RELATIVE RISK OF MORTALITY IN HEMODIALYSIS PATIENTS PRESCRIBED CALCIUM-FREE AND CALCIUM-CONTAINING PHOSPHATE BINDING AGENTS.

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INTRODUCTION AND AIMS: Observational studies in haemodialysis patients have found hyperphosphataemia consistently associated with a higher risk of mortality, which could be reduced using phosphate binding agents (PBAs). In addition, there is evidence of a class–driven effect of PBAs on survival. The objective of this analysis was to study the association between the prescription of calcium-free PBAs and relative risk of all-cause mortality compared with calcium-containing PBAs in COSMOS (Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study).

METHODS: COSMOS is a multicentre, open-cohort, prospective observational study with 36 months of follow-up. The present analysis includes 6307 patients from 220 centres at 20 European countries, 4318 recruited at baseline and 1989 to replace patients lost to follow-up. Demographics, comorbidities, treatments and monthly biochemical laboratory parameters (calcium, phosphorus, PTH, albumin and haemoglobin) were collected every 6 months. Data were gathered between February 2005 and July 2010. Cox' proportional hazard regression analysis with time-dependent covariates was used. The exposure was the prescription of sevelamer, lanthanum or lanthanum combined with sevelamer compared with calcium-containing PBAs (time dependent variable) and the outcome all-cause mortality. Three progressive multivariate models were used to adjust the Hazard Ratio (HR). Model 1 included demographics and comorbidities (10 parameters), Model 2 included previous model plus treatments (17 parameters) and Model 3 the two previous models plus biochemical parameters (22 parameters).

RESULTS: During the 3-year follow-up 1642 patients died (13.3 deaths per 100 patient-years). Mean time follow-up was 23.5±12 months (median 24 months). Baseline characteristics of the full cohort of patients are described in table 1. Evolution of the prescription of the different PBAs during follow-up is shown in figure 1. Prescription of calcium-containing PBAs decreased, sevelamer remained stable meanwhile lanthanum increased progressively during the 36 months of follow-up. Lanthanum, sevelamer or the combination of both PBAs was associated with significant lower relative risk of mortality in the univariate analysis (fig. 2). In the multivariate analysis the HR was lower but not significant in the other 3 models in the whole population, reaching statistical significance in the lanthanum prescribed patients older than 65 years (fig.2).

Table 1- Baseline characteristics of the full cohort of patients.

	All patients (N=6307)	Not prescribed lanthanum (N=6159)	Prescribed lanthanum (N=148)	p-value*
Sex (% males)	60.7	60.6	66.2	0.2
Age (years) (Mean±SD)	64.0±14.4	64.1±14.4	59.1±14.8	<0.001
BMI (kg/m²) (Mean±SD)	25.3±5.1	25.3±5.0	25.9±5.9	0.2
Current smokers (%)	13.9	13.7	25.0	<0.001
Diabetics (%)	30.7	30.6	31.1	1.0
CVD history (%)	72.1	72.0	73.0	0.9
Parathyroidectomy (%)	4.9	4.9	5.4	0.9
Months on HD (Mean±SD)	38.9±49.5	39.2±49.7	28.1±40.9	0.002
Hours of HD per week (Mean±SD)	12.0±2.1	12.0±2.1	12.1±1.8	0.5
Dialysis technique				0.8
HD conventional low flux (%)	54.1	54.1	52.7	
HD conventional high flux (%)	37.1	37.1	37.2	
Hemodiafiltration & other (%)	8.8	8.8	10.1	
Calcium concentration in dialysate				0.011
2.5 mEq/L (%)	30.0	29.8	39.0	
3.0 mEq/L (%)	50.0	50.3	37.5	
3.5 mEq/L (%)	19.9	19.8	23.5	
Patients prescribed PBAs. (%)	85.0	84.7	100.0	<0.001
Calcium-containing PB	62.0	62.6	36.5	<0.001
Sevelamer	26.4	26.5	21.6	0.2
Aluminium-containing PB	10.9	11.0	6.8	0.1
Lanthanum containing PB	2.3	0.0	100.0	-----
Magnesium containing PB	2.3	2.4	0.7	0.3
Other PB	5.3	5.4	2.0	0.1
Native vitamin D or calcidiol (%)	28.9	28.9	30.8	0.7
Patients prescribed VDRAs				<0.001
Calcitriol (%)	19.9	20.0	12.2	
Alfacalcidol (%)	24.0	24.0	25.0	
Paricalcitol (%)	3.6	3.3	16.2	
Patients prescribed calcimimetics (%)	6.2	5.9	17.6	<0.001
Patients prescribed ESAs (%)	90.4	90.3	94.6	0.1
PTH (pg/mL) (Median [IQR])	210.8[269.0]	209.0[269.0]	285.1[309.8]	<0.001[a]
Calcium (mg/dL) (Mean±SD)	9.1±0.7	9.1±0.7	9.1±0.7	0.5
Phosphorus (mg/dL) (Mean±SD)	5.4±1.4	5.4±1.4	6.0±1.3	<0.001
Albumin (g/dL) (Mean±SD)	3.8±0.5	3.8±0.5	3.8±0.4	0.6
Haemoglobin (mg/dL)	11.4±1.4	11.4±1.4	11.5±1.4	0.8

BMI: Body mass index, CVD: Cardiovascular disease, HD: Hemodialysis, PBAs: Phosphate binding agents, PB: Phosphate binder, ESAs: Erythropoietin stimulating agents, VDRAs: Vitamin D receptor activators. * p-value was calculated by using chi-squared test for qualitative variables and Student t test for continuous variables. [a]Mann Withney U test.

Fig.1- Number of patients prescribed different phosphate binders every six months during follow-up.

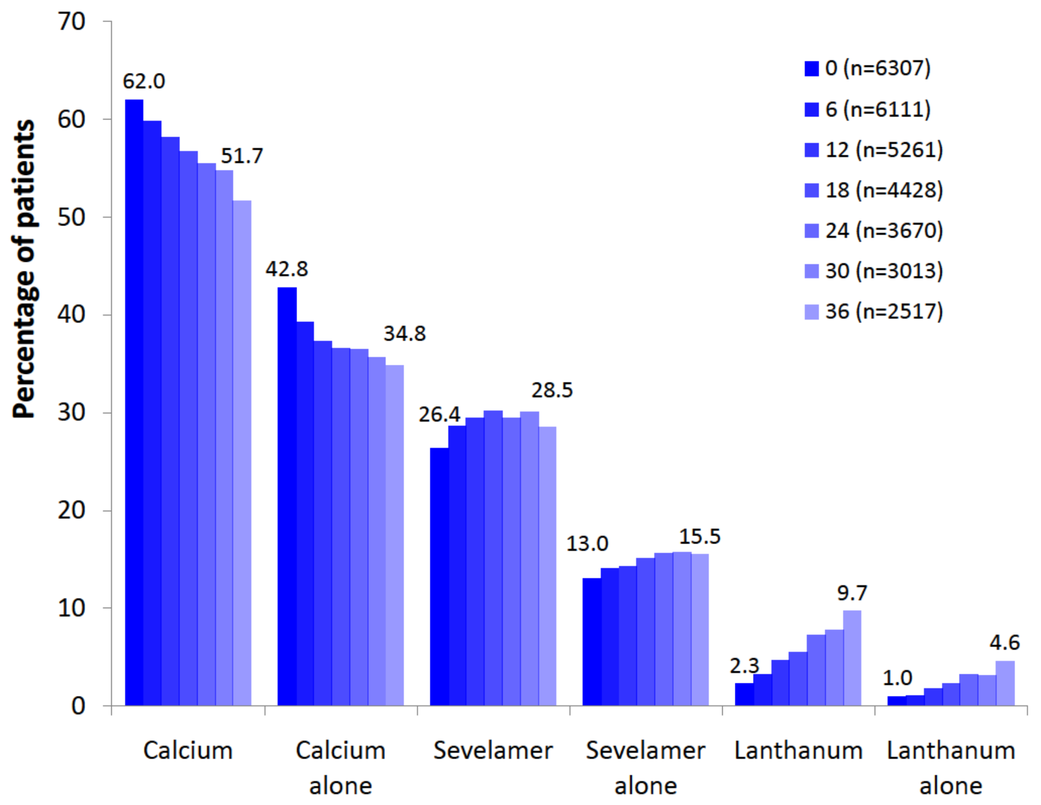
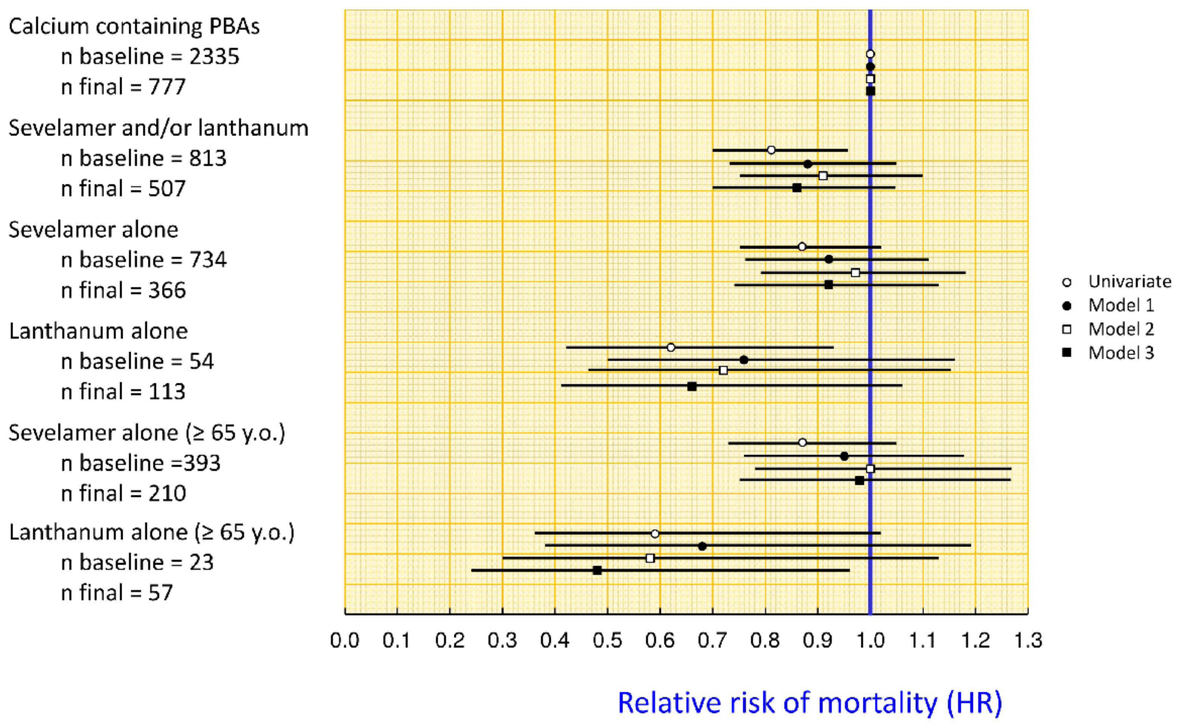


Fig. 2- Relative risk of mortality of patients prescribed calcium-free PBAs (Sevelamer and lanthanum) compared with calcium-containing PBAs.



Model 1: age, sex, BMI*, smoking habit, time on HD, aetiology of CKD, diabetes, CVD, calcification (valvular, vascular or calciphylaxis), and parathyroidectomy*. **Model 2:** + HD type*, calcium in the dialysate*, hours of haemodialysis per week*, ESAs*, VDRAs*, native vitamin D or calcidol*, PBAs* and calcimimetics* **Model 3:** + haemoglobin*, albumin*, calcium* , phosphorus*, and PTH*.
* Time dependent variables.

CONCLUSION: In COSMOS, a representative study of the European HD population, the use of calcium-free PBAs was not associated with significant better survival compared with calcium-containing PBAs, except in patients older than 65 years receiving lanthanum.

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