Non-calcium based phosphate binders confer survival benefit independent of phosphate reduction

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Introduction

- Non-calcium based phosphate binders (NCBPB) have been shown to be associated with a decreased risk of all-cause mortality compared with calcium-based phosphate binders (CPB) in patients with chronic kidney disease (1).
- However, randomised controlled trials have compared NCBPB with CPB which does not reflect usage of phosphate lowering therapy in many jurisdictions where NCBPB is often prescribed *in addition* to CPB due to inadequate phosphate control. This is predominantly due to the high cost of NCBPB as compared to CBPB.
- Nephrologists commonly titrate the prescription of phosphate binder(s) to phosphate levels, attempting to reach a target range. This presumes that lowering phosphate to this range is beneficial in preventing bone and cardiovascular disease and hence reduces mortality. However, there is a lack of evidence to support this practice.

Objectives

The aims of this observational study were:

- to determine whether there was a difference in survival in patients prescribed CPB versus NCBPB+/-CPB
- to determine whether change in phosphate levels alters survival

Methods

- Retrospective analysis of prospectively collected information on a provincial cohort of prevalent dialysis (HD and PD) patients, registered in the PROMIS database, with initial prescription of phosphate binders from 2006 to 2012. Patients were followed for 5 years or until June 30 2014 from phosphate binders initiation. Laboratory, demographic and medication data is all entered as part of the provincial program for all patients.
- Groups were determined based on whether they were prescribed CPB or NCPBP for a minimum of 3 months. Patients who were commenced on NCBPB could be concurrently or previously prescribed CPB. Note that there are protocols in BC whereby access to NCBPB are prescribed under specific circumstances. Patients prescribed with cinacalcet at any time were further excluded.
- Groups (CPB/NCBPB) were matched 1:1 based on the propensity score from a logistic regression model (covariates: age, sex, race, dialysis vintage, diabetes, cardiovascular disease, hemoglobin, phosphate (Pi), calcium (Ca) and parathyroid hormone levels (PTH)), quintiles of dialysis vintage and quartiles of baseline phosphate level.
- A linear mixed effect model was used to examine the difference in the annual rate of change for Pi, Ca and PTH between groups.
- Piece-wise proportional hazard model with competing risk approach (where transplantation as a competing event) was used to examine the cumulative incidence of death between groups and the rate of change in Pi in tertiles.

Results

Figure 1: Study cohorts derivation – 420 patients in each group

80% of patients on NCBPB were also on CPB

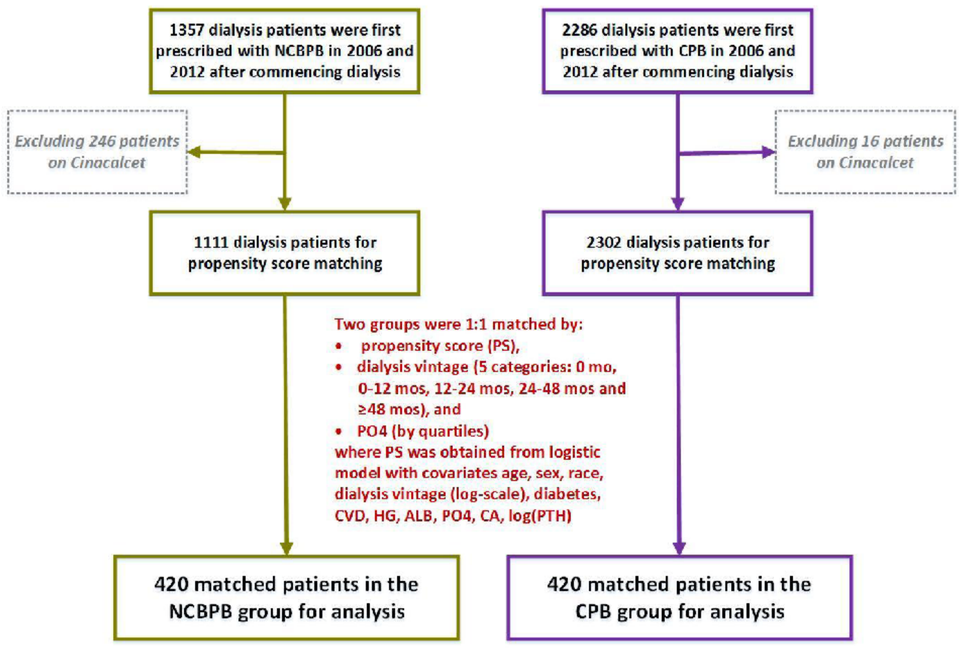


Table 1: Baseline characteristics of study cohorts

All variables were comparable between groups except NCBPB had slightly higher dialysis vintage and calcium level.

	1:1 Matching on propensity score, dialysis vintage (5 levels), PO4 (4 levels)		p-value
	CPB	NCBPB	
# Patients	420	420	
Age (Mean (SD))	64.49 (15.51)	63.30 (14.39)	0.25
Male (n (%))	226 (53.81%)	219 (52.14%)	0.63
Dialysis Vintage (in months; Median [IQR])	5.71 [1.94-14.61]	7.62 [3.56-15.07]	0.01
Diabetes (n (%))	219 (52.14%)	209 (49.76%)	0.49
CVD (n (%))	243 (57.86%)	231 (55.00%)	0.40
Hemoglobin (g/L; Mean (SD))	112.70 (17.23)	114.07 (16.35)	0.24
Albumin (g/L; Mean (SD))	33.84 (4.78)	33.94 (4.76)	0.76
Serum Calcium (mmol/L; Mean (SD))	2.21 (0.18)	2.25 (0.22)	0.01
Serum Calcium (categorical; n (%))			0.11
<2.18 mmol/L	167 (39.76%)	158 (37.62%)	
2.18-2.58 mmol/L	242 (57.62%)	239 (56.90%)	
>2.58 mmol/L	11 (2.62%)	23 (5.48%)	
Parathyroid Hormone (pmol/L; Median [IQR])	28.55 [14.65-50.50]	28.15 [10.00-59.25]	0.68
Serum Phosphate (mmol/L; Mean (SD))	1.89 (0.50)	1.86 (0.50)	0.35
Serum Phosphate (Categorical; n (%))			0.42
<0.8 mmol/L	2 (0.48%)	6 (1.43%)	
0.8-1.8 mmol/L	186 (44.29%)	183 (43.57%)	
>1.8 mmol/L	232 (55.24%)	231 (55.00%)	

Figure 2: Cumulative Incidence of Death by CPB vs NCBPB (Left) and by tertiles of Rate of Change in Pi (Right)

→ Improved survival evident after 24 months in NCBPB compared to CPB

→ Decreased in phosphate increased the risk of mortality in the first 12 months, but no differences thereafter

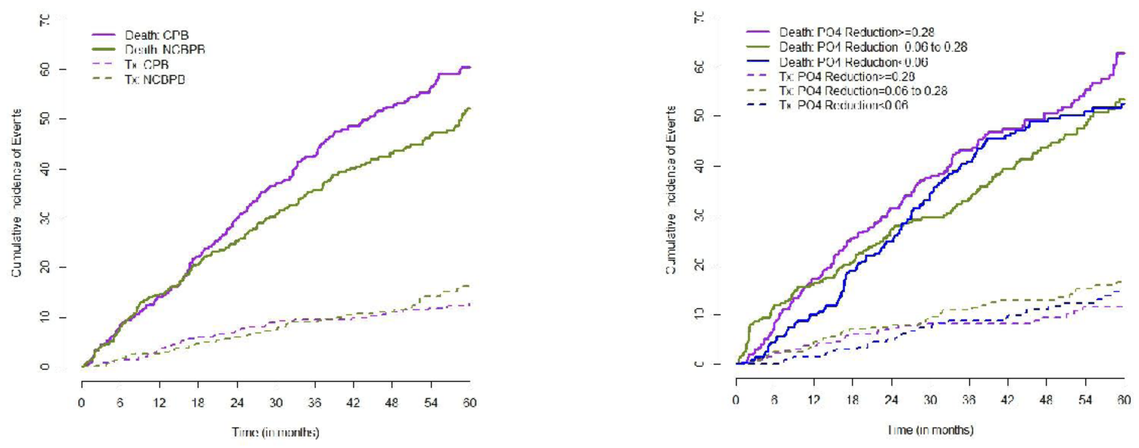
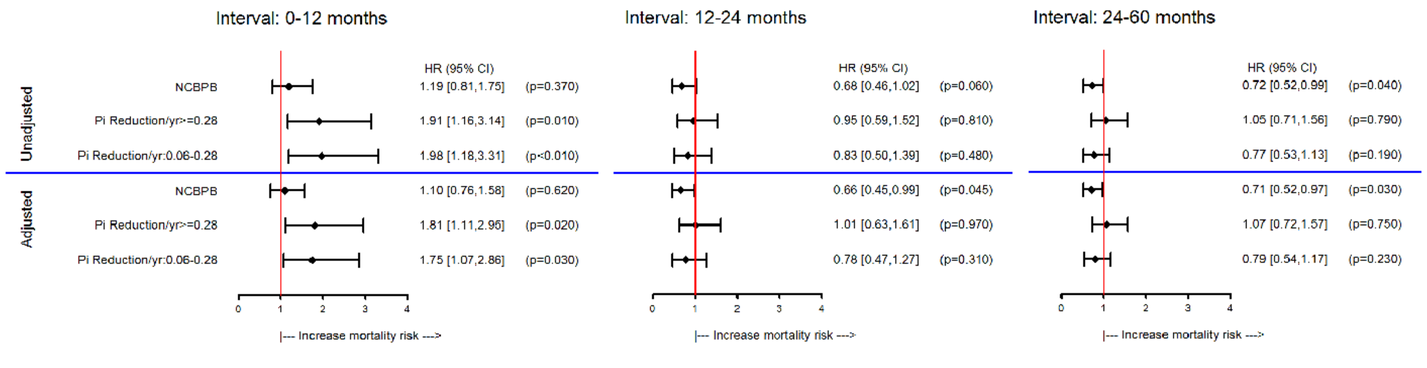


Figure 3: Estimated Subdistribution Hazard Ratios



Conclusions

- Previous studies have shown that NCBPB may lend a reduction in mortality as compared to CPB (2). This study shows that the survival benefit of NCBPB is present even when patients are consuming CPB suggesting that the benefit of NCBPB does not result merely from an absence of exposure to CPB.
- Furthermore, as patients prescribed NCBPB did not have a greater reduction in phosphate levels, this survival benefit was not related to a superior control of phosphate.

References

1. Jamal SA, Vandermeer B, Raggi P, et al. Effect of calcium-based versus non-calcium based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet 382 (9900): 1268 – 1277, 2013.
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