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Use of phosphate-binding agents is associated with a lower risk of mortality

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Hyperphosphatemia has been associated with higher mortality risk in CKD 5 patients receiving dialysis. Here, we determined the association between the use of single and combined phosphate-binding agents and survival in 6797 patients of the COSMOS study: a 3-year follow-up, multicenter, open-cohort, observational prospective study carried out in 227 dialysis centers from 20 European countries. Patient phosphate-binding agent prescriptions (time-varying) and the case-mix–adjusted facility percentage of phosphate-binding agent prescriptions (instrumental variable) were used as predictors of the relative all-cause and cardiovascular mortality using Cox proportional hazard regression models. Three different multivariate models that included up to 24 variables were used for adjustments. After multivariate analysis, patients prescribed phosphate-binding agents showed a 29 and 22% lower all-cause and cardiovascular mortality risk, respectively. The survival advantage of phosphate-binding agent prescription remained statistically significant after propensity score matching analysis. A decrease of 8% in the relative risk of mortality was found for every 10% increase in the case-mix–adjusted facility prescription of phosphate-binding agents. All single and combined therapies with phosphate-binding agents, except aluminum salts, showed a beneficial association with survival. The findings made in the present association study need to be confirmed by randomized controlled trials to prove the observed beneficial effect of phosphate-binding agents on mortality.

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During the past decade, knowledge on the pathogenesis and management of chronic kidney disease mineral bone disorders (CKD-MBD) has grown considerably, and the diagnosis, prognosis, and management of these disorders is

now formally systematized in specific KDIGO guidelines.[1–4] The control of serum phosphorus at all stages of CKD is considered key to improve clinical outcomes in CKD-MBD, including survival.[5–10] In clinical and experimental studies, phosphorus accumulation has been shown to have a negative impact in several aspects of the CKD-MBD constellation, such as parathyroid hyperplasia, vascular calcification, cardiovascular disease, bone strength, bone mass, and bone fractures.[2,10–14] The potential adverse effects of high serum phosphorus and/or phosphorus accumulation for human health are not limited to patients with end-stage kidney disease and extends to stages 2–4 CKD[7] and to the general population.[15]

Maintaining a serum phosphorus level as close to normal values as possible has become a challenge in the management of CKD-MBD. Several new phosphate-binding agents (PBAs) have been developed and reached the market just at turn of the last century.[16,17] So far, all available PBAs have proven to be effective in reducing serum phosphorus, but their effects on clinical outcomes remain unknown, and the need of large-scale trials based on clinical end points cannot be overemphasized. However, funding and organizing such trials remains a tantalizing undertaking. In this scenario, observational studies testing the comparative effectiveness of PBAs may provide important information to further explore the hypothesis that these medications may reduce mortality in stage 5D-CKD patients. In this regard, a large cohort study by Isakova *et al.*[18] showed that treatment with phosphorus binders is independently associated with decreased mortality, whereas in other analyses based on an incident USRDS cohort that started dialysis in 1996–1997—at a time when only calcium-containing phosphate binders were used in the United States—no association was found between the use of these agents and mortality.[19] The use of instrumental variable analysis techniques may help answer the question.[20] The death risk in European patients on chronic dialysis is lower than that of US patients, and risk factors in these two populations differ in part.[21] For example, body mass index (BMI) is substantially higher in American patients[22] than in European patients.[23] These differences are of potential relevance because the prescription of phosphate binders is strongly associated with better nutritional status, i.e., higher BMI and other nutritional indicators.[24] Thus, exploring the link between the use of phosphate binders and major clinical outcomes in European patients may provide relevant information for advancing knowledge on this issue.

One of the main aims of the Current management Of Secondary hyperparathyroidism: A Multicenter Observational Study (COSMOS), which included randomly selected patients in 227 dialysis centers from 20 European countries, was to investigate the association between PBA prescription and survival in European patients on dialysis. In the analyses presented herein, in order to limit bias by indication, we modeled the relationship between PBA prescription and clinical outcomes by time-varying, multivariable Cox regression analysis, propensity score matching, and instrumental variable analysis.

RESULTS

A total of 6797 patients were recruited for COSMOS, 4500 of them randomly selected at baseline and 2297 to replace patients lost to follow-up. Patients who had only baseline data (no follow-up) or patients with lacking information on prescription of PBAs were excluded. After exclusions, 6297 patients (4313 (68.5%) randomly selected and 1984 (31.5%) replacements) were available for analysis.

The main baseline characteristics of the patients included in the study are detailed in Table 1. Patients not prescribed PBAs represented 14.9% of the full cohort, whereas PBAs-prescribed patients made up the remaining 85.1%. The latter were younger, with higher BMI; there were more men and smokers, and fewer diabetics. They referred less events related to cardiovascular disease, they had been on HD for a longer period, and they received more hours of dialysis per week. In the group of patients prescribed PBAs, there were also more patients who were prescribed Vitamin D receptor activators (VDRAs), calcimimetics, and erythropoietin-stimulating agents, and they showed higher serum levels of phosphorus, parathyroid hormone (PTH), and albumin. The propensity score–matched subcohorts showed no differences in the characteristics of patients prescribed or not prescribed PBAs (Table 1).

The comparison between random baseline and replacement patients is shown in the Supplementary Material online. The replacement patients were younger, with more men and higher BMIs. Diabetes as a cause of end-stage renal failure was more frequent, and consequently there were more diabetics on HD. Replacement patients showed a lower number of patients with cardiovascular disease history and parathyroidectomies; conventional high-flux dialysis was less used in this group.

During the 3-year follow-up, the overall COSMOS crude all-cause mortality rate was 13.3 deaths per 100 patient-years, 14.2 in baseline random patients, and 10.8 in replacement patients. The crude cardiovascular mortality rate was 5.9 cardiovascular deaths per 100 patient-years, 6.4 in baseline random patients, and 4.6 in replacement patients. During that period, 1642 patients died (26.1%). The mean time of follow-up was 23.5 months (median 24.0), in the whole study, 25.2 months (median 30.0) in the random baseline patient group, and 19.9 months (median 18) in the replacement patients group. During the 3-year follow-up, 4430 patients were always prescribed PBAs, 451 were never prescribed PBAs, and 1416 were required to either stop or initiate PBA prescription during follow-up. The percentages of patient-years prescribed PBAs either as monotherapy or combined therapy were as follows: monotherapy: calcium-containing PBAs, 36.7%; sevelamer, 14.9%; aluminum salts, 3.3%; lanthanum carbonate, 2.5%; and others, 2.6%. Combined therapy: calcium-containing + sevelamer, 11.1%; calcium-containing + aluminum salts, 3.3%; calcium-containing + lanthanum carbonate, 1.6%; sevelamer + aluminum salts, 1.4%; sevelamer + lanthanum carbonate, 0.8%; and other combinations, 4.4%.

Table 1 | Main baseline characteristics of patients included in the study

		Full cohort			Propensity score–matched cohort		
	All patients (6297)	Untreated ($N=941$)	Treated ($N=5356$)	*P*-value	Untreated ($N=823$)	Treated ($N=823$)	*P*-value
Sex (% males)	60.8	57.4	61.4	0.021	56.7	56.1	0.8
Age (years) (mean ± s.d.)	64.0 ± 14.4	69.1 ± 12.7	63.1 ± 14.5	<0.001	69.0 ± 12.6	69.0 ± 12.6	0.9
BMI (kg/m^2) (mean ± s.d.)	25.4 ± 6.3	24.7 ± 5.1	25.6 ± 6.5	<0.001	24.7 ± 5.1	24.6 ± 4.4	0.6
Current smokers (%)	13.9	10.6	14.5	0.002	10.9	10.7	0.9
Diabetics (%)	30.6	36.3	29.6	<0.001	35.7	35.8	1.0
CVD history (%)	72.0	75.3	71.5	0.016	74.8	74.7	1.0
Parathyroidectomy (%)	4.9	3.8	5.1	0.1	4.0	3.6	0.7
Months on HD (mean ± s.d.)	38.9 ± 49.5	32.3 ± 50.1	40.1 ± 49.2	<0.001	32.9 ± 52.5	33.4 ± 40.2	0.8
Hours of dialysis per week (mean ± s.d.)	12.0 ± 2.1	11.6 ± 2.3	12.1 ± 2.1	<0.001	11.7 ± 2.4	11.6 ± 2.0	0.6
Dialysis technique				0.4			0.9
HD conventional low flux (%)	54.1	55.3	53.9		56.6	56.1	
HD conventional high flux (%)	37.1	35.3	37.5		32.8	33.8	
Hemodiafiltration and others (%)	8.8	9.5	8.7		10.6	10.1	
Calcium concentration in dialysate				<0.001			0.7
2.5 mEq/l (%)	30.0	21.6	31.5		20.9	20.8	
3.0 mEq/l (%)	50.0	53.7	49.4		55.3	53.8	
3.5 mEq/l (%)	19.9	24.7	19.1		23.8	25.4	
Patients treated with VDRAs (%)	47.5	39.5	48.9	<0.001	40.2	41.4	0.7
Patients treated with calcimimetics (%)	6.2	3.7	6.6	0.001	3.3	2.9	0.7
Patients treated with ESAs (%)	90.4	87.7	90.9	0.002	87.8	88.1	0.9
PTH (pg/ml) (median (IQR))	201.0 (275.2)	186.5 (232.9)	206.0 (287.0)	<0.001	182.0 (230.0)	162.4 (220.5)	0.8
Calcium (mg/dl) (mean ± s.d.)	9.1 ± 0.9	9.0 ± 0.8	9.1 ± 0.9	0.1	9.1 ± 0.8	9.1 ± 0.9	0.2
Phosphorus (mg/dl) (mean ± s.d.)	5.4 ± 1.7	4.7 ± 1.6	5.5 ± 1.7	<0.001	4.7 ± 1.6	4.8 ± 1.5	0.4
Albumin (g/dl) (mean ± s.d.)	3.8 ± 0.5	3.7 ± 0.6	3.8 ± 0.5	<0.001	3.7 ± 0.6	3.7 ± 0.5	1.0
Hemoglobin (g/dl) (mean ± s.d.)	11.5 ± 1.5	11.5 ± 1.5	11.5 ± 1.5	0.9	11.5 ± 1.5	11.5 ± 1.5	1.0

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; ESAs, erythropoietin-stimulating agents; HD, hemodialysis; IQR, interquartile range; PTH, parathyroid hormone; VDRAs, vitamin D receptor activators.

Table 2 | Relative all-cause and cardiovascular mortality in patients prescribed versus not prescribed PBAs

	All-cause mortality			Cardiovascular mortality		
	No. of patients	Hazard ratio (95% CI)	*P*-value	No. of patients	Hazard ratio (95% CI)	*P*-value
Univariate	6297	0.47 (0.42–0.52)	<0.001	6297	0.58 (0.49–0.69)	<0.001
Model 1 (general and demographic characteristics)	5912	0.59 (0.52–0.67)	<0.001	5181	0.75 (0.61–0.91)	0.004
Model 2 (model 1 + treatments)	5666	0.63 (0.55–0.72)	<0.001	4885	0.76 (0.62–0.93)	0.009
Model 3 (models 1 + 2 + biochemical parameters)	5276	0.71 (0.61–0.82)	<0.001	4531	0.78 (0.62–0.97)	0.029

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; ESAs, erythropoietin-stimulating agents; HD, hemodialysis; PBAs, phosphate-binding agents; VDRAs, vitamin D receptor activators.
General and demographic characteristic variables: country, center funding type (public or private), age, sex, BMI*, smoking habit, etiology of CKD, time on HD, diabetes, cardiovascular disease, calcification (valvular + vascular + calciphylaxis), and parathyroidectomy*.
Treatment variables*: dialysis type, dialysate calcium, hours of HD per week, native vitamin D or calcidiol, VDRAs (calcitriol, alfacalcidol, or paricalcitol), calcimimetics, and ESAs.
Biochemical parameter variables*: serum calcium, phosphorus, parathyroid hormone, and albumin plus hemoglobin.
*Variables included in the multivariate model as time-dependent covariates.
All multivariate analyses were stratified by facility.

In univariate analyses, patients prescribed PBAs showed a 53% (95% confidence interval (CI): 48–58%) and a 42% (95% CI: 31–51%) lower all-cause and cardiovascular mortality risk, respectively, as compared with patients not prescribed PBAs (Table 2). After adjustments additively using the three different multivariate models, the PBA-prescribed patients still showed lower all-cause and cardiovascular mortality risks (model 3) with hazard ratios of 0.71 and 0.78, respectively. As Figure 1 shows, unadjusted relative risk of mortality was significantly lower in most patients prescribed PBAs. This was the case in the vast majority of sensitivity analyses by stratification.

Patients prescribed PBAs at least once since baseline had a lower relative risk of all-cause and cardiovascular mortality

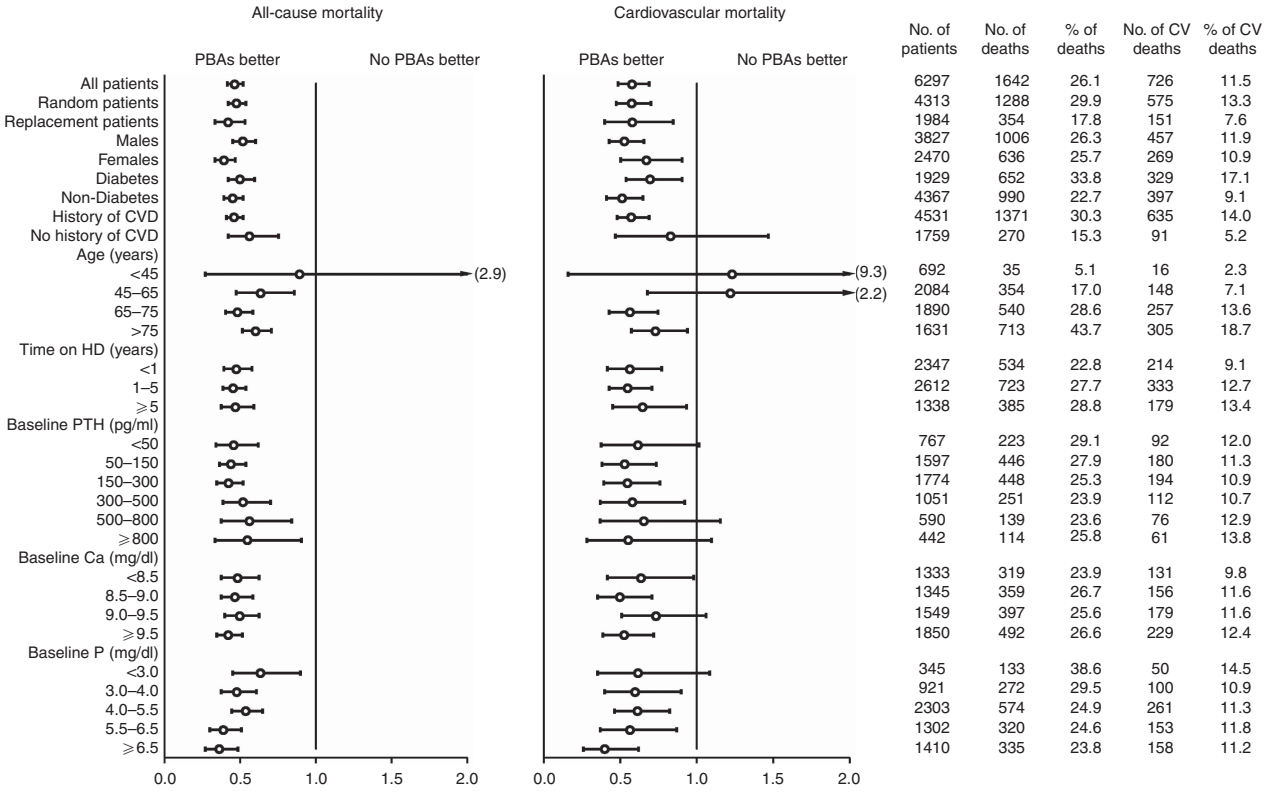

Figure 1 | Hazard ratios of unadjusted relative all-cause and cardiovascular mortality in different subgroups of patients prescribed or not prescribed phosphate-binding agents (PBAs). CV, cardiovascular; CVD, cardiovascular disease.

than patients never prescribed PBAs during the follow-up period (fully adjusted hazard ratio (aHR) = 0.56 (95% CI:0.45–0.68) and aHR = 0.59 (95% CI:0.43–0.81), respectively). After excluding the 1416 patients who required either stopping or initiation of PBA therapy, the analyses of the remaining 4881 patients revealed that patients prescribed PBAs had a lower relative risk of all-cause mortality (aHR = 0.63 (95% CI: 0.51–0.79)). Similar results were observed in cardiovascular mortality, except that the fully adjusted model was not statistically significant (aHR = 0.73 (95% CI: 0.52–1.04))—exposure variable was considered as a fixed covariate, not time-varying, in these last two analyses. The analyses performed by excluding the 4309 patients who used VDRAs at least once showed that patients prescribed PBAs, but had never used VDRAs, also exhibited a lower relative risk of all-cause mortality (aHR = 0.73 (95% CI: 0.56–0.93)). Similar results were observed in cardiovascular mortality, but the fully adjusted hazard ratio was not statistically significant (aHR = 0.72 (95% CI: 0.49–1.06)).

The analysis of all-cause mortality in the propensity score–matched cohorts and in all propensity score quartiles showed a significantly lower relative all-cause mortality risk in patients prescribed PBAs. Similar results were observed in cardiovascular mortality, but no significant differences were found in the third and fourth quartiles (Table 3).

The median case-mix–adjusted facility percentage of PBA prescription was 88.5% (ranging from 0 to 100%). Small differences in patient baseline characteristics were observed among the different quartile categories of this variable (Table 4). Patients in the highest quartiles were slightly younger and there were a lower percentage of diabetics, but very similar values in the biochemical parameters were found across categories (including serum phosphorous). The instrumental variable analyses showed an 8 and 7% decrease in all-cause and cardiovascular mortality risk, respectively, per every 10% increase in the case-mix–adjusted facility percentage of PBA prescription in the fully adjusted model (Table 5).

Analyses revealed that all types of PBA prescription, either individually or combined, were associated with a statistically significant lower all-cause mortality risk except in three cases: the aluminum-containing phosphate binder on its own, and the combinations of calcium-containing binders with aluminum, and with other phosphate binders (Figure 2). The same trend was observed in the analyses of cardiovascular mortality, but with fewer groups achieving statistical significance. The analyses of all-cause mortality with PBAs excluding those grouped as 'others', either as a monotherapy or combined therapy, are detailed in Figure 3, which shows that after all adjustments, all PBAs with the exception of aluminum salts were associated with a statistically significant reduction in mortality, with HR ranging from 0.28 to 0.73.

To rule out the possibility of a bias by indication, patients prescribed aluminum- or lanthanum-containing PBAs were

Table 3 | Unadjusted relative all-cause and cardiovascular mortality in PBA-prescribed versus non-prescribed patients using a matched cohort by propensity score and different propensity score quartiles in the full cohort

	All-cause mortality		Cardiovascular mortality	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
PS-matched cohort ($N=1646$)	0.48 (0.41–0.58)	<0.001	0.64 (0.49–0.83)	0.001
Full cohort (N = *5597*)				
PS quartile 1 ($N=1399$)	0.60 (0.50–0.71)	<0.001	0.71 (0.54–0.94)	0.018
PS quartile 2 ($N=1399$)	0.47 (0.38–0.60)	<0.001	0.57 (0.41–0.81)	0.001
PS quartile 3 ($N=1400$)	0.64 (0.47–0.89)	0.006	0.73 (0.46–1.17)	0.2
PS quartile 4 ($N=1399$)	0.54 (0.36–0.83)	0.004	0.71 (0.36–1.41)	0.3

Abbreviations: CI, confidence interval; PBAs, phosphate-binding agents; PS, propensity score.
Propensity score was calculated by using binary logistic regression. Baseline treatment with phosphate binders was introduced as a dependent variable, whereas all the baseline variables used for the full adjustment in Table 2 were included as independent variables. PS quartile 1 is the lowest quartile.

compared with patients prescribed calcium-containing PBAs, which were the most frequently used PBAs. There were a few differences in patients prescribed aluminum- or lanthanum-containing PBAs compared with those prescribed calcium-containing PBAs, i.e., patients prescribed aluminum salts showed a significantly higher serum phosphorus, calcium, and PTH levels and more time on HD, and patients prescribed lanthanum were prescribed more VDRAs and calcimimetics (data not shown).

DISCUSSION

In the COSMOS study, a lower relative risk of all-cause mortality and cardiovascular mortality was found to be associated with PBA prescription in European hemodialysis (HD) patients.

The survival advantage was observed despite higher serum phosphorus and PTH levels, higher percentages of men and smokers, and longer dialysis vintage, factors that have all been associated with higher relative risk of mortality in CKD. On the other hand, in patients prescribed PBAs, other factors that have been related to lower mortality risk were found,

Table 4 | Baseline characteristics of patients by quartiles of adjusted facility percentage of PBA prescription

	Prescription of PBAs			
	<77.0% ($N=1569$)	77.0–88.3% ($N=1568$)	88.3–96.0% ($N=1580$)	>96.0% ($N=1580$)
Sex (% males)	58.6	61.0	60.9	62.5
Age (years) (mean ± s.d.)	66.3 ± 14.1	64.7 ± 14.2	62.8 ± 14.3	62.1 ± 14.7
BMI (kg/m^2) (mean ± s.d.)	25.4 ± 5.3	25.9 ± 9.1	24.9 ± 4.9	25.5 ± 4.8
Current smokers (%)	14.1	13.4	15.1	13.2
Diabetics (%)	34.9	32.4	29.7	25.6
CVD history (%)	73.4	73.0	68.2	73.6
Calcification (%)	40.0	36.7	39.6	33.8
Parathyroidectomy (%)	4.6	4.0	5.3	5.6
Months on HD (mean ± s.d.)	39.3 ± 50.8	36.9 ± 48.0	40.3 ± 51.6	39.0 ± 47.6
PTH (pg/ml) (median (IQR))	200.0 (269.1)	190.9 (260.0)	198.0 (286.0)	224.0 (292.7)
Calcium (mg/dl) (mean ± s.d.)	9.0 ± 0.9	9.2 ± 0.8	9.1 ± 0.9	9.1 ± 0.9
Phosphorus (mg/dl) (mean ± s.d.)	5.3 ± 1.7	5.4 ± 1.7	5.4 ± 1.7	5.4 ± 1.7
Albumin (g/dl) (mean ± s.d.)	3.7 ± 0.6	3.8 ± 0.5	3.9 ± 0.5	3.8 ± 0.5
Hemoglobin (g/dl) (mean ± s.d.)	11.6 ± 1.5	11.6 ± 1.4	11.5 ± 1.5	11.3 ± 1.7

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HD, hemodialysis; IQR, interquartile range; PBAs, phosphate-binding agents; PTH, parathyroid hormone.

Table 5 | Relative all-cause and cardiovascular mortality per every 10% increase in the case-mix–adjusted center percentage of PBA prescription

	All-cause mortality			Cardiovascular mortality		
	No. of patients	Hazard ratio (95% CI)	*P*-value	No. of patients	Hazard ratio (95% CI)	*P*-value
Univariate	6293	0.92 (0.88–0.95)	<0.001	6285	0.92 (0.86–0.97)	0.003
Model 1 (general and demographic characteristics)	6256	0.94 (0.90–0.98)	0.003	6248	0.94 (0.88–0.99)	0.033
Model 2 (model 1 + treatments)	5992	0.94 (0.90–0.98)	0.002	5982	0.94 (0.88–1.00)	0.052
Model 3 (models 1 + 2 + biochemical parameters)	5582	0.92 (0.89–0.96)	<0.001	5569	0.93 (0.87–0.99)	0.018

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HD, hemodialysis; IQR, interquartile range; PBAs, phosphate-binding agents; PTH, parathyroid hormone; VDRAs, vitamin D receptor activators.
General and demographic characteristics variables: center funding type (public or private), age, sex, BMI*, smoking habit, etiology of CKD, time on HD, diabetes, cardiovascular disease, calcification (valvular + vascular + calciphylaxis), and parathyroidectomy*.
Treatment variables*: dialysis type, dialysate calcium, hours of HD per week, native vitamin D or calcidiol, VDRAs (calcitriol, alfacalcidol, or paricalcitol), calcimimetics, and erythropoietin-stimulating agents.
Biochemical parameter variables*: serum calcium, phosphorus, PTH, albumin, and hemoglobin.
*Variables included in the multivariate model as time-dependent covariates.
All the regression models were stratified by country.

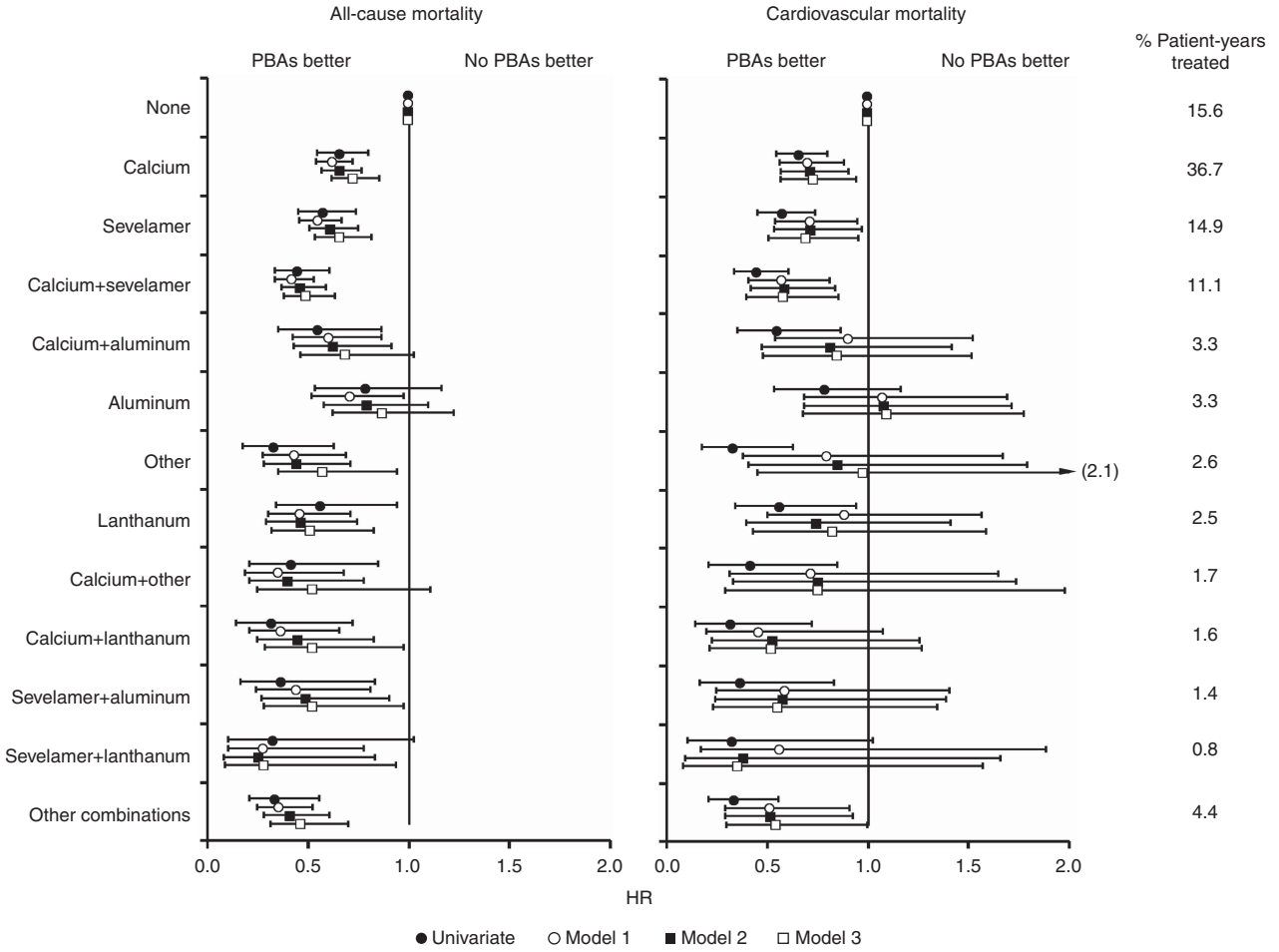

Figure 2 | Relative all-cause and cardiovascular mortality in patients prescribed different types of phosphate-binding agents (PBAs). Unadjusted (univariate) and after adjustments with the three multivariate models used. HR, hazard ratio.

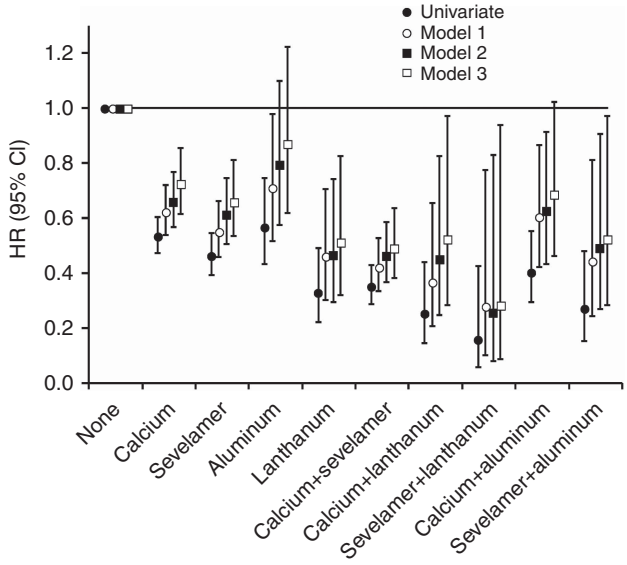

Figure 3 | Relative all-cause mortality in patients prescribed the most currently used phosphate-binding agents (PBAs) excluding those labeled as 'others'. Unadjusted (univariate) and after adjustments with the three multivariate models used. CI, confidence interval; HR, hazard ratio.

such as less number of diabetics, younger age, more use of VDRAs, and numerically slightly (but statistically significant) higher serum albumin levels.[25–27] Owing to the known effects of all these and other confounding factors, appropriate multivariate adjustments, propensity score matching, and an instrumental variable methodology, intended to reduce the effects of unknown and unmeasured variables,[20,24] were performed.

A reduced risk for all-cause mortality in patients receiving PBAs was found in random baseline and replacement patients. This was seen in men and women, diabetics and non-diabetics, patients having or not having a history of cardiovascular disease, and patients with different levels of serum phosphorous calcium and PTH (Figure 1). Similarly, but not in all groups, a beneficial effect was observed in cardiovascular mortality. Sensitivity analyses supported the possibility that the use of PBAs may lead to a survival advantage.

The benefits in survival associated with the use of PBAs in dialysis patients have been already addressed in previous studies, and the results of these studies are controversial.[18,19,24] Isakova *et al.*[18] did find a survival

advantage in PBA-treated incident HD patients, which persisted after extensive statistical adjustment and propensity score matching, whereas in another study by Winkelmayer *et al.*[19] the apparently protective effect of calcium-containing phosphate binders almost entirely vanished in propensity score–matched analyses. In COSMOS, after 3 years of follow-up, a survival advantage of PBA prescription was observed in both the random baseline and the replacement cohorts. Furthermore, the survival advantage was maintained in the two subcohorts despite important differences in other factors known to be associated with poor outcomes. By the time they entered the study, the random baseline cohort had been 50.1 months on HD in contrast with the 14.4 months of the replacement cohort (Supplementary Material online). Besides HD vintage, other differences between the prevalent and incident cohorts were also present. Some of them, such as younger age and higher BMI, may partly explain the lower percentage of cardiovascular events observed in the incident cohort and the lower rate of all-cause (10.8 vs. 14.2 deaths per 100 patient-years) and cardiovascular (4.6 vs. 6.4 cardiovascular deaths per 100 patient-years) mortality observed in the incident and the prevalent COSMOS cohorts. Overall, all-cause mortality rate was found to be 13.3 deaths per 100 patient-years, a rate similar to that reported in previous studies for European countries.[28] Some of the differences between COSMOS results and those reported in previous studies can be owing to several factors, such as different HD populations and health-system scenarios (United States and Europe) and a different design (COSMOS used a random-selection methodology; it is prospective, with a longer follow-up).

In COSMOS, after using the three multivariate models that progressively adjusted for up to 24 variables including important demographic, comorbid, socioeconomic, therapeutic, and pathogenetic factors, the survival advantages associated with PBA prescription remained highly significant, ranging from 41 to 29% (full adjustment) in all-cause mortality and from 25 to 22% in cardiovascular mortality. In addition, the use of the same adjustment models in specific analysis of subgroups of patients in whom some known beneficial factors were excluded showed similar results in the analysis of patients prescribed PBAs at least once since baseline compared with those never prescribed PBAs, and in patients prescribed PBAs during the whole study and in the subgroup of patients that never received VDRAs during the 3-year follow-up. This is an important aspect, as the use of VDRAs has been associated in previous studies with better survival.[26,27] Furthermore, the survival advantage of patients prescribed PBAs remained statistically significant in the propensity score–matched cohorts, as it was found previously by Isakova *et al.*[18]

The control of the serum bone and mineral biochemical parameters and their association with morbidity and mortality merits a special attention. Several studies have addressed the important role of hemoglobin, serum calcium, PTH, and phosphorus.[5,8,9,29] However, until recently, the influence of serum albumin as a useful indirect marker of nutrition has been underestimated. Zitt *et al.*[30] found that, in incident dialysis patients, the association of serum phosphorus and albumin concentration and mortality can vary over time; thus, the therapeutic reduction of serum phosphorus that occurs at the expense of decreases in serum albumin can have a negative impact on CKD patients. Lopes *et al.*[24] have recently reported a 7% decrease in the relative all-cause mortality per every 10% increase in the case-mix–adjusted facility percentage of phosphate binder prescription in the Dialysis Outcomes and Practice Patterns Study (DOPPS), but this survival advantage could be explained, at least in part, by a better nutritional status. The inclusion of nutritional factors in the multivariate model (BMI, creatinine, normalized protein catabolic rate, albumin, and cachexia) reduced the survival advantage from 7 to 5%. In COSMOS, a similar decrease in the relative risk of mortality was found (8% for all-cause mortality and 7% for cardiovascular mortality) per every 10% increase in the case-mix–adjusted facility percentage of PBAs prescription; however, the inclusion of the available nutritional factors (BMI and albumin) in the multivariate models did not modify the mortality risk (data not shown). This difference with DOPPS could be owing to the fact that in COSMOS the nutritional factors used for adjustment were weaker indicators of nutritional status than that used in DOPPS.

In the COSMOS study, the differences in serum albumin, BMI, and phosphorus levels between patients prescribed and not prescribed PBAs were not only statistically significant but may also be clinically relevant. BMI, serum albumin, and phosphate were, respectively, 4, 3, and 17% higher in patients prescribed PBAs than in patients not prescribed these medications, pointing to the likely better nutritional status of the former. The above-mentioned factors suggest that the PBA prescription may improve survival by allowing a more liberal diet and therefore improving nutritional status as it was also suggested by other authors.[24] Besides this, other potential mechanisms beyond phosphorus metabolism related to a likely additional class-effect benefits of some PBAS may contribute to explain the lower mortality risk. Among them, some effects of sevelamer, such as its bile acid sequestrant capacity to reduce serum total cholesterol[31] and uric acid levels,[32] and the increase of serum fetuin-a levels, may have a role.[33] In addition, the reduction of FGF23, a factor that has been independently associated with a higher risk of mortality,[34] observed with the use of lanthanum carbonate[35] and with the combination of calcium carbonate with sevelamer[36] may have contributed to the lower mortality risk found in patients prescribed PBAs.

The final analyses of this paper focused on the likely protective effect of the monotherapy and combined PBAs therapies available. As aluminum salt–containing PBAs have been progressively replaced owing to their well-known and proven toxicity,[37,38] calcium-containing PBAs became, for more than one decade, the first and almost unique therapeutic option as a PBA. At first, calcium-containing

PBAs were considered harmless and even beneficial for the parathyroid gland–bone axis. Later on, however, their use has become controversial,[19,39–41] and many studies have drawn the attention on several undesirable and negative effects of calcium load on different aspects of the CKD-MBD.[17,39,40,42] At the end of the 90s, the polyanionic gel sevelamer became available as the first non-calcium-containing PBA,[16] and some years later lanthanum carbonate was also introduced.[43–46] Although the list of PBAs is enlarging,[47,48] at the time the COSMOS study started and during the 3-year follow-up, calcium salts, sevelamer, aluminum salts, and lanthanum carbonate (either as single or combined therapies) were the more used PBAs, accounting for 88.3% of all PBA prescription in COSMOS.

As Figure 2 shows, all PBAs used, either as monotherapy or combined therapy, were associated with relative risk reductions in all-cause mortality, except for the aluminum salts. To rule out any bias by indication, patients prescribed aluminum salts were compared with those precribed calcium salts, which were the most frequently used PBAs. There were no statistically significant differences, except for more time in dialysis and more severe hyperparathyroidism in patients receiving aluminum salts. Similar beneficial trends were observed with PBA prescription in cardiovascular mortality. However, only calcium-containing phosphate binders, sevelamer, and calcium + sevelamer, plus other combinations—which included several options—showed statistically significant results. The lack of statistically significant results in cardiovascular mortality could be partly explained by the reduction in the number of events, in fact, 48.5% of all deaths were cardiovascular, and by the disparity and reduced number of PBAs prescription as mono or combined therapies ($<5\%$ of patient-years each) in the remaining eight groups, a fact which makes the 95% CI wider and therefore there is a lesser chance of achieving statistical significance (Figure 2). Actually, the four groups in which statistical significance was achieved included the greatest percentage (67.1%) of the PBAs prescribed in the COSMOS study.

If in all-cause mortality we specifically analyzed the groups of PBAs more currently used, excluding those labeled as 'others', in whom several unknown PBAs were included, the relative risk of protection offered by the nine remaining known PBAs (Figure 3) ranged from 27 to 72%. In monotherapy, the best results were obtained with lanthanum carbonate, and in combined therapy with sevelamer plus lanthanum carbonate.

The COSMOS study is a cohort study based on a random sample of the European dialysis population. Its main scope is to identify important aspects related to the management of CKD-MDB throughout a 3-year period. A relevant strength of COSMOS is the fact that it included 20 European countries with a uniform widespread distribution of centers offering the possibility of giving useful information about the European HD scenario. Among the limitations, despite the very precise patient- and center-specific questionnaire forms used, the great number of centers included and the differences in country practice patterns involve an unavoidable degree of heterogeneity and amplifies the risk of residual confounding.[49] In addition, the observational nature of the study does not allow for the control of several aspects that may have exerted some influence, e.g., the cause of death and the intake of the drugs prescribed. The former relies on medical history, and thus a risk of misclassification exists particularly in deaths occurring at home. In the latter example, even though the drug prescriptions were recorded, compliance and adherence to them are unknown. Therefore, the results apply to PBA prescription but not to actual treatment with PBAs. The observational nature of the study also precludes from making conclusions on the causality and rather brings up the associations. The prospective and detailed design of COSMOS including the random-selection methodology and the multiple analyses performed (multivariate adjustment, propensity score matching, and instrumental variable methodology) aimed at minimizing all these aspects, but unfortunately it is not possible to exclude them all. In summary, in COSMOS, after 3 years of follow-up, a statistically significant association between PBA prescription and survival was found. Similar results, but lower in magnitude, were observed in the case of cardiovascular mortality. Complementary analyses such as the use of propensity scores attenuated, but did not eliminate, the apparently protective effect of phosphate binders. Instrumental variable methodology, which minimizes the effect of unknown or unmeasured confounders, also associated PBA prescription with a lower mortality risk. The results of this study make even more compelling the need of a clinical trial to test the effect of PBAs on mortality and other major clinical end points.

MATERIALS AND METHODS

Brief description of the study design

COSMOS is a 3-year, multicenter, open-cohort, prospective study designed to survey bone and mineral disturbances in adult chronic HD patients with no previous kidney transplant from 227 dialysis centers. Patients and facilities were randomly selected among the complete list of hospital and satellite dialysis units of the 20 European participating countries.[49,50] The number of patients recruited by a given country was proportional to the dialysis population of that country; each center was expected to recruit 20 patients and to keep track of them for 3 years. Patient recruitment was initiated in February 2005 and completed in July 2007. The follow-up lasted for 3 years, and the collection of data ended in July 2010, more than 5 years after the initiation of the recruitment period. During the 3-year follow-up, patients who died, those who were transplanted, those who switched to peritoneal dialysis, or those who were lost to follow-up were replaced by new incident patients. The scope of this open-cohort design guaranteed the same number of patients over the 3-year follow-up by replacing lost baseline randomly selected patients by new incident patients. At baseline, demographics, etiology of CKD, vintage on HD, comorbidities, drug prescription, serum biochemical parameters, and other relevant information were collected. More detailed information about the COSMOS design and baseline description of the population has been already published.[49,50] At baseline, the

serum biochemical parameters of the previous 6 months were collected retrospectively. During the entire follow-up period, and every 6 months, the same serum biochemical parameters together with the additional relevant data and clinical outcomes were collected.[49,50] All the procedures were in accordance with the the Declaration of Helsinki Principles of 1975 (and as revised in 1983).

Outcomes and exposures

In case a patient was referred to another HD unit, transplanted, switched to peritoneal dialysis, died, or was not followed up owing to other reasons, the date of the event was registered. The cause of death (cardiovascular-related disorder, non-cardiovascular, other causes, or unknown causes) was recorded from medical history but was not confirmed by autopsies. The exposure variable was any kind of PBA prescription. This variable was used as a time-varying covariate in most of the statistical analyses, unless otherwise indicated. The exposure variable was collected at baseline and every 6 months. Information about outcomes and exposures were obtained from medical records and entered into the database by each site investigator. The time-varying model was constructed using the last recorded information available about exposure by the time the event occurred.

Additional analyses were carried out by dividing patients into two groups: patients never prescribed PBAs at any time and patients prescribed PBAs at least once since the baseline examinations. Sensitivity analyses excluded patients who switched groups (discontinued or initiated PBAs prescription) during the follow-up. In these cases, exposure was considered as a fixed variable instead of a time-varying variable. Exposure to one type of PBA or to combinations of them was also analyzed. Patients were considered at risk from baseline until the first occurrence of death, until they were lost to follow-up, or until the completion of the 3-year follow-up.

The association of the mortality risk with PBA prescription was also assessed by using an instrumental variable, the case-mix–adjusted facility percentage of patients prescribed PBAs at the start of the follow-up.

Exposure to single PBAs or to combinations of them

During the 3-year follow-up, patients were prescribed different PBAs, either as a single or combined therapy; further, 12 groups of PBAs were formed. Five included patients with PBA monotherapy: calcium-containing, sevelamer, lanthanum carbonate, aluminum salts, and other PBAs. The remaining seven groups were combinations of PBAs: calcium-containing + sevelamer, calcium-containing + aluminum salts, calcium-containing + lanthanum carbonate, calcium-containing + other PBAs, sevelamer + aluminum salts, sevelamer + lanthanum carbonate, and other combinations of PBAs. The percentage of patient-years prescribed PBAs was calculated and used to select a cutoff. All PBAs used in percentages higher than 0.8% patient-years were included in the present analysis.

Statistical analysis

Unpaired Student's *t*-tests and χ^2 test were used to compare baseline characteristics of patients prescribed and not prescribed PBAs. Cox proportional hazard regression models with time-varying covariates were used to analyze the relative risk of all-cause and cardiovascular mortality.

Three different multivariate models were used to adjust the relative risk of all-cause and cardiovascular mortality. Model 1—multivariate adjustment including the 12 following variables: country, center funding type (public or private), age, sex, BMI, smoking habit, etiology of CKD, time on HD, diabetes, history of cardiovascular disease, calcifications (vascular, valvular, and calciphylaxis), and parathyroidectomy. Model 2 included 20 variables—the previous 12 plus 7 treatment-related variables: dialysis type, dialysate calcium, hours of HD per week, native vitamin D or calcidiol, VDRAs—calcitriol, alfacalcidol, or paricalcitol—calcimimetics, and erythropoietin-stimulating agents. Model 3 included the previous 20 variables plus five biochemical parameters: serum calcium, phosphorus, PTH, albumin, and hemoglobin. The biochemical parameters were categorized as follows: serum calcium <8.5, 8.5–9.0, 9.0–9.5, $\geqslant 9.5$ mg/dl; serum phosphorus <3.0, 3.0–4.0, 4.0–5.5, 5.5–6.5, $\geqslant 6.5$ mg/dl; serum PTH <50, 50–150, 150–300, 300–500, 500–800, $\geqslant 800$ pg/ml; serum albumin <3.5 and $\geqslant 3.5$ g/dl; and hemoglobin <10, 10–11, 11–12, 12–13, $\geqslant 13$ g/dl. All variables in models 2 and 3, as well as BMI and parathyroidectomy in model 1, were included in the multivariate model as time-varying covariates. The last observation carried forward strategy was used to manage missing data in the time-varying multivariate models. To take into account potential influences of each center, all the multivariate models were stratified by facility.

To minimize potential bias and confounding effects due to 'treatment by indication', a propensity score of likelihood of PBA prescription was calculated by using binary logistic regression. For this calculation, all 24 baseline variables included in the fully adjusted multivariate model 3 in the Cox regression model were used as independent variables. Propensity score percentiles 5, 10, 15,... up to 95 were calculated to create 20 groups with the same number of patients. Within each group, for each patient prescribed PBAs, a PBA that was not prescribed was randomly chosen in order to have a subcohort of matched exposed and unexposed pairs at baseline. Univariate relative all-cause and cardiovascular mortality risk was calculated for this propensity score–matched subcohort of patients. In addition, the full cohort was also divided into propensity score quartiles and the relative mortality risk was calculated for each quartile.

An instrumental variable was also used to minimize the effect of unmeasured or unknown confounders. A facility instrument, the case-mix–adjusted percentage of PBAs prescription by facility, was used as the instrumental variable, as previously reported by other authors.[24] The case-mix–adjusted facility percentage of PBA prescription was calculated by using a linear regression model with patient PBA prescription (yes/no) as the dependent variable and a facility indicator together with age, sex, time on HD, cardiovascular disease, calcification, diabetes, and serum phosphorous as predictors. This case-mix–adjusted facility percentage of PBAs prescription was used as a predictor in the assessment of the mortality risk by Cox proportional hazard regression analysis. Univariate and the three multivariate models quoted before were used for adjustment. All these analyses were stratified by country.

SPSS for Windows version 15.0 (SPSS, Chicago, IL) was used for all the statistical procedures. Statistical significance was considered whenever $P<0.05$.

DISCLOSURE

All the authors declared no competing interests.

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COSMOS participating centers: (see Supplementary Appendix 1).

SUPPLEMENTARY MATERIAL

Appendix 1: COSMOS participating centers.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

REFERENCES

1. Slatopolsky E, Moe S. 50 years of research and discovery in chronic kidney disease and mineral & bone disorder: the central role of phosphate. *Kidney Int Suppl* 2011; **121**: S1–S2.
2. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. *Kidney Int* 2008; **74**: 276–288.
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009; **76**(S113): S1–S130.
4. Locatelli F, Cannata-Andia JB, Drueke TB *et al.* Management of disturbances of calcium and phosphate metabolism in chronic renal insufficiency, with emphasis on the control of hyperphosphataemia. *Nephrol Dial Transplant* 2002; **17**: 723–731.
5. Floege J, Kim J, Ireland E *et al.* Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant* 2011; **26**: 1948–1955.
6. Cannata-Andia JB, Naves-Diaz M. Phosphorus and survival: key questions that need answers. *J Am Soc Nephrol* 2009; **20**: 234–236.
7. Zoccali C, Ruggenenti P, Perna A *et al.* Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J Am Soc Nephrol* 2011; **22**: 1923–1930.
8. Palmer SC, Hayen A, Macaskill P *et al.* Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA* 2011; **305**: 1119–1127.
9. Naves-Diaz M, Passlick-Deetjen J, Guinsburg A *et al.* Calcium, phosphorus, PTH and death rates in a large sample of dialysis patients from Latin America. The CORES Study. *Nephrol Dial Transplant* 2011; **26**: 1938–1947.
10. Pelletier S, Roth H, Bouchet JL *et al.* Mineral and bone disease pattern in elderly haemodialysis patients. *Nephrol Dial Transplant* 2010; **25**: 3062–3070.
11. Goodman WG. Vascular calcification in chronic renal failure. *Lancet* 2001; **358**: 1115–1116.
12. Roman-Garcia P, Carrillo-Lopez N, Fernandez-Martin JL *et al.* High phosphorus diet induces vascular calcification, a related decrease in bone mass and changes in the aortic gene expression. *Bone* 2010; **46**: 121–128.
13. Hruska K, Mathew S, Lund R *et al.* Cardiovascular risk factors in chronic kidney disease: does phosphate qualify? *Kidney Int Suppl* 2011; **79**(S121): S9–S13.
14. Wigner NA, Luderer HF, Cox MK *et al.* Acute phosphate restriction leads to impaired fracture healing and resistance to BMP-2. *J Bone Miner Res* 2010; **25**: 724–733.
15. Foley RN. Phosphorus comes of age as a cardiovascular risk factor. *Arch Intern Med* 2007; **167**: 873–874.
16. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 2002; **62**: 245–252.
17. Raggi P, Vukicevic S, Moyses RM *et al.* Ten-year experience with sevelamer and calcium salts as phosphate binders. *Clin J Am Soc Nephrol* 2010; **5**(Suppl 1): S31–S40.
18. Isakova T, Gutierrez OM, Chang Y *et al.* Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol* 2009; **20**: 388–396.
19. Winkelmayer WC, Liu J, Kestenbaum B. Comparative effectiveness of calcium-containing phosphate binders in incident US dialysis patients. *Clin J Am Soc Nephrol* 2011; **6**: 175–183.
20. Stel VS, Dekker FW, Zoccali C *et al.* Instrumental variable analysis. *Nephrol Dial Transplant.* 2012; in press (doi:10.1093/ndt/gfs310).
21. Goodkin DA, Bragg-Gresham JL, Koenig KG *et al.* Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 2003; **14**: 3270–3277.
22. Kramer HJ, Saranathan A, Luke A *et al.* Increasing body mass index and obesity in the incident ESRD population. *J Am Soc Nephrol* 2006; **17**: 1453–1459.
23. Hecking E, Bragg-Gresham JL, Rayner HC *et al.* Haemodialysis prescription, adherence and nutritional indicators in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2004; **19**: 100–107.
24. Lopes AA, Tong L, Thumma J *et al.* Phosphate binder use and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS): evaluation of possible confounding by nutritional status. *Am J Kidney Dis* 2012; **60**: 90–101.
25. Palmer SC, McGregor DO, Macaskill P *et al.* Meta-analysis: vitamin D compounds in chronic kidney disease. *Ann Intern Med* 2007; **147**: 840–853.
26. Naves-Diaz M, Alvarez-Hernandez D, Passlick-Deetjen J *et al.* Oral active vitamin D is associated with improved survival in hemodialysis patients. *Kidney Int* 2008; **74**: 1070–1078.
27. Teng M, Wolf M, Lowrie E *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; **349**: 446–456.
28. Robinson BM, Port FK. International hemodialysis patient outcomes comparisons revisited: the role of practice patterns and other factors. *Clin J Am Soc Nephrol* 2009; **4**(Suppl 1): S12–S17.
29. Eddington H, Hoefield R, Sinha S *et al.* Serum phosphate and mortality in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2010; **5**: 2251–2257.
30. Zitt E, Lamina C, Sturm G *et al.* Interaction of time-varying albumin and phosphorus on mortality in incident dialysis patients. *Clin J Am Soc Nephrol* 2011; **6**: 2650–2656.
31. Nolan CR, Qunibi WY. Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis. *Kidney Int Suppl* 2005; **67**(S95): S13–S20.
32. Garg JP, Chasan-Taber S, Blair A *et al.* Effects of sevelamer and calcium-based phosphate binders on uric acid concentrations in patients undergoing hemodialysis: a randomized clinical trial. *Arthritis Rheum* 2005; **52**: 290–295.
33. Caglar K, Yilmaz MI, Saglam M *et al.* Short-term treatment with sevelamer increases serum fetuin-a concentration and improves endothelial dysfunction in chronic kidney disease stage 4 patients. *Clin J Am Soc Nephrol* 2008; **3**: 61–68.
34. Gutierrez OM, Mannstadt M, Isakova T *et al.* Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; **359**: 584–592.
35. Gonzalez-Parra E, Gonzalez-Casaus ML, Galan A *et al.* Lanthanum carbonate reduces FGF23 in chronic kidney disease stage 3 patients. *Nephrol Dial Transplant* 2011; **26**: 2567–2571.
36. Koiwa F, Kazama JJ, Tokumoto A *et al.* Sevelamer hydrochloride and calcium bicarbonate reduce serum fibroblast growth factor 23 levels in dialysis patients. *Ther Apher Dial* 2005; **9**: 336–339.
37. Cannata-Andía JB. Aluminium toxicity: its relationship with bone and iron metabolism. *Nephrol Dial Transplant* 1996; **11**(Suppl 3): 69–73.
38. Cannata-Andia JB, Fernandez-Martin JL. The clinical impact of aluminium overload in renal failure. *Nephrol Dial Transplant* 2002; **17**(Suppl 2): 9–12.

39. West SL, Swan VJ, Jamal SA. Effects of calcium on cardiovascular events in patients with kidney disease and in a healthy population. *Clin J Am Soc Nephrol* 2010; **5**(Suppl 1): S41–S47.
40. Bolland MJ, Avenell A, Baron JA *et al.* Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; **341**: c3691.
41. Block GA, Raggi P, Bellasi A *et al.* Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007; **71**: 438–441.
42. Langman CB, Cannata-Andia JB. Calcium in chronic kidney disease: myths and realities. Introduction. *Clin J Am Soc Nephrol* 2010; **5**(Suppl 1): S1–S2.
43. Hutchison AJ, Barnett ME, Krause R *et al.* Lanthanum carbonate treatment, for up to 6 years, is not associated with adverse effects on the liver in patients with chronic kidney disease Stage 5 receiving hemodialysis. *Clin Nephrol* 2009; **71**: 286–295.
44. Wilson R, Zhang P, Smyth M *et al.* Assessment of survival in a 2-year comparative study of lanthanum carbonate versus standard therapy. *Curr Med Res Opin* 2009; **25**: 3021–3028.
45. Sprague SM, Abboud H, Qiu P *et al.* Lanthanum carbonate reduces phosphorus burden in patients with CKD stages 3 and 4: a randomized trial. *Clin J Am Soc Nephrol* 2009; **4**: 178–185.
46. Sprague SM, Ross EA, Nath SD *et al.* Lanthanum carbonate vs. sevelamer hydrochloride for the reduction of serum phosphorus in hemodialysis patients: a crossover study. *Clin Nephrol* 2009; **72**: 252–258.
47. Block GA, Brillhart SL, Persky MS *et al.* Efficacy and safety of SBR759, a new iron-based phosphate binder. *Kidney Int* 2010; **77**: 897–903.
48. Jean G, Vanel T. Phosphate binders in a European haemodialysis population. *Nephrol Dial Transplant* 2011; **26**: 2057–2058.
49. Fernández-Martín J, Carrero JJ, Benedik M *et al.* COSMOS: The dialysis scenario of CKD-MBD in Europe. *Nephrol Dial Transplant* 2012; in press (doi:10.1093/ndt/gfs418).
50. Cannata-Andia JB, Fernandez-Martin JL, Zoccali C *et al.* Current management of secondary hyperparathyroidism: a multicenter observational study (COSMOS). *J Nephrol* 2008; **21**: 290–298.