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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%.