Nephrol Dial Transplant (2020) 35: 1794–1801
doi: 10.1093/ndt/gfaa054
Advance Access publication 29 June 2020

ORIGINAL ARTICLE

Impact of longer term phosphorus control on cardiovascular mortality in hemodialysis patients using an area under the curve approach: results from the DOPPS

Marcelo Barreto Lopes[1], Angelo Karaboyas[1], Brian Bieber[1], Ronald L. Pisoni[1], Sebastian Walpen[2], Masafumi Fukagawa[3], Anders Christensson[4], Pieter Evenepoel[5,6], Marisa Pegoraro[7], Bruce M. Robinson[1] and Roberto Pecoits-Filho[1]

[1]Arbor Research Collaborative for Health, Ann Arbor, MI, USA, [2]Vifor Pharma, Glattbrugg, Switzerland, [3]Department of Internal Medicine, Division of Nephrology, Endocrinology, and Metabolism, Tokai University School of Medicine, Isehara, Japan, [4]Department of Clinical Sciences Malmö, Lund University, Skåne University Hospital, Malmö, Sweden, [5]Department of Microbiology and Immunology, Laboratory of Nephrology, Leuven, Belgium, [6]Department of Nephrology, University Hospitals Leuven, Leuven, Belgium and [7]S.C. Nefrologia, Dialisi e Trapianto Renale, ASST, Grande Ospedale Metropolitano Niguarda, Milano, Italy

Correspondence to: Roberto Pecoits-Filho; E-mail: Roberto.Pecoits@arborresearch.org

ABSTRACT

Background. Serial assessment of phosphorus is currently recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, but its additional value versus a single measurement is uncertain.

Methods. We studied data from 17 414 HD patients in the Dialysis Outcomes and Practice Patterns Study, a prospective cohort study, and calculated the area under the curve (AUC) by multiplying the time spent with serum phosphorus >4.5 mg/dL over a 6-month run-in period by the extent to which this threshold was exceeded. We estimated the association between the monthly average AUC and cardiovascular (CV) mortality using Cox regression. We formally assessed whether AUC was a better predictor of CV mortality than other measures of phosphorus control according to the Akaike information criterion.

Results. Compared with the reference group of AUC = 0, the adjusted hazard ratio (HR) of CV mortality was 1.12 [95% confidence interval (CI) 0.90–1.40] for AUC > 0–0.5, 1.26 (95% CI 0.99–1.62) for AUC > 0.5–1, 1.44 (95% CI 1.11–1.86) for AUC > 1–2 and 2.03 (95% CI 1.53–2.69) for AUC > 2. The AUC was predictive of CV mortality within strata of the most recent phosphorus level and had a better model fit than other serial measures of phosphorus control (mean phosphorus, months out of target).

Conclusions. We conclude that worse phosphorus control over a 6-month period was strongly associated with CV mortality. The more phosphorus values do not exceed 4.5 mg/dL the better is survival. Phosphorus AUC is a better predictor of CV death than the single most recent phosphorus level, supporting with real-world data KDIGO's recommendation of serial assessment of phosphorus to guide clinical decisions.

Keywords: cardiovascular disease, hemodialysis, mineral bone disease, phosphorus, survival

INTRODUCTION

The impact of mineral bone disease (MBD) on hemodialysis (HD) patients' morbidity and mortality has been well documented [1]. High levels of phosphorus are particularly associated with worse clinical outcomes, even in studies that have used a single baseline phosphorus value as a predictor [2, 3]. However, there is insufficient evidence to identify the ideal serum phosphorus target in HD patients [3]. While large observational studies suggest that an elevated risk of adverse events is only observed at very high (>6.0 mg/dL) phosphorus levels [1, 4, 5], the latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines suggest lowering phosphate levels toward the normal range (2.5–4.5 mg/dL) for adults [6].

The association of a single phosphorus measurement with patient outcomes can be confounded by variations in food intake [6, 7], drug adherence, intra-assay coefficient variation and the time interval between dialysis sessions [8]. To overcome this limitation, KDIGO guidelines recommend that an assessment of serial phosphorus along with calcium and parathyroid hormone (PTH) measurements may identify trends in MBD [9] that may lead to improvement in the management of patients with chronic kidney disease (CKD) Stages 3a–5d.

Different longitudinal approaches, e.g. the mean of serial monthly phosphorus measurements and the number of months with phosphorus on target, have not shown significant improvement in risk prediction [10, 11]. Danese *et al.* [7] found that patients with serum phosphorus on target during all four calendar quarters had the lowest mortality rate, while Tangri *et al.* [8] did not find evidence of an association between serum phosphorus control and mortality using this approach. Importantly, both of these studies used the more liberal Kidney Disease Outcomes Quality Initiative (K/DOQI) upper phosphorus target of 5.5 mg/dL [9]. Due to this conflicting evidence, the cumulative effect of hyperphosphatemia on patients' morbidity and mortality remains unknown.

In this study we explore the potential burden of serum phosphorus excursions observed during serial measurements, assessing the combination of the magnitude of hyperphosphatemia and the cumulative exposure, as conceptually proposed in the KDIGO guideline. We also aimed to evaluate the potential improvement in risk prediction of this approach compared with the single most recent value of serum phosphorus in patients participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

MATERIALS AND METHODS

The DOPPS is an international prospective cohort study of randomly selected adult HD patients from nationally representative samples of facilities. Study approval and patient consent were obtained as required by national and local ethics committee regulations. We analyzed data from 17 414 subjects enrolled in Phases 4–6 (2009–18) of the study from Belgium, France, Italy, Germany, Japan, Spain, Sweden, the UK and the USA. Demographic characteristics, comorbidities, laboratory values and prescribed medications and treatments were abstracted from medical records. Mortality data were collected during study follow-up.

To calculate our primary exposure over the 6-month run-in period, we first added the surface areas of six trapezoids created by the amount of time spent with serum phosphorus >4.5 mg/dL and the extent to which this threshold was exceeded over the 6-month period. We then divided the total area under the curve (AUC) by six to calculate the average AUC per month. This mean monthly phosphorus AUC measure represents the extent to which serum phosphorus was uncontrolled >4.5 mg/dL on average each month during the 6-month run-in period (see Figure 1 for more details on the AUC calculation). Patients with serum phosphorus consistently ≤4.5 mg/dL during the entire 6 months had an AUC = 0, while patients with higher AUC values had worse phosphorus control (e.g. a patient maintaining a phosphorus of exactly 5.5 or 6.5 over 6 months would have an AUC of 1 or 2, respectively).

The primary outcome was CV mortality, defined as death, with known cause, due to acute myocardial infarction, pericarditis, cardiac tamponade, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, congestive heart failure or stroke. As secondary composite outcomes, we analyzed combinations of CV mortality with hospitalizations caused primarily by a CV disease. These combinations equated to what is known in the cardiology literature [12] as major adverse CV events and nonfatal congestive heart failure [MACE + CHF (a composite of CV death with nonfatal stroke, nonfatal unstable angina, nonfatal myocardial infarction and nonfatal CHF)]. Research staff at participating facilities coded events (i.e. hospitalization, death) using a standardized coding list developed for DOPPS, which includes diagnosis and procedure codes. Research staff used a range of source documents to determine the data, including patient notes, discharge summaries and their associated

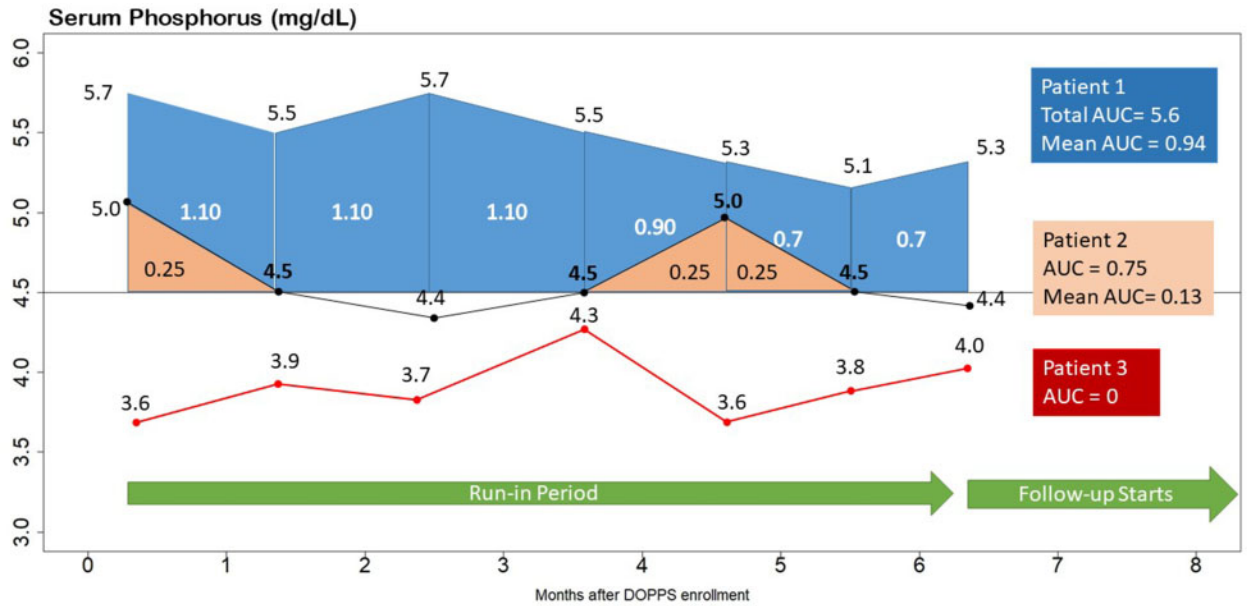


FIGURE 1: Calculation of the AUC for phosphorus control during the 6-month run-in period for three example patients, with most recent phosphorus of 5.3 mg/dL (Patient 1), 4.4 mg/dL (Patient 2) and 4.0 mg/dL (Patient 3). The monthly AUC is depicted inside of each trapezoid. The total AUC is the sum of each monthly AUC. The mean monthly phosphorus AUC is an average of the 6 monthly AUCs.

hospital discharge codes. For comparison, we also analyzed the association of the AUC with all-cause and non-CV death. For all outcomes, follow-up started immediately after the 6-month run-in period and continued until the outcome occurred, 7 days after leaving the facility due to transfer or change in kidney replacement therapy modality, loss to follow-up or end of the study phase (whichever event occurred first).

Patients were excluded if they died or were lost to follow-up within 6 months of DOPPS enrollment, had less than four phosphorus measurements during the run-in period or previously had a parathyroidectomy, due to its possible impact in phosphate metabolism. We also excluded DOPPS facilities that did not report cause of death. We chose to have a run-in period of 6 months, as it allows us to have multiple phosphorus values to calculate the AUC, optimizing sample size for analytical power.

We used Cox models to estimate the association between the AUC and CV death. Models were stratified by country and DOPPS phase. We accounted for facility clustering using robust sandwich covariance estimators. To investigate the degree to which the unadjusted associations between the AUC and CV death were affected, we used a series of five progressively adjusted models. The models, distinguished by their set of potential confounders were (i) unadjusted; (ii) adjusted for age, sex and years since start of dialysis (dialysis vintage); (iii) Model 2 plus mean serum albumin over the 6-month period and low phosphorus, as a binary variable of 6-month mean phosphorus <2.8 mg/dL (together these served as nutritional markers); (iv) Model 3 plus a history of diabetes, hypertension, congestive heart failure, peripheral vascular disease, coronary artery disease, other cardiovascular (CV) disease (i.e. cardiac arrest ever, atrial or ventricular arrhythmias, valvular or pericardial disease, prosthetic heart valve, implanted pacemaker or defibrillator), cerebrovascular disease, lung disease, gastrointestinal bleeding (in the last 12 months) and cancer (other than skin) and (v) Model 4 plus PTH.

We compared our model fit to other previously established hyperphosphatemia predictors of mortality, including baseline phosphorus (single most recent value prior to start of follow-up), the mean of all monthly reported phosphorus values during the 6 months and the number of months during which phosphorus was >5.5 mg/dL. We used the Akaike information criterion (AIC) to compare the predictive power of each of these approaches by the goodness of fit of their respective statistical models. We further evaluated the additional predictive power of the AUC by assessing the association between the AUC and CV mortality within strata of the single most recent phosphorus measurement. We present a single model with categories of each measures and also P-values for the AUC as a continuous variable within each stratum.

The majority of patients (83%) had all seven phosphorus measurements needed to calculate the 6-month AUC. To deal with missing serum phosphorus data, we interpolated the slope between the previous and subsequent monthly phosphorus values. To deal with missing model covariate data, we used multiple imputation, assuming data were missing at random. Missing covariate values were imputed using the Sequential Regression Multiple Imputation Method by IVEware [13]. Results from the imputed data sets were combined for the final analysis using Rubin's formula [14]. The proportion of missing data was <6% for all variables used for covariate adjustment.

RESULTS

The source population consisted of 23 046 HD patients treated in facilities that reported cause of death in DOPPS Phases 4–6 (2009–18) from Belgium, France, Germany, Italy, Japan, Spain, Sweden, the UK and the USA. The number of patients excluded for various reasons is illustrated in Figure 2. Across our sample of 17 414 patients, the median follow-up time was 17 [interquartile range (IQR) 7–27] months. There were 2802 deaths during the study (death rate 11.2/100 patient-years). Of the 2448 deaths reported, 1012 (41%) were of a CV cause.

The mean monthly AUC was 0.92 for having a serum phosphorus >4.5 mg/dL over 6 months and ranged from 0.55 in Spain to 1.15 in Germany (Figure 3). The proportion of patients with AUC = 0 was 9%, and ranged from 5% in Japan to 19% in France and Spain (Figure 3).

We describe patient characteristics by AUC categories in Table 1. Patients with AUC > 2 were on average 15 years younger than patients with AUC = 0. Not surprisingly, due to the difference in age, the prevalence of some CV comorbidities (e.g. coronary artery disease, congestive heart failure, other CV disease and cerebrovascular disease) was also lower among patients with higher AUCs. However, there was no clear relationship between the AUC and diabetes or hypertension. Patients with a lower AUC had lower serum PTH and lower serum albumin, with the latter representing factors known to be associated with adverse outcomes, such as inflammation and malnourishment. There was no clear association between the AUC and the number of years receiving dialysis and vitamin D prescription. In contrast, cinacalcet and phosphate binder use were higher with a greater AUC.

In unadjusted analyses, the AUC did not appear to be associated with CV mortality (Table 2, Model 1). However, after adjustment for age and sex (Table 2, Model 2), we observed a clear, monotonic association with CV mortality, which became even stronger after further adjustment for appropriate confounders, as shown in Models 3–5. In the main model (Table 2, Model 5) there was a 2-fold higher hazard of CV mortality for those with the highest versus lowest AUC.

The association between the AUC and various CV-related outcomes is shown in Figure 4. We observed a consistently strong association between the AUC and CV mortality or MACE + CHF, which appear to be the main drivers of the mortality risk. The relation between the AUC and all-cause mortality was weaker due to a lack of association between the AUC and non-CV events up until the highest levels of the AUC.

Table 3 illustrates the risk of CV mortality by categories of AUC and the single most recent value of serum phosphorus (measured at the end of the 6-month period) compared with a common reference of AUC = 0 and the most recent value <4.5 mg/dL. Within strata of the single most recent phosphorus, the AUC remained strongly predictive of CV mortality. In particular, patients with phosphorus <4.5 mg/dL had a 'hidden'

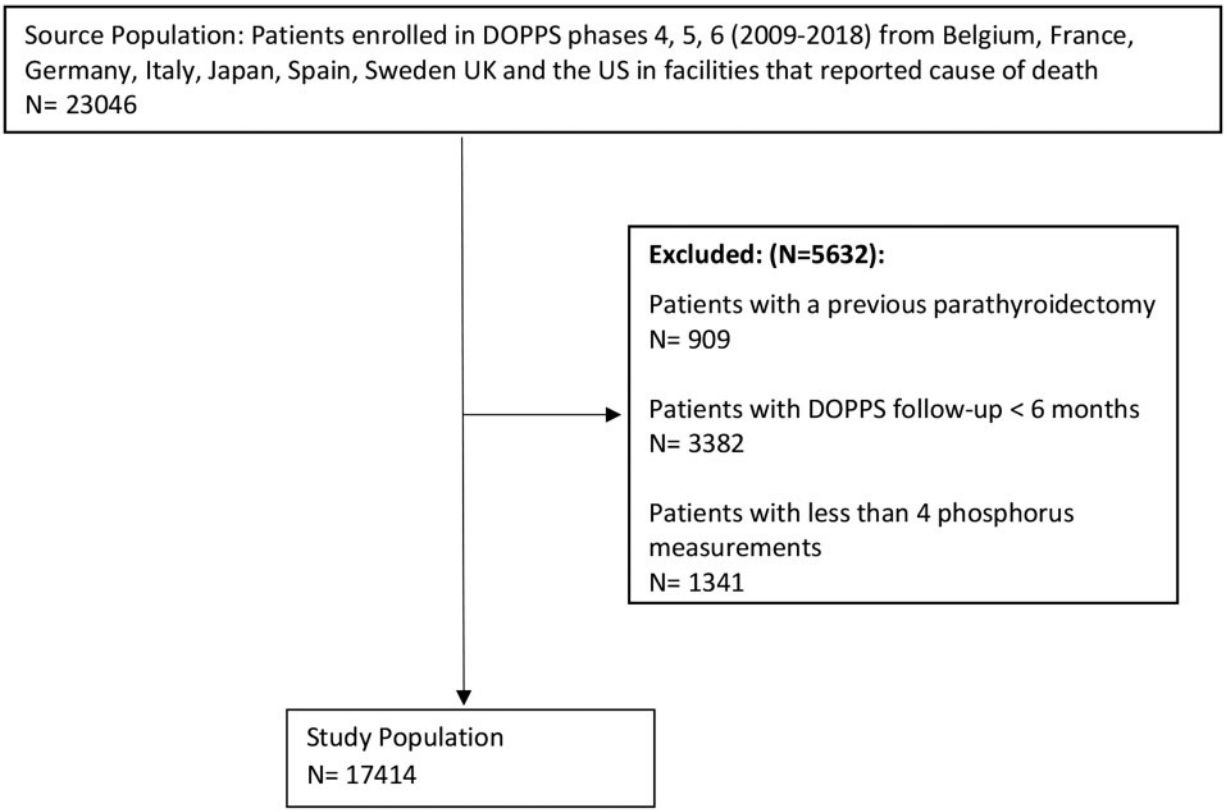


FIGURE 2: Flow chart of DOPPS patients selected for study analysis.

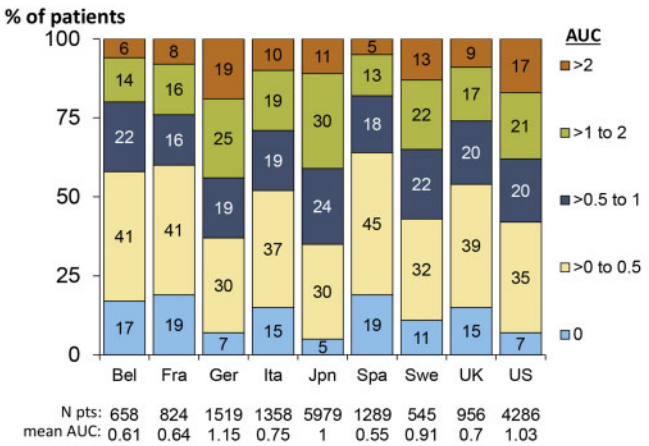


FIGURE 3: Distribution of mean monthly phosphorus AUC by country in DOPPS Phases 4–6 (2009–18). AUC measured during the 6 months after study enrollment.

excess CV risk when the AUC was high (P = 0.02) and patients with phosphorus >6.5 mg/dL had an attenuated CV risk when the AUC was low (P = 0.02).

We also evaluated model fit for the AUC compared with the single most recent value, using categories to model the U-shape; mean phosphorus over the 6-month run-in period and the number of months with phosphorus >5.5 mg/dL, consistent with prior publications [1, 3, 7, 8, 10]. The AIC showed that the AUC was the strongest predictor of CV risk among all of these parameterizations of phosphorus control.

DISCUSSION

In this real-world multinational study, we present a novel AUC approach to monitoring hyperphosphatemia that considers the intensity of excursions over a 6-month period of serial measurements. The phosphorus AUC was identified as a strong predictor of mortality, an effect mainly driven by the increased risk of CV events. The additional value of the AUC approach compared with the single most recent value of serum phosphorus supports the consideration of serial measurements to improve risk assessment.

Patients with a higher AUC were younger and had higher albumin; the group with AUC = 0 tended to be more frail and have a higher prevalence of comorbidities. Hence the lack of difference in the unadjusted hazard between the AUC groups was almost certainly due to the confounding effect of age and nutrition and not to excessive use of phosphate binders. In fact, patients with AUC = 0 used phosphate binders less often than any other group (59% versus 94% in patients with AUC > 2).

In our study, a higher AUC was clearly associated with CV events, but not with deaths due to other non-CV causes. The CV events thus appeared to be the main driver of all-cause death for HD patients with hyperphosphatemia. This association reinforces the potential mechanism linking hyperphosphatemia and the risk of atherosclerotic CVD and direct effects on the myocardium, as previously described [11, 15, 16]. The association of the highest levels of the AUC with non-CV events is consistent with studies that showed a higher risk of fractures and infection in the dialysis population [17–19] for HD patients with severe

Table 1. Patient characteristics by mean monthly phosphorus AUC

Patient characteristics	Mean monthly phosphorus AUC				
	0	>0–0.5	>0.5–1	>1–2	>2
Patients, *n* %	1621 (9)	5931 (34)	3641 (21)	3994 (23)	2227 (13)
Demographics					
Age (years), mean (SD)	72 (13)	68 (13)	66 (14)	63 (14)	57 (15)
Male (%)	65	62	61	62	63
Dialysis vintage (years), median (IQR)	3.0 (1.1–6.4)	2.6 (0.9–6.0)	2.7 (0.9–6.2)	2.9 (0.9–7.0)	2.9 (0.9–6.3)
Laboratory values, mean (SD)					
Phosphorus (mg/dL)[a]	3.4 (0.5)	4.3(0.4)	5.1 (0.3)	5.9 (0.3)	7.4 (0.8)
Albumin (g/dL)[a]	3.6 (0.4)	3.7 (0.4)	3.7 (0.4)	3.7 (0.4)	3.8 (0.4)
PTH (pg/mL)	233 (223)	250 (231)	270 (260)	296 (295)	422 (417)
Calcium (mg/dL)	8.9 (0.7)	8.9 (0.7)	9.0 (0.7)	8.9 (0.8)	8.9 (0.9)
Comorbidities (%)					
Diabetes	43	47	46	47	46
Hypertension	86	87	86	85	89
Coronary heart disease	37	33	32	30	26
Congestive heart failure	23	21	21	20	20
Other CV disease	32	27	26	23	20
Peripheral vascular disease	30	27	24	23	24
Cerebrovascular disease	18	15	15	12	10
Cancer (other than skin)	16	15	14	11	10
MBD-related treatment (%)					
Vitamin D	52	62	66	65	61
Vitamin D IV	26	36	38	37	39
Vitamin D oral	27	28	32	31	26
Cinacalcet	11	15	19	22	27
Phosphate binder	59	78	88	91	94
Calcium-based binder	40	48	51	52	51
Noncalcium-based binder	25	40	50	56	63

$N = 17\,414$ patients. Age, dialysis vintage, laboratory and prescription data are from the end of the 6-month run-in period over which phosphorus AUC was measured immediately before follow-up for clinical outcomes.
SD, standard deviation; IV, intravenous.
[a]We included the mean of 6-month phosphorus and albumin.

Table 2. Association between mean monthly phosphorus AUC and CV mortality, by level of adjustment

Mean monthly phosphorus AUC	Model 1	Model 2	Model 3	Model 4	Model 5
0	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
>0–0.5	0.94 (0.76–1.16)	1.08 (0.88–1.33)	1.16 (0.93–1.45)	1.13 (0.90–1.41)	1.12 (0.90–1.40)
>0.5–1	0.97 (0.77–1.21)	1.24 (0.99–1.55)	1.32 (1.03–1.69)	1.28 (1.00–1.63)	1.26 (0.99–1.62)
>1–2	0.94 (0.75–1.19)	1.38 (1.09–1.74)	1.48 (1.15–1.90)	1.46 (1.12–1.88)	1.43 (1.11–1.86)
>2	0.99 (0.77–1.28)	1.85 (1.43–2.40)	2.00 (1.52–2.63)	2.08 (1.58–2.74)	2.03 (1.53–2.70)

$N = 17\,414$ patients, $n = 1012$ CV deaths. Hazard ratio (95% CI) reported.
Model 1: Stratified by country and phase. Model 2: Model 1 + adjusted for age, sex and dialysis vintage. Model 3: Model 2 + mean 6-month albumin and mean 6-month phosphorus <2.8 mg/dL. Model 4: Model 3 + history of diabetes, hypertension, congestive heart failure, peripheral vascular disease, cancer, coronary artery disease, other CV disease, cerebrovascular disease, gastrointestinal bleeding and lung disease. Model 5: Model 4 + PTH (most recent value prior to start of follow-up).

hyperphosphatemia [20]. Hyperphosphatemia excursions have been associated with increased mortality [8]. Accounting for phosphorus variability over time is one advantage of the AUC method compared with the use of a single, baseline phosphorus measurement. This reassessment of risk of baseline phosphorus levels by the AUC shows how the method adds value to the way that most clinicians diagnose CKD-MBD.

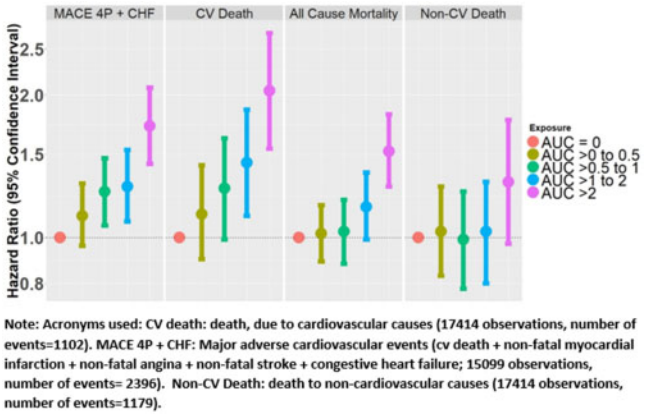
Our reclassification of risk analysis showed that patients with a normal baseline phosphorus (<4.5 mg/dL) and with AUC > 2 had a hazard 2-fold higher than patients with the same category of baseline phosphorus but AUC = 0. Similarly, patients with baseline phosphorus >6.5 mg/dL had a far smaller risk of CV death if the AUC was low. In other words, patients with a single phosphorus <4.5 mg/dL had a 'hidden' excess CV risk when the AUC was high due to previous excursions, and patients with a single phosphorus >6.5 mg/dL had attenuated CV risk when the AUC was lower than expected due to previous measurements in target. Also supporting the benefit of the AUC compared with current approaches, the Cox model that included the AUC as a predictor has a better fit (i.e. lower AIC) than models using a single, most recent phosphorus measurement as a predictor. The AUC model also demonstrated better

fit than models that used serial phosphorus measurements, including a 6-month mean phosphorus and months of phosphorus control. This is not surprising, as in its concept the AUC incorporates long-term phosphorus control, which combines both approaches used for comparison.

Intuitively, the method accounts for monthly variations in phosphorus measurements. It uses a conservative cutoff point of 4.5 mg/dL of serum phosphorus, considering that most studies with a single measure only found high risk at >5.5 mg/dL. Despite the clinical importance of hyperphosphatemia, no clinical trials have tested the optimal serum phosphorus target in dialysis patients, thus the causality of phosphorus related to mortality has not been established [21]. A meta-analysis of randomized controlled trials (RCTs) showed uncertainty in defining a clear phosphorus target for binder therapy, likely due to a paucity of placebo-controlled studies for patients with CKD Stage 5D [22]. The ongoing pragmatic trials, the HiLo and PHOSPHATE trials, have been designed to explore the comparison of a liberal phosphorus target strategy (6–7 mg/dL in the HiLo and 6.2–7.7 mg/dL in the PHOSPHATE) with a strict, near normal (<5.0 mg/dL) cutoff point achieved by the use of phosphate binders and diet. The AUC approach, presented in this study, could provide complementary information based on the risk due to serum levels of phosphorus used to guide the strategies in the trial.

The TARGET trial, an exploratory randomized trial, with calcium carbonate withdrawal or titration as the intervention, compared an intensive approach (serum phosphorus treatment goal of 2.33–4.66 mg/dL) to phosphate binder therapy with a more liberal approach (6.20–7.75 mg/dL). In this study, although there was separation of serum phosphorus across groups, on average only 27.5% of participants achieved phosphorus >6.20 mg/dL in the liberalized group and no difference in outcomes was observed [23]. Nearly half of patients in the intensive group achieved their phosphate targets with calcium carbonate alone and most participants in the liberal phosphate target group achieved their target without the use of binders at all. The SPIRIT trial, which randomized 104 HD patients to a lower (2.5–4.3 mg/dL) or higher phorphorus target (5.6–7.4 mg/dL) also achieved a clinically significant sustained separation over 12 months [24]. It would have been interesting to see what role the AUC approach could have to better define the two target strategies used in this trial. From our findings, accounting for previous excursions is a way of reassessing risk for a single phosphorus measurement, and we are confident that it will assist in guiding the approach to binder treatment.

In terms of therapy for CKD-MBD, it seems that the use of binders is associated with better outcomes over the use of a restrictive diet for phosphorus control. Sevelamer has been shown to reduce intima-media thickness and acceleration of coronary calcification in dialysis patients [21, 25, 26] and to reduce mortality in a subset of older and longer dialysis vintage patients compared with calcium-based binders [26]. Noncalcium-based phosphate binders are associated with a decreased risk of



Note: Acronyms used: CV death: death, due to cardiovascular causes (17414 observations, number of events=1102). MACE 4P + CHF: Major adverse cardiovascular events (cv death + non-fatal myocardial infarction + non-fatal angina + non-fatal stroke + congestive heart failure; 15099 observations, number of events= 2396). Non-CV Death: death to non-cardiovascular causes (17414 observations, number of events=1179).

FIGURE 4: Association of mean monthly phosphorus AUC with MACE + CHF, CV death (primary outcome), all-cause mortality and non-CV mortality, with the same covariate set as Model 5 from Table 2. CV death: death due to CV causes (17 414 observations, number of events = 1102). MACE + CHF (CV death + nonfatal myocardial infarction + nonfatal angina + nonfatal stroke + congestive heart failure; 15 099 observations, number of events = 2396); non-CV death: death due to non-CV causes (17 414 observations, number of events = 1179).

Table 3. Risk of CV mortality by mean monthly phosphorus AUC and the single most recent value of serum phosphorus

Baseline phosphorus categories[a]	Mean 6-month phosphorus AUC categories					P for trend
	0	>0–0.5	>0.5–1	>1–2	>2	
≤4.5 mg/dL, *n* (%); HR (95% CI)	1621 (9); 1 (Reference)	3229 (18); 1.27 (0.99–1.62)	960 (6); 1.29 (0.92–1.81)	513 (3); 1.49 (1.00–2.20)	101 (1); 2.16(0.98–4.76)	0.02
>4.5–5 mg/dL, *n* (%); HR (95% CI)	0–	1267 (7); 1.06 (0.77–1.45)	707 (4); 1.16 (0.79–1.71)	478 (3); 1.47 (0.93–2.30)	69 (1); 2.38 (1.07–5.31)	0.07
>5–5.5 mg/dL, *n* (%); HR (95% CI)	0–	794 (5); 1.28 (0.91–1.80)	743 (4); 1.45 (1.01–2.08)	682 (4); 1.17 (0.77–1.77)	153 (1); 1.30 (0.60–2.81)	0.40
>5.5–6.5 mg/dL, *n* (%); HR (95% CI)	0–	535 (3); 0.78 (0.47–1.28)	892 (5); 139 (1.00–1.94)	1367 (7); 1.36 (0.98–1.88)	478 (3); 1.63 (1.06–2.52)	0.09
>6.5 mg/dL, *n* (%); HR (95% CI)	0–	106 (1); 1.29 (0.56–3.00)	339 (2); 1.56 (0.96–2.53)	954 (5); 2.07 (1.50–2.87)	1426 (8); 2.23 (1.66–2.96)	0.02
Total, *n* (%)	1621 (9)	5931 (34)	3641 (21)	3994 (23)	2227 (13)	

N = 17 414 patients, *n* = 1012 CV deaths. Model adjusted with same covariates as the main model in the primary analysis. P for trend computed from the model using continuous AUC as a predictor within each stratum of baseline phosphorus. Percentages = [(*N* for each cell/17414)*100].
[a]Single phosphorus measurement from the end of the 6-month run-in period over which the phosphorus AUC was calculated.

all-cause mortality compared with calcium-based phosphate binders in patients with CKD in a recent meta-analysis of RCTs [27]. The use of sevelamer as an add-on or alternative therapy to calcium-based phosphate binders is associated with improved survival in patients on maintenance HD [28]. Previous observational studies have shown that high phosphate intake is directly associated with mortality [29]; however, a restrictive phosphorus diet might also be harmful [30]. A low phosphorus diet essentially lacks protein and could result in frailty and increased risk of adverse events. Phosphate binders can lower serum phosphorus levels, while also enhancing nutritional status, by allowing for a less protein-restricted diet [31] and possibly due to a decrease of PTH and fibroblast growth factor 23 (FGF-23) levels [32].

The balance of nutrition in the control of phosphorus has also raised concerns about the bioavailability of phosphorus in processed foods, especially with additives that cannot be quantified [33]. Since previous studies have shown that low phosphorus is also associated with mortality, we included hypophosphatemia in the model adjustments, considering that it could be more of a reflection of malnourishment or morbidity than the result of dietary restriction or phosphate binder treatment. The mean 6-month albumin was also added as an adjustment, as a marker of both nutrition and inflammation.

Our study has some limitations. Due to the observational design, it is not possible to determine causality. Due to the dimension of DOPPS data collection and its multinational features, it is not feasible to adjudicate all causes of death as it is commonly performed in clinical trials. We cannot exclude the presence of bias due to unmeasured confounding. Other potentially important biomarkers of MBD and inflammation (e.g. FGF-23, C-reactive protein and interleukin 6) were not available in this analysis. FGF-23 is an important regulator of phosphate homeostasis and increasing levels have been associated with mortality in HD patients, an effect that is independent of phosphorus [34]. Data on phosphate binder use prior to study entry—covering the time prior to HD initiation and the time between HD initiation and study entry—are not available for all patients in the DOPPS. The large sample size and standardized protocol for data collection are important strengths of this study. Given the random sampling design of the DOPPS, our study sample can be viewed as representative of the HD population in each participating country. It is therefore reasonable to predict that the distribution of the AUC categories, along with the mortality risk identified herein, can be generalized to a wider HD patient population.

In summary, the AUC approach demonstrates the importance of long-term phosphorus control in patients with regular follow-up evaluations at the HD clinic in a real-world scenario. Most importantly, our results reinforce the CV burden of past hyperphosphatemia excursions in assessing the risk of adverse outcomes and support the current recommendation of following longitudinal trends to improve the management of CKD-MBD. Past phosphorus excursions evaluated by the AUC could be considered either to complement or even guide the therapeutic decision-making in CKD-MBD.

ACKNOWLEDGEMENTS

Jennifer McCready-Maynes, an employee of Arbor Research Collaborative for Health, provided editorial assistance for this article.

FUNDING

Global support for the ongoing DOPPS programs is provided without restriction on publications by a variety of funders. For details, see https://www.dopps.org/AboutUs/Support.aspx. This manuscript was directly supported by Vifor (International).

AUTHORS' CONTRIBUTIONS

M.B.L., A.K., B.B., R.P.-F., R.L.P. and B.M.R. conceived and/or designed the work that led to the submission, acquired data and/or played an important role in interpreting the results. M.B.L., A.K., B.B., R.P.-F., R.L.P., B.M.R., S.W., M.F., A.C. and P.E. drafted or revised the manuscript. M.B.L., A.K., B.B., R.P.-F., M.F., S.W., P.E. and M.P approved the final version. The results presented in this article have not been published previously in whole or part, except in abstract form.

CONFLICT OF INTEREST STATEMENT

M.B.L., A.K., B.B., R.L.P., B.M.R. and R.P.-F. are employees of Arbor Research Collaborative for Health, which administers the DOPPS. Global support for the ongoing DOPPS programs is provided without restriction on publications by a variety of funders. For details, see https://www.dopps.org/AboutUs/Support.aspx. This manuscript was directly supported by Vifor (International). S.W. has stock in Vifor Pharma and is employed by Vifor Pharma. M.F. declares consulting fees or paid advisory board fees from Kyowa Kirin, Ono Pharmaceutical, Kissei Pharmaceutical and Torii Pharmaceutical; lecture fees from Kyowa Kirin and Bayer Japan and grants-in-aid from Japan (Kaken-hi) and Kyowa Kirin. A.C. has nothing to declare. P.E. declares consulting fees or paid advisory board fees from Medice and Vifor FMC, lecture fees from Vifor FMC and Amgen and is negotiating grant support from Sanofi. M.P. declares lecture fees as a scientific coordinator for two study days on bone mineral density.

REFERENCES

1. Tentori F, Blayney MJ, Albert JM *et al.* Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2008; 52: 519–530
2. Hou Y, Li X, Sun L *et al.* Phosphorus and mortality risk in end-stage renal disease: a meta-analysis. *Clin Chim Acta* 2017; 474: 108–113
3. Block GA, Klassen PS, Lazarus JM *et al.* Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004; 15: 2208–2218
4. Block GA, Hulbert-Shearon TE, Levin NW *et al.* Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; 31: 607–617

5. 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
6. Ketteler M, Block GA, Evenepoel P *et al*. Executive summary of the 2017 KDIGO chronic kidney disease-mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. *Kidney Int* 2017; 92: 26–36
7. Danese MD, Belozeroff V, Smirnakis K *et al*. Consistent control of mineral and bone disorder in incident hemodialysis patients. *Clin J Am Soc Nephrol* 2008; 3: 1423–1429
8. Tangri N, Wagner M, Griffith JL *et al*. Effect of bone mineral guideline target achievement on mortality in incident dialysis patients: an analysis of the United Kingdom Renal Registry. *Am J Kidney Dis* 2011; 57: 415–421
9. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39(2 Suppl 1): S1–266
10. Block GA, Kilpatrick RD, Lowe KA *et al*. CKD-mineral and bone disorder and risk of death and cardiovascular hospitalization in patients on hemodialysis. *Clin J Am Soc Nephrol* 2013; 8: 2132–2140
11. 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
12. Hicks KA, Mahaffey KW, Mehran R *et al*. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *Circulation* 2018; 137: 961–972
13. Raghunathan TE, Solenberger PW, Berglund J *et al*. *IVEware: Imputation and Variance Estimation Software*. Survey Methodology Program, Survey Research Center, Institute for Social Research, University of Michigan. https://www.src.isr.umich.edu/software/
14. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. Hoboken, NJ: Wiley, 1987
15. Sampaio MS, Molnar MZ, Kovesdy CP *et al*. Association of pretransplant serum phosphorus with posttransplant outcomes. *Clin J Am Soc Nephrol* 2011; 6: 2712–2721
16. Palmer SC, Teixeira-Pinto A, Saglimbene V *et al*. Association of drug effects on serum parathyroid hormone, phosphorus, and calcium levels with mortality in CKD: a meta-analysis. *Am J Kidney Dis* 2015; 66: 962–971
17. Alem AM, Sherrard DJ, Gillen DL *et al*. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 2000; 58: 396–399
18. Ball AM, Gillen DL, Sherrard D *et al*. Risk of hip fracture among dialysis and renal transplant recipients. *JAMA* 2002; 288: 3014–3018
19. Tentori F, McCullough K, Kilpatrick RD *et al*. High rates of death and hospitalization follow bone fracture among hemodialysis patients. *Kidney Int* 2014; 85: 166–173
20. Plantinga LC, Fink NE, Melamed ML *et al*. Serum phosphate levels and risk of infection in incident dialysis patients. *Clin J Am Soc Nephrol* 2008; 3: 1398–1406
21. Marcuccilli M, Chonchol M, Jovanovich A. Phosphate binders and targets over decades: do we have it right now? *Semin Dial* 2017; 30: 134–141
22. Ruospo M, Palmer SC, Natale P *et al*. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). *Cochrane Database Syst Rev* 2018; 8: CD006023
23. Wald R, Rabbat CG, Girard L *et al*. Two phosphAte taRGets in end-stage renal disease trial (TARGET): a randomized controlled trial. *Clin J Am Soc Nephrol* 2017; 12: 965–973
24. Bhargava R, Kalra PA, Hann M *et al*. A randomized controlled trial of different serum phosphate ranges in subjects on hemodialysis. *BMC Nephrol* 2019; 20: 37
25. Boaz M, Katzir Z, Schwartz D *et al*. Effect of sevelamer hydrochloride exposure on carotid intima media thickness in hemodialysis patients. *Nephron Clin Pract* 2011; 117: c83–c88
26. Frazao JM, Adragao T. Treatment of hyperphosphatemia with sevelamer hydrochloride in dialysis patients: effects on vascular calcification, bone and a close look into the survival data. *Kidney Int* 2008; 74(Suppl 111): S38–S43
27. 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* 2013; 382: 1268–1277
28. Komaba H, Wang M, Taniguchi M *et al*. Initiation of sevelamer and mortality among hemodialysis patients treated with calcium-based phosphate binders. *Clin J Am Soc Nephrol* 2017; 12: 1489–1497
29. Noori N, Kalantar-Zadeh K, Kovesdy CP *et al*. Association of dietary phosphorus intake and phosphorus to protein ratio with mortality in hemodialysis patients. *Clin J Am Soc Nephrol* 2010; 5: 683–692
30. Shinaberger CS, Greenland S, Kopple JD *et al*. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr* 2008; 88: 1511–1518
31. 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
32. Oliveira RB, Cancela AL, Graciolli FG *et al*. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? *Clin J Am Soc Nephrol* 2010; 5: 286–291
33. Fouque D, Horne R, Cozzolino M *et al*. Balancing nutrition and serum phosphorus in maintenance dialysis. *Am J Kidney Dis* 2014; 64: 143–150
34. Arnlov J, Carlsson AC, Sundstrom J *et al*. Serum FGF23 and risk of cardiovascular events in relation to mineral metabolism and cardiovascular pathology. *Clin J Am Soc Nephrol* 2013; 8: 781–786

Received: 17.9.2019; Editorial decision: 12.2.2020