We chose not to study specific phosphorus binder types because patients were often treated with different classes of binders at different time points often in combinations and because comparisons of specific binders were the focus of previous randomized trials,[22–25] whereas no studies have compared any therapy *versus* none. Certain basic laboratory tests are performed monthly on all dialysis patients, but serum phosphate levels can be measured more frequently when medications such as phosphorus binders are being actively titrated; therefore, we examined the frequency of additional testing of serum phosphate levels beyond the standard monthly measures as a method of validating the ascertainment of phosphorus binder therapy in ArMORR. In support of the accuracy of the primary exposure, patients who were noted as being treated with phosphorus binders had a 50% higher number of extra serum phosphate measurements than those who were noted to be untreated ($P < 0.0001$).

We classified patients into three groups according to their exposure to phosphorus binders: (*1*) pretreated: those who had begun therapy before initiating hemodialysis and, thus, before enrollment in ArMORR ($n = 1434$); (*2*) treated: those who began treatment during the first 90 d after initiating hemodialysis ($n = 3555$); and (*3*) untreated: those who were untreated during the first 90 d ($n = 5055$). In an effort to mimic a randomized trial, we performed an intention-to-treat analysis of the treated and untreated groups ($n = 8610$) in which patients who did not take binders during the first 90 d were analyzed

in the untreated group regardless of subsequent "crossover" to treatment, whereas those who discontinued therapy at any time after it was begun during the first 90 d remained in the treated group. We also conducted as-treated analyses in which survival time before therapy began was credited to the untreated group and only after therapy began was subsequent survival time credited to the treated group. Like the intention-to-treat analyses, once patients initiated phosphorus binders, they remained in the treated group for the remainder of their follow-up time until death or censoring. The pretreated group was excluded from these analyses to reduce selection bias and because we could not adjust for covariates measured at the time the decision was made to initiate phosphorus binders in that group because this occurred before the initiation of hemodialysis when ArMORR commenced.

In an effort to minimize potential selection bias and confounding by indication in this observational study, we performed additional analyses after calculating a propensity score of likelihood of receiving phosphorus binders using logistic regression.[32] Baseline predictors that are clinically related to phosphorus binder use were used to estimate the propensity score and included age, gender, race and ethnicity (ascertained *via* self-report); BP; body mass index; cause of renal failure; albumin, creatinine, calcium, phosphate, PTH, and hemoglobin levels; history of coronary artery disease and congestive heart failure; hemodialysis access; and baseline use of activated vitamin D. To account for local differences in overall quality of care, we also included individual hemodialysis units' standardized mortality rates in the propensity score estimation.[38] An investigator (Y.C.) who was blinded to outcomes used the propensity score to generate a subcohort of 3186 pairs of treated and untreated patients who were matched one-to-one by propensity score ±0.03, as has been done previously.[39] These patients were also matched by baseline serum phosphate quartile to ensure that the propensity score–matched pairs remained intact for prespecified stratified analyses within each phosphate quartile.

Statistical Analysis

We used two-sample *t*, Wilcoxon rank sum, and χ^2 tests to compare baseline characteristics and laboratory results according to the phosphorus binder treatment groups in both the unmatched and matched cohorts. After confirming the proportionality assumption, we used Cox proportional hazards analyses to examine the crude and multivariable-adjusted risk for mortality associated with phosphorus binder therapy in the unmatched cohort, censoring at the time of kidney transplantation (3%), spontaneous recovery of renal function (4%), or transfer out of the Fresenius Medical Care system (12%) that occurred before completing the 1-yr of follow-up. There was no difference in the frequency of censoring between the treated and untreated groups (18.6 *versus* 19.6%; $P = 0.27$). The multivariable analyses included the same covariates used to calculate the propensity score. We tested for interaction between phosphorus binder therapy and demographic and laboratory characteristics and report stratum-specific HRs in the unmatched cohort. Treatment with activated vitamin D has been associated with improved survival on hemodialysis,[37] and phosphorus binders could alter serum levels of calcium, phosphate, and PTH and thereby influence the decision to administer vitamin D; therefore, we also adjusted for the use of vitamin D therapy

during the follow-up period as a time-dependent covariate. To account for differences in quality of care at different dialysis units, we analyzed models stratified by facility-specific standardized mortality rate. Because the matching strategy eliminated virtually all differences in baseline characteristics between the treated and untreated groups, we compared their survival in the matched cohort using Kaplan-Meier curves, as has been done previously,[40] with Cox models used to adjust for residual differences in age.

To explore whether the effect of phosphorus binders on survival was altered by changes in follow-up serum phosphate levels, we examined the change in point estimate for binder treatment in models that included the quarterly mean of follow-up serum phosphate levels modeled as time-varying covariates. To test whether the results were robust to early mortality on dialysis, we repeated the intention-to-treat analyses in the unmatched cohort after excluding patients who died during the first 90 d of initiating hemodialysis in a prespecified subgroup analysis and performed additional sensitivity analyses that incrementally excluded deaths that occurred during the 15-d intervals from the initiation of dialysis through day 90. In addition, we tested the specificity of the phosphorus binder effect by examining the associations between aspirin and angiotensin-converting enzyme inhibitors and survival in multivariable models. Finally, we compared the survival of the previously excluded pretreated patients (those who began binders before initiating dialysis) with that of the treated and untreated groups. Analyses were performed using SAS 9.1 (SAS Institute, Cary, NC). Two-sided $P < 0.05$ was considered statistically significant.

ACKNOWLEDGMENTS

DISCLOSURES

REFERENCES

1. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM: Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 15: 2208–2218, 2004
2. Sehgal AR, Sullivan C, Leon JB, Bialostosky K: Public health approach to addressing hyperphosphatemia among dialysis patients. *J Ren Nutr* 18: 256–261, 2008
3. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB: Coronary-

artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 342: 1478–1483, 2000
4. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, Akizawa T, Kurokawa K, Bommer J, Piera L, Port FK: Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 67: 1179–1187, 2005
5. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK: Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 12: 2131–2138, 2001
6. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL: Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol* 16: 520–528, 2005
7. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G: Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 112: 2627–2633, 2005
8. Dhingra R, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB Sr, Gaziano JM, Vasan RS: Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med* 167: 879–885, 2007
9. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 42: S1–S201, 2003
10. McBride R: After Renvela filing, Genzyme renews focus on Renagel. *Mass High Tech: The Journal of New England Technology.* Available at: http://www.masshightech.com/stories/2007/01/15/story13-After-Renvela-filing-Genzyme-renews-focus-on-Renagel.html. Accessed April 4, 2008
11. Slatopolsky E, Weerts C, Lopez-Hilker S, Norwood K, Zink M, Windus D, Delmez J: Calcium carbonate as a phosphate binder in patients with chronic renal failure undergoing dialysis. *N Engl J Med* 315: 157–161, 1986
12. Emmett M, Sirmon MD, Kirkpatrick WG, Nolan CR, Schmitt GW, Cleveland MB: Calcium acetate control of serum phosphorus in hemodialysis patients. *Am J Kidney Dis* 17: 544–550, 1991
13. Chertow GM, Burke SK, Lazarus JM, Stenzel KH, Wombolt D, Goldberg D, Bonventre JV, Slatopolsky E: Poly[allylamine hydrochloride] (RenaGel): A noncalcemic phosphate binder for the treatment of hyperphosphatemia in chronic renal failure. *Am J Kidney Dis* 29: 66–71, 1997
14. Slatopolsky EA, Burke SK, Dillon MA: RenaGel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers serum phosphorus and parathyroid hormone. The RenaGel Study Group. *Kidney Int* 55: 299–307, 1999
15. Mitka M: Study probes best choice of drug to reduce phosphate in patients on dialysis. *JAMA* 298: 1995–1996, 2007
16. Winkelmayer WC, Tonelli M: Phosphate binder choice in dialysis patients: A call for evidence-based rather than marketing-based clinical practice. *Am J Kidney Dis* 51: 362–365, 2008
17. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM: Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension* 38: 938–942, 2001
18. Klassen PS, Lowrie EG, Reddan DN, DeLong ER, Coladonato JA, Szczech LA, Lazarus JM, Owen WF Jr: Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA* 287: 1548–1555, 2002
19. Ayus JC, Mizani MR, Achinger SG, Thadhani R, Go AS, Lee S: Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: A prospective, controlled study. *J Am Soc Nephrol* 16: 2778–2788, 2005
20. Silberberg JS, Barre PE, Prichard SS, Sniderman AD: Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 36: 286–290, 1989
21. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA: The mechanism of phosphorus as a cardiovascular risk factor in CKD. *J Am Soc Nephrol* 19: 1092–1105, 2008

22. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 62: 245–252, 2002

23. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM: Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 71: 438–441, 2007

24. Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, Ling BN, Chasan-Taber S, Dillon MA, Blair AT, Burke SK: Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 72: 1130–1137, 2007

25. St Peter WL, Liu J, Weinhandl E, Fan Q: A comparison of sevelamer and calcium-based phosphate binders on mortality, hospitalization, and morbidity in hemodialysis: A secondary analysis of the Dialysis Clinical Outcomes Revisited (DCOR) Randomized Trial Using Claims Data. *Am J Kidney Dis* 51: 445–454, 2008

26. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, Juppner H, Wolf M: Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol* 16: 2205–2215, 2005

27. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, Smith K, Lee H, Thadhani R, Juppner H, Wolf M: Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 359: 584–592, 2008

28. Koiwa F, Kazama JJ, Tokumoto A, Onoda N, Kato H, Okada T, Nii-Kono T, Fukagawa M, Shigematsu T: Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients. *Ther Apher Dial* 9: 336–339, 2005

29. Nagano N, Miyata S, Abe M, Kobayashi N, Wakita S, Yamashita T, Wada M: Effect of manipulating serum phosphorus with phosphate binder on circulating PTH and FGF23 in renal failure rats. *Kidney Int* 69: 531–537, 2006

30. Shariff SZ, Cuerden MS, Jain AK, Garg AX: The secret of immortal time bias in epidemiologic studies. *J Am Soc Nephrol* 19: 841–843, 2008

31. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R: Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 72: 1004–1013, 2007

32. D'Agostino RB Jr, D'Agostino RB Sr: Estimating treatment effects using observational data. *JAMA* 297: 314–316, 2007

33. Winkelmayer WC, Levin R, Avorn J: The nephrologist's role in the management of calcium-phosphorus metabolism in patients with chronic kidney disease. *Kidney Int* 63: 1836–1842, 2003

34. US Renal Data System: *USRDS 2007 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007

35. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–2047, 2007

36. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004

37. Teng M, Wolf M, Ofsthun MN, Lazarus JM, Hernan MA, Camargo CA Jr, Thadhani R: Activated injectable vitamin D and hemodialysis survival: A historical cohort study. *J Am Soc Nephrol* 16: 1115–1125, 2005

38. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R: Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 349: 446–456, 2003

39. Gupta R, Plantinga LC, Fink NE, Melamed ML, Coresh J, Fox CS, Levin NW, Powe NR: Statin use and hospitalization for sepsis in patients with chronic kidney disease. *JAMA* 297: 1455–1464, 2007

40. Schermerhorn ML, O'Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon BE: Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. *N Engl J Med* 358: 464–474, 2008

See related editorial, "Phosphorus and Survival: Key Questions That Need Answers," on pages 234–236.