Association of changes in bone-mineral parameters with mortality in hemodialysis patients: insights from the European AROii-cohort

Claudia Lamina[1], Florian Kronenberg[1], Peter Stenvinkel[2], Marc Froissart[3], Lukas Forer[1], Sebastian Schönherr[1], David C. Wheeler[4], Kai-Uwe Eckardt[5], Jürgen Floege[6]

[1] Division of Genetic Epidemiology, Department of Medical Genetics, Molecular and Clinical Pharmacology, Medical University of Innsbruck, Innsbruck, Austria;

[2] Department of Renal Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden;

[3] Centre Hospitalier Universitaire Vaudois, Clinical Trial Unit, Lausanne, Switzerland;

[4] University College London, Center for Nephrology, London, United Kingdom;

[5] Department of Nephrology and Medical Intensive Care, Charité – Universitätsmedizin Berlin, Germany;

[6] Division of Nephrology, RWTH University of Aachen, Aachen, Germany

Address of correspondence:

Jürgen Floege

Division of Nephrology

RWTH University of Aachen

Aachen, Germany

jfloege@ukaachen.de

Abstract

Background: There is little information in hemodialysis (HD) patients on whether temporal changes in serum calcium, phosphate or iPTH are associated with mortality.

Methods: We analyzed associations of phosphate, total calcium and iPTH with all-cause and cardiovascular mortality in 8817 incident HD patients from the European AROii cohort enrolled in 2007–2009, which were prospectively followed for a median period of 3 years, using time-dependent Cox Proportional Hazards models. We evaluated changes in risk over time depending on changes in phosphate, calcium or iPTH.

Results: The association of phosphate and iPTH with all-cause mortality was U-shaped with lowest risk ranges between 1.20-1.89 mmol/L for phosphate and 239-710 ng/L for iPTH. For total calcium, the associations were J-shaped with an increased risk for all-cause mortality at levels above 2.36 mmol/L. Lowest risk ranges for cardiovascular mortality did not change markedly for all three parameters. If iPTH was below the lowest risk range at baseline (iPTH<239 ng/L) a subsequent increase in levels was associated with improved survival. For phosphate, an increase and decrease out of the lowest risk range was associated with increased mortality risk. For calcium this was only the case, when the values increased above the lowest risk range.

Conclusion: In the AROii cohort, the ranges of bone-mineral biomarkers associated with the lowest mortality ranges were largely consistent with the current KDIGO CKD-MBD guideline recommendations. Allowing a suppressed iPTH to increase was associated with a lowered mortality whereas shifts of phosphate or calcium outside the lowest risk range increased mortality.

Introduction

In patients on maintenance hemodialysis, disturbances of serum phosphate, calcium and intact parathyroid hormone (iPTH) are associated with severe consequences, including cardiovascular disease (CVD) and abnormalities in bone turnover (1). Importantly, increased and decreased serum phosphorus, calcium and PTH have all been found to be associated with a higher risk of mortality in patients requiring dialysis in most observational studies (2–7). Consequently, the current KDIGO guidelines for dialysis patients recommend lowering elevated phosphate and calcium towards normal and to maintain iPTH in a range encompassing the 2- to 9-fold upper normal limit of the assay used (8). However, we lack prospective interventional studies targeting different levels of these parameters. In addition, while many dialysis patients have single serum parameters in the recommended range, control of all three, i.e. calcium, phosphate and iPTH, is rarely observed (9,10). While studies are planned addressing these issues, for example by targeting two different phosphate levels (11), so far the associations between mortality and disturbances in bone mineral disorders in chronic kidney disease (CKD) are largely based on retrospective, observational data.

An important advance in the above discussion has been an analysis of temporal shifts in bone mineral parameters and how these relate to subsequent mortality. A few North-American studies focused on the very early phase of dialysis initiation (12) or examined the effect of shifting into or out of target ranges recommended by guidelines (13). The first study to assess a large European patient group was an analysis of the COSMOS cohort (14). This prospective non-interventional study included 6797 adult prevalent HD patients followed for 3-years in 20 European countries. Unlike previous studies, that analysis not only assessed cross-sectional associations of bone and mineral parameters with subsequent mortality but also asked how changes in these parameters over time modulate the mortality risk. Central findings were that decreases of a previously elevated serum phosphorus and calcium and increases of a previously low serum PTH associated with improved survival (14).

Here we addressed and extended a similar question as in the above COSMOS study, i.e. do changes in mineral bone parameters over time associate with changes in mortality of hemodialysis patients. For this we used data from HD patients recruited from European Fresenius Medical Care (EU-FMC) facilities, which constitute the AROii cohort (Analysing data, Recognizing excellence, Optimising outcomes in ESRD) following our earlier AROi cohort (15).

Compared to COSMOS, the AROii cohort is also observational and prospective but larger (n=11211 altogether, n=8817 available for current analysis), more homogenous (all dialysis provided by the same company network) and most importantly purely composed of incident HD patients followed for up to 8 years.

Material and Methods

Study population and covariates of interest

The ARO research initiative has been described in detail elsewhere (15,16). The present study is based on the AROii cohort, which enrolled incident HD patients from 334 EU-FMC facilities from 15 European countries and followed them prospectively (17). Pseudonymized patient-level medical history, longitudinal laboratory, dialysis, and medication data, plus ICD-10-coded hospitalization and death data were captured in a validated clinical database (18). All ethical and regulatory obligations concerning patient data were met locally and informed consent was obtained from all patients (15).

Between 2007 and 2009 11211 incident patients were recruited into AROii. The database for follow-up was closed on 31st Dec 2014. The current analysis dataset comprised of those patients, who were still followed at 3 months after entering the database and who had non-missing values for age, gender, renal diagnosis, medical history and at least one available value for serum phosphate, total calcium and iPTH (n=8817). Average measurement intervals were 4 weeks for phosphate and calcium and 3 months for iPTH. Information on medical history included etiology of CKD, history of CVD (defined as peripheral vascular disease, congestive heart failure, coronary artery disease, myocardial infarction, angina, cerebrovascular accident or transient ischemic attack) and history of diabetes (defined as a recorded history of diabetes, diagnosis of diabetic nephropathy or history of diabetic medications use at baseline). Laboratory data included markers of inflammation (CRP and albumin), hemoglobin, ferritin, total cholesterol and blood leukocyte count.

Statistical methods

Baseline was defined as follow-up (FU) start plus three months. Lab parameters that were measured repeatedly during the follow-up period were updated at the time-point, when they

were measured. The baseline value was set as the last available non-missing value before the end of the first 3-month period. Missing values were replaced by the last measured value ("last observation carried forward" approach). The primary outcome was all-cause mortality, the secondary outcome cardiovascular mortality. To assess the association of the time-updated variables serum phosphate, calcium and iPTH on the outcome variables, a time-dependent Cox analysis was performed using nonlinear p-splines for the quantitative variables of interest. To avoid a disproportionately high impact of immediate changes before death or potential reverse causality, a 4 week time-delay was inserted for all analyses. This means, each entry in the time-variable for the Cox analyses was shifted by 4 weeks forward. Different adjustment models were applied: 1. a univariable model on each of the parameters phosphate, calcium and iPTH separately; 2. adjustment for age, gender, renal diagnosis, diabetes history, CVD history and for the time-updated variables phosphate, calcium, iPTH, hemoglobin, albumin, ferritin, white blood cell count and eKt/V; and 3. extended adjustment model: as model 2 plus additional adjustment for smoking and BMI at baseline and the time-updated variables C-reactive protein and total cholesterol. Model 2 was selected as the main adjustment model, since there were too many missing values in the variables added in model 3. In each of the Cox models, strata for the participating centers were included and the person identifier was included as a cluster variable to account for correlated observations within each person. These three adjustment models were applied on the complete observation period. The main adjustment model on all-cause mortality was also carried out for men and women separately.

To obtain the minimal risk range for phosphate, calcium and iPTH, the values associated with the minimal risk were estimated and set as the reference (Hazard Ratio; HR=1), using the main adjustment model. The minimal risk ranges were defined as all values with a HR of ≤ 1.1. If the 95% CI at that threshold level included 1, which corresponds to a non-significant risk increase, the maximum value for the lower threshold (or minimum value for the upper threshold) with the following properties was selected: HR >1.1 and 95%-CI not including 1.

To evaluate changing risk over time in several ways, additional analysis strategies were applied, but only using the main adjustment model:

i) delayed starting time: to mimic a prevalent HD cohort, the baseline was set at 12 or 24 months after start of follow-up. These cohorts were followed until the end of the complete observation period.

ii) censored follow-up time: to investigate shorter follow-up times, the follow-up time was limited to 24 months and 48 months from baseline.

iii) shifted time-intervals: non-overlapping time-intervals were created. The first interval covers months 0 to 24 from baseline (months 3-27 from FU-start) mimicking an incident population restricted to post-HD initiation period, the second starts from month 24 from baseline (month 27 from FU-start), and thus mimics a prevalent cohort, till the end of the complete observation period.

In addition to changing risk over time, we evaluated, whether it is beneficial to remain at a stable level of a particular analyte or to increase or decrease phosphate, calcium or iPTH, respectively. For this particular analysis, all values from each patient, including serum phosphate, calcium and iPTH were averaged over FU-months 3-6 to obtain baseline average values. For all measured values over the complete observation time, changes to these average baseline values were calculated and used as a time-updated variable. Then, risk of change (in absolute values) was obtained for those being below, within or above the minimal risk range (HR ≤1.1). In addition, categorical changes from one to another risk category were also analyzed, e.g. moving from the minimal risk range to above the minimal risk etc. For iPTH above the minimal risk range, models based on absolute changes were numerically unstable due to low sample size within this category. Therefore, for this parameter, the analysis of change was only based on the categorical change between risk categories using a restricted adjustment model (only adjusted for age, gender and renal diagnosis). The statistical program R version 3.5.0 (19) was used including the package “survival” (20,21).

Results

Descriptive statistics of all 8817 patients in the analysis data set can be found in Table 1. 3502 (40%) of the patients were female and mean age at baseline was 64.3 years. They were followed-up for up to 8 years (median follow-up 3 years). During follow-up 3100 patients died (35%), 1399 of them from cardiovascular causes. 2076 (23.5%) patients were censored at the database closure date, 2472 (28.0%) were lost to follow-up and 1169 (13.3%) received a kidney transplantation and were censored for the analysis at the time point of transplantation.

Association of phosphate with mortality over the complete observation period

In all three adjustment models, high and low values of phosphate were associated with a higher all-cause mortality risk (Figure S1). The minimum relative risk in the main adjustment model was found at 1.55 mmol/L, with the lowest risk (HR ≤1.1) ranging from 1.21-1.89 (Figure 1). Averaged over the first three months after baseline, 61% of patients were found within this range (Table 2). Values below and above this range were associated with a higher mortality risk (HR below=1.32, HR above=1.32, Table 3, Figure 1). For cardiovascular mortality (Figure S2), the shape of the relationship was comparable with all-cause mortality, with the lowest risk range spanning from 1.13-1.89 (Table 2, Table 3). When separating for men and women (Figure S3), the U-shaped curve could only be observed for men. In women, the risk increase was attenuated for higher values and even decreased for phosphate > 2.8 mmol/L.

Association of calcium with mortality over the complete observation period

In the unadjusted model, high and low values of calcium were associated with a higher all-cause mortality risk, whereas only high values were associated with higher risk in both of the adjustment models (Figure S1). To assess, if it was the adjustment for albumin which led to the attenuation of the risk for low calcium values, the main adjustment model was repeated but without adjusting for albumin. The resulting spline curve resembled the curve from the unadjusted model. The minimum relative risk in the main adjustment model was found at 2.12 mmol/L, with the lowest risk (HR ≤1.1) below 2.36 mmol/L (Figure 1). Averaged over the first three months after baseline, 84% of patients were found within this range (Table 2). Values above this threshold were associated with a higher mortality risk (HR=1.37, Table 3, Figure 1). For cardiovascular mortality (Figure S2), the shape of the relationship and the threshold for higher risk was comparable (>2.34 mmol/L, HR=1.21, Table 2). The linear splines separated for men and women did not show any relevant differences (Figure S3).

Association of iPTH with mortality over the complete observation period

In all three adjustment models, high and low values of iPTH were associated with a higher mortality risk (Figure S1). The minimum relative risk in the main adjustment model was found at 453 ng/L, with the lowest risk (HR ≤1.1) ranging from 239-710 ng/L (Figure 1). Averaged over the first three months after baseline, 35% of patients were found within this range (Table 2). The majority of patients (60%) were below the threshold of 239 ng/L, which carried a higher mortality risk (HR=1.18, Table 3). Values above the lowest risk range were also associated with

a higher mortality risk (HR=1.34, Table 3, Figure 1). For cardiovascular mortality (Figure S2), the shape of the relationship was comparable but with wide confidence bands at the upper tail, which shifted the upper threshold to higher values (214-981 ng/L) (Table 2, Table 3). Figure S3 depicts the nonlinear splines separated for men and women, which showed a risk increase for men but not for women for very high values of iPTH.

Change of mortality risk depending on follow-up time

Figure S4 shows the nonlinear splines for the main model (3 months) as well as those models with delayed starting times (i.e. 12 and 24 months, respectively) to mimic prevalent HD cohorts. For all three parameters, splines and corresponding confidence bands almost completely overlapped, indicating no difference due to FU starting time. Increasing follow-up time from 2 to 4 years or to complete FU time (main model) also did not lead to substantial differences with the exception of iPTH (Figure S5). Here, no risk increase for higher values was observed within the first four years.

For the evaluation of non-overlapping time intervals, the first two years of observation of the incident cohort were compared with an analysis neglecting the first two years. There was hardly a difference for phosphate and calcium. This was also true for low iPTH values. However, high iPTH values were only significantly associated with higher mortality risk when the first two years after HD initiation were not considered in the analysis (Figure S6).

Association between changes in phosphate, calcium or iPTH and mortality risk

Patients being within the minimum risk range at baseline for each of the three parameters of interest continued to experience the lowest risk, when they stayed within these risk ranges (Table 4). Each decrease below the lower threshold or increase above the higher threshold was associated with increased risk, which was not statistically significant though for an increase of iPTH above the threshold. The same observation was made, when we analyzed absolute changes of all three parameters (Figures 2-4).

In patients below the minimal risk range at baseline, the most favorable outcome was found, when they moved into the respective minimal risk range (Table 4). Similar results were found for absolute changes (Figures 2 and 4). In contrast, each further decrease, especially for iPTH, was associated with increasing risk (Figure 2 and 4).

Finally, in patients above the minimal risk range at baseline, most favorable outcomes were found, when patients with hypercalcemia moved into the respective minimal risk range (Table 4). A risk decrease was also observed for iPTH, but this did not reach statistical significance. For patients within the highest phosphate category at baseline, no survival benefit could be observed when moving into the minimal risk category.

Discussion

The present study confirms risk relationships for the main bone and mineral parameters phosphate, calcium and PTH in hemodialysis patients and adds to the emerging evidence that changes in these biomarkers over time towards a low risk range are associated with risk reduction for most of the analytes.

The study thereby expands findings of the previous COSMOS study in prevalent European HD patients (14) by investigating a purely incident European HD cohort with extended follow-up. While the COSMOS study collected information on clinical and biochemical parameters every 6 months, average measurement intervals in our study were 4 weeks for phosphate and calcium and 3 months for iPTH. With data at such high granularity and a follow-up time of up to 8 years, we were able to evaluate different possible scenarios of changing risk over time, which would not be possible with prevalent cohorts and/or cohorts with shorter follow-up time.

In contrast to an earlier North-American study (12), we deliberately omitted the first 3 months after dialysis initiation from our analysis. Various studies, including one in our AROii cohort, demonstrated an excess cardiovascular mortality in the first 2-4 months after starting HD (22–24). To which extent this excess in mortality is related to bone and mineral parameters is unknown, but it appears more likely to be due to circumstances of dialysis initiation. Other prior studies investigated the effects of bone mineral parameters shifting into or out of target ranges recommended in guidelines (KDOQI or KDIGO) and came to variable conclusions with some demonstrating a benefit of staying in these ranges (13,25,26) and others not finding any benefit (10). In contrast, similar to the European COSMOS cohort (14), we first determined the lowest mortality range in relation to bone mineral parameters specifically for patients under study and then assessed the relevance of shifts into or out of this range.

Remarkably, despite different approaches and different study populations risk relationships for all three parameters are similar across studies: our minimum risk ranges almost mirrored those detected in the COSMOS cohort (14), i.e. phosphate 1.20-1.89 mmol/L (COSMOS 1.16-1.68 mmol/L), calcium <2.36 mmol/L (COSMOS 1.98-2.38 mmol/L), and iPTH 239-710 ng/L (COSMOS 168-674 ng/L). These ranges correspond well with those recommended by KDIGO for phosphate, where lowering towards normal (i.e. 0.84 – 1.45 mmol/L) is suggested. In the case of calcium avoidance of hypercalcemia (i.e. >2.65 mmol/L) is suggested by KDIGO, and both COSMOS and AROii support the notion that serum calcium in the low or even mildly decreased range is associated with the lowest mortality. Finally, for iPTH the KDIGO recommended target range is roughly 140 – 630 ng/L, i.e. lower than the lowest risk range observed in AROii. Whereas the majority of AROii patients were in the lowest risk ranges for calcium and phosphate, namely 60% and 84%, respectively, a mere 35% were in the minimal risk range for iPTH, supporting observations, for example in the COSMOS cohort (14) and in the United Kingdom (10). We also provide evidence that incident and prevalent HD patients behave similarly with respect to bone mineral parameters and associated mortality. However, if limited to the first two years the strength of association of PTH with mortality diminished somewhat suggesting that in this early phase other determinants are more important for survival, which supports our baseline definition.

We also found minor gender-differences in the association of phosphate and iPTH with mortality: High values were only associated with increased risk in men, but not in women. Confidence bands widely overlapped, though. But since the impact of gender on associations between risk factors) and mortality in chronic kidney disease patients has been neglected so far, further research is warranted to explore this point further.

We also noted that cardiovascular mortality closely mirrored all-cause mortality, which is in line with the notion that bone mineral disease affects survival largely via effects on the cardiovascular system (1), further supporting the key importance of CVD in determining survival of HD patients.

With respect to serum phosphate shifts over time, we were unable to confirm the COSMOS data (14) that lowering an elevated baseline phosphate to values below 1.68 mmol/L was associated with a 10-15% reduction in subsequent mortality risk. However, in COSMOS this only applied to a small range, since any reduction by more than 0.65 mmol/L increased risk again as in our current analysis.

Low serum calcium at baseline has been reported to be associated mortality in dialysis patients in a few studies (3,4), whereas others noted either no association (7,28) or even a reduced risk with hypocalcemia (2,29). In line with the latter observations we failed to detect an increase in mortality in HD patients with low calcium, which supports the current guideline recommendation that mild hypocalcemia may be acceptable (8) and our findings in the EVOLVE trial, where calcimimetic-induced hypocalcemia was not associated with an increased risk for subsequent cardiovascular events (30). As in the COSMOS study (14), there was no significant reduction in mortality risk, when hypercalcemia resolved, whereas the risk was aggravated in those patients with progressive hypercalcemia. However, the obvious limitation of all studies on serum calcium is that even albumin-corrected serum calcium only loosely correlates with ionized calcium values in renal patients (31).

Another key finding of our analysis is that there was a pronounced association with reduced mortality risk, when a baseline low iPTH concentration (<239 ng/L) subsequently rose above that threshold. Similar observations have been made in the COSMOS cohort (14) and a North American analysis (13). A recent French study also found that using KDIGO guideline targets to categorize baseline serum concentrations of phosphate, calcium and iPTH as too low or too high, only the category “iPTH too low” (i.e. lower than about 130 ng/L) was associated with an increase in mortality (4). This risk increases further if low iPTH levels are combined with high serum phosphate or calcium (32). Taken together, these data provide a rationale to prospectively study how to avoid low iPTH levels, observed in 60 % of our patients early after initiation of HD. Unlike the COSMOS analysis (14), we had sufficient data to assess the course of patients where an initially high iPTH was lower in subsequent periods. In these patients we observed a trend towards lower mortality. This mirrors insights from the EVOLVE trial, which randomized patients with iPTH baseline levels above 300 ng/L to a calcimimetic or placebo (33). At the same time there was notable increase in risk associated with high iPTH in the AROii cohort, if the first four years after the start of HD were ignored, possibly suggesting that control of an elevated PTH becomes more important as time on HD increases and/or, as in the case of phosphate, that effects of an elevated iPTH are cumulative over time.

Key strengths of the present study include the relatively uniform design of the cohort with a single dialysis provider, high data granularity, relatively long follow-up times and a high event rate with 40% of the patients dying during follow-up and low loss of follow-up. In addition, the inclusion of only incident HD patients avoided selection bias for “survivors” as in a prevalent

HD cohort. Of course, this kind of bias could have occurred in one of those analyses that attempted to mimic a prevalent study (FU starting time at 12 or 24 months). Nevertheless, despite the large size of our cohort, only a limited number of subgroup analyses was feasible. For example, our statistical power to analyze patients with a high baseline iPTH was low so that we may have missed an association of lowering iPTH with changes in mortality. Moreover, an inherent major limitation due to the observational nature of the study is the fact that it can not prove causality, in particular as we have insufficient information to assess whether changes in bone mineral parameters occurred spontaneously or were treatment-related.

In summary, we detected U-shaped relationships between baseline bone and mineral parameters and mortality or between shifts of these parameters and mortality. The only notable exception was that an increase in low baseline iPTH was associated with decreased mortality risk. Our data further help designing prospective studies to test whether therapeutic manipulation of bone mineral parameters can reduce the massively increased mortality in HD patients.

Acknowledgements

This study was supported by an unrestricted grant from Amgen, Thousand Oaks, CA. The help and advice of Karly Louie, Amgen, Uxbridge UK and Bruno Fouqueray, Amgen, Zug, Switzerland in accessing the database is gratefully acknowledged. JF has received lecture fees from Amgen, Fresenius, Sanofi, Shire and Vifor. PS has received fees for lectures and/or advisory boards from Astra Zeneca, Corvidia, Baxter, Pfizer, BSM and Akeiba. KUE has received fees for lectures and advisory functions from Akebia, Bayer, Sanofi Aventis and Vifor. DW has received consultancy or lecture fees from Amgen, Fresenius and Vifor.

References

1. Hruska KA, Seifert M, Sugatani T. Pathophysiology of the chronic kidney disease-mineral bone disorder. Curr Opin Nephrol Hypertens. 2015 Jul;24(4):303–9.

2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004 Aug;15(8):2208–18.

3. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, 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 Sep;52(3):519–30.

4. Fouque D, Roth H, Pelletier S, London GM, Hannedouche T, Jean G, et al. Control of mineral metabolism and bone disease in haemodialysis patients: which optimal targets? Nephrol Dial Transplant. 2013 Feb;28(2):360–7.

5. Rivara MB, Ravel V, Kalantar-Zadeh K, Streja E, Lau WL, Nissenson AR, et al. Uncorrected and Albumin-Corrected Calcium, Phosphorus, and Mortality in Patients Undergoing Maintenance Dialysis. J Am Soc Nephrol. 2015 Jul 1;26(7):1671–81.

6. Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, et al. Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding. Am J Kidney Dis. 2014 Jun;63(6):979–87.

7. Floege J, Kim J, Ireland E, Chazot C, Drueke T, de Francisco A, et al. Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. Nephrol Dial Transplant. 2011 Jun 1;26(6):1948–55.

8. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, 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 Jul;92(1):26–36.

9. Block GA, Kilpatrick RD, Lowe KA, Wang W, Danese MD. CKD-mineral and bone disorder and risk of death and cardiovascular hospitalization in patients on hemodialysis. Clin J Am Soc Nephrol. 2013 Dec 6;8(12):2132–40.

10. Tangri N, Wagner M, Griffith JL, Miskulin DC, Hodsman A, Ansell D, 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 Mar;57(3):415–21.

11. Wald R, Rabbat CG, Girard L, Garg AX, Tennankore K, Tyrwhitt J, et al. Two phosphAte taRGets in End-stage renal disease Trial (TARGET): A Randomized Controlled Trial. Clin J Am Soc Nephrol. 2017 Jun 7;12(6):965–73.

12. Soohoo M, Feng M, Obi Y, Streja E, Rhee CM, Lau WL, et al. Changes in Markers of Mineral and Bone Disorders and Mortality in Incident Hemodialysis Patients. Am J Nephrol. 2016;43(2):85–96.

13. Streja E, Wang H-Y, Lau WL, Molnar MZ, Kovesdy CP, Kalantar-Zadeh K, et al. Mortality of combined serum phosphorus and parathyroid hormone concentrations and their changes over time in hemodialysis patients. Bone. 2014 Apr;61:201–7.

14. Fernández-Martín JL, Martínez-Camblor P, Dionisi MP, Floege J, Ketteler M, London G, et al. Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. Nephrol Dial Transplant. 2015 Sep;30(9):1542–51.

15. de Francisco ALM, Kim J, Anker SD, Belozeroff V, Canaud B, Chazot C, et al. An epidemiological study of hemodialysis patients based on the European Fresenius Medical Care hemodialysis network: results of the ARO study. Nephron Clin Pract. 2011 Dec 10;118(2):c143-54.

16. Stenvinkel P, Gillespie IA, Tunks J, Addison J, Kronenberg F, Drueke TB, et al. Inflammation Modifies the Paradoxical Association between Body Mass Index and Mortality in Hemodialysis Patients. J Am Soc Nephrol. 2016 May 1;27(5):1479–86.

17. Floege J, Gillespie IA, Kronenberg F, Anker SD, Gioni I, Richards S, et al. Development and validation of a predictive mortality risk score from a European hemodialysis cohort. Kidney Int. 2015 May;87(5):996–1008.

18. Steil H, Amato C, Carioni C, Kirchgessner J, Marcelli D, Mitteregger A, et al. EuCliD--a medical registry. Methods Inf Med. 2004;43(1):83–8.

19. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria; https://www.r-project.org/;

20. Therneau T. A Package for Survival Analysis in S. version 2.38. 2015.

21. Therneau T, Grambsch P. Modeling Survival Data: Extending the Cox Model. New York: Springer; 2000.

22. Eckardt K-U, Gillespie IA, Kronenberg F, Richards S, Stenvinkel P, Anker SD, et al. High cardiovascular event rates occur within the first weeks of starting hemodialysis. Kidney Int. 2015 Nov;88(5):1117–25.

23. Robinson BM, Zhang J, Morgenstern H, Bradbury BD, Ng LJ, McCullough KP, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. Kidney Int. 2014 Jan;85(1):158–65.

24. Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K. Patterns and predictors of early mortality in incident hemodialysis patients: new insights. Am J Nephrol. 2012;35(6):548–58.

25. Danese MD, Belozeroff V, Smirnakis K, Rothman KJ. Consistent control of mineral and bone disorder in incident hemodialysis patients. Clin J Am Soc Nephrol. 2008 Sep 30;3(5):1423–9.

26. Cozzolino M, Messa P, Brancaccio D, Cannella G, Bolasco P, Di Luca M, et al. Achievement of NKF/K-DOQI recommended target values for bone and mineral metabolism in incident hemodialysis patients: results of the FARO-2 cohort. Blood Purif. 2014;38(1):37–45.

27. Yoo KD, Kang S, Choi Y, Yang SH, Heo NJ, Chin HJ, et al. Sex, Age, and the Association of Serum Phosphorus With All-Cause Mortality in Adults With Normal Kidney Function. Am J Kidney Dis. 2016 Jan;67(1):79–88.

28. Wald R, Sarnak MJ, Tighiouart H, Cheung AK, Levey AS, Eknoyan G, et al. Disordered mineral metabolism in hemodialysis patients: an analysis of cumulative effects in the Hemodialysis (HEMO) Study. Am J Kidney Dis. 2008 Sep;52(3):531–40.

29. Kalantar-Zadeh K, Kuwae N, Regidor DL, Kovesdy CP, Kilpatrick RD, Shinaberger CS, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int. 2006 Aug;70(4):771–80.

30. Floege J, Tsirtsonis K, Iles J, Drueke TB, Chertow GM, Parfrey P. Incidence, predictors and therapeutic consequences of hypocalcemia in patients treated with cinacalcet in the EVOLVE trial. Kidney Int. 2018 Jun;93(6):1475–82.

31. Gauci C, Moranne O, Fouqueray B, de la Faille R, Maruani G, Haymann J-P, et al. Pitfalls of measuring total blood calcium in patients with CKD. J Am Soc Nephrol. 2008 Aug 11;19(8):1592–8.

32. Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol. 2004 Mar;15(3):770–9.

33. EVOLVE Trial Investigators, Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012 Dec 27;367(26):2482–94.

Tables

Table 1: Characteristics of all patients (n=8817) at the defined baseline

Parameter	N_{base}	N_{min}	Mean±sd or n (%)	25, 50, 75% Percentile
Age	8817	8817	64.3±14.8	55.0, 67.0, 76.0
Sex (female)	8817	8817	3502 (39.7%)	
BMI [kg/m²]	7708	7708	26.4±5.4	22.7, 25.7, 29.4
Smoking	5808	5808		
Non-Smoker			3515 (60.5%)	
Former smoker			1581 (27.2%)	
Current smoker			712 (12.3%)	
Underlying renal disease	8817	8817		
Hypertension/vascular			1468 (16.7%)	
Glomerulonephritis			863 (9.8%)	
Diabetic Nephropathy			2167 (24.6%)	
Tubulo-interstitial			995 (11.3%)	
Polycystic Kidney Disease			504 (5.71%)	
Miscellaneous/Other			2820 (32.0%)	
CVD history prior to FU	8817	8817	2955 (33.5%)	
Diabetes history prior to FU	8817	8817	3184 (36.1%)	
S-Phosphate [mmol/L]	8604	8817	1.56±0.50	1.23, 1.50, 1.84
S- Total Calcium [mmol/L]	8553	8817	2.21±0.19	2.10, 2.20, 2.32
S-iPTH [ng/L]	7488	8817	278.1±292.3	106.0, 201.0, 345.5
Hemoglobin [g/L]	8625	8817	113.1±16.5	102.8, 113.0, 124.0
S-Albumin [g/L]	7879	8724	37.7±5.1	35.0, 38.0, 41.0
S-Ferritin [pmol/L]	8120	8781	727±574	301, 559, 1000
S-Total cholesterol [mmol/L]	6796	8602	4.37±1.15	3.57, 4.25, 5.05
S-CRP [mg/L]	7036	8817	15.5±27.2	0.00, 2.30, 6.40
White blood cell count [G/L]	8056	8649	7.20±2.56	5.63, 6.90, 8.40
eKt/V	8297	8806	1.32±0.32	1.12, 1.29, 1.50
Mortality	8817	8817	3100 (35.2%)	
CVD mortality	8817	8817	1399 (15.9% of all, 54.1% of all, who died)	

N_{base}: information available at baseline; N_{min}: at least one value available in complete observation period
FU, follow-up

Table 2: Minimal risk ranges (HR ≤ 1.1, main adjustment model) for all-cause mortality (top panel) and CV mortality (bottom panel) for phosphate, calcium and iPTH, with percentage of patients within each risk category averaged above months 3 (defined baseline) to 6

Outcome and lab parameters		Below minimal	Within minimal	Above minimal
All-cause mortality				
Phosphate (mmol/L)	Range	<1.20	1.20-1.89	>1.89
	N (%)	1750 (20.34%)	5224 (60.72%)	1630 (18.94%)
Calcium (mmol/L)	Range		1.50-2.36*	>2.36
	N (%)		7223 (84.45%)	1330 (15.55%)
iPTH (ng/L)	Range	<239	239-710	>710
	N (%)	4518 (60.34%)	2606 (34.80%)	364 (4.86%)
Cardiovascular mortality				
Phosphate (mmol/L)	Range	<1.13	1.13-1.89	>1.89
	N (%)	1273 (14.79%)	5701 (66.26%)	1630 (18.94%)
Calcium (mmol/L)	Range		1.50-2.34**	>2.34
	N (%)		6947 (81.22%)	1606 (18.78%)
iPTH (ng/L)	Range	<214	214-981***	>981
	N (%)	3244 (43.32%)	4080 (54.49%)	164 (2.19%)

*lower threshold level of 1.5 is associated with a HR of 1.16 compared to the reference
**lower threshold level of 1.5 is associated with a HR of 1.36
*** upper threshold level of 981 is associated with a HR of 1.25 compared to the reference

Table 3: Hazard Ratios for all-cause (top panel) and CV mortality (bottom panel) [95% CI], below and above the minimal risk range (main adjustment model); The minimal risk range is set as the reference category (HR=1).

Outcome and lab parameters	Below minimal risk range		Above minimal range	
	HR [95% CI]	p-value	HR [95% CI]	p-value
All-cause mortality				
Phosphate	1.32 [1.22,1.44]	<0.001	1.32 [1.17, 1.50]	<0.001
Calcium			1.37 [1.23, 1.52]	<0.001
iPTH	1.18 [1.08, 1.29]	<0.001	1.34 [1.13, 1.60]	0.001
Cardiovascular mortality				
Phosphate	1.37 [1.20,1.56]	<0.001	1.34 [1.13, 1.59]	<0.001
Calcium			1.21 [1.05, 1.41]	0.010
iPTH	1.14 [1.00, 1.29]	0.035	1.57 [1.08, 2.27]	0.017

Table 4: Mortality risk associated with changing the risk range categories of phosphate, calcium and iPTH, using main adjustment model; Reference with HR=1: Staying within the group the patient was categorized in at months 3-6 at baseline.

	Move below minimal risk range			Move within minimal risk range			Move above minimal risk range		
Risk category within months 3-6 after dialysis start	**Change***	**HR [95% CI]**	**p-value**	**Change***	**HR [95% CI]**	**p-value**	**Change***	**HR [95% CI]**	**p-value**
Phosphate									
Below minimal risk range (<1.20), n=1750	[-0.19, -0.05, 0.05]	1.00	--	[0.23, 0.37, 0.55]	0.78 [0.64-0.95]	0.015	[0.93, 1.23, 1.41]	0.99 [0.61-1.62]	0.977
Within minimal risk range (1.20-1.89), n=5224	[-0.63, -0.45, -0.29]	1.21 [1.09-1.37]	<0.001	[-0.19, -0.02, 0.13]	1.00	--	[0.32, 0.50, 0.71]	1.37 [1.16-1.61]	<0.001
Above minimal risk range (>1.89), n=1630	[-1.31, -1.08, -0.93]	0.99 [0.69-1.41]	0.947	[-0.77, -0.57, -0.37]	0.94 [0.72-1.21]	0.622	[-0.21, 0.01, 0.24]	1.00	--
Calcium									
Below minimal risk range n=0									
Within minimal risk range (1.50-2.36), n=7223				[-0.08, 0.00, 0.08]	1.00	--	[0.14, 0.22, 0.32]	1.38 [1.22-1.56]	<0.001
Above minimal risk range (>2.36), n=1330				[-0.32, -0.21, -0.13]	0.74 [0.57-0.97]	0.030	[-0.05, 0.01, 0.08]	1.00	--
iPTH **									
Below minimal risk range (<239), n=4511	[-38, 0, 43]	1.00	--	[128, 201, 193]	0.80 [0.70-0.92]	0.001	[617, 734, 923]	1.04 [0.66-1.65]	0.859
Within minimal risk range (239-710), n=2595	[-288, -193, -120]	1.19 [1.01-1.41]	0.037	[-61, 6, 99]	1.00	--	[345, 498, 730]	1.19 [0.89-1.60]	0.232
Above minimal risk range (>710)[#], n=345	[-1073, -786, -644]	0.79 [0.26-1.77]	0.683	[-652, -474, -328]	0.91 [0.47-1.77]	0.778	[-86, 29, 402]	1.00	--

*[25%,50%,75%] percentile of change, compared to average value within months 3-6

** patients undergoing parathyroidectomy during the follow-up period (n=52) were excluded for this analysis

[#] only adjusted for age, gender and renal diagnosis, since model did not converge for fully adjusted main model

Figures

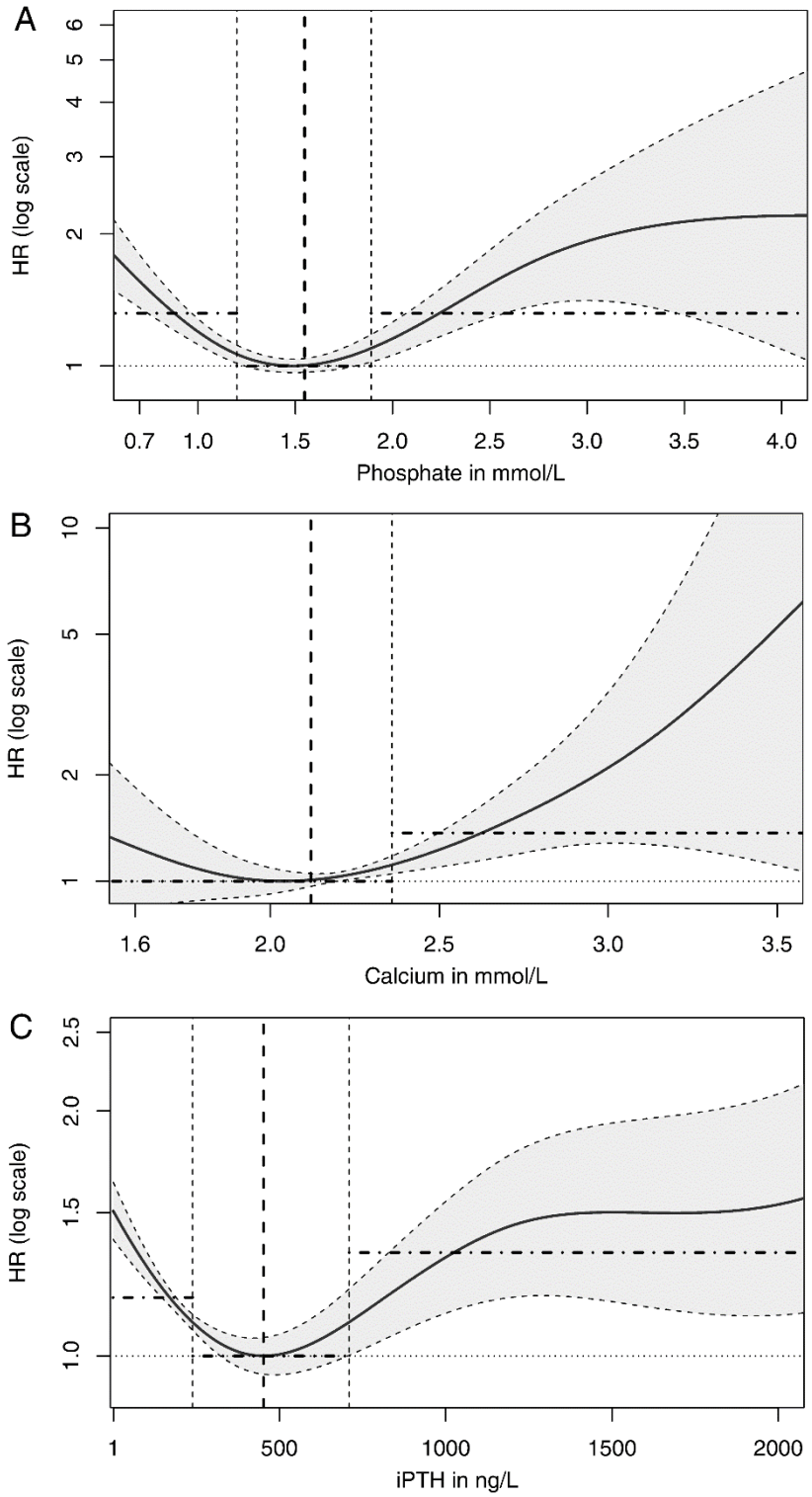

Figure 1: Relative risk of all-cause mortality for time-updated values of (A) phosphate, (B) calcium and (C) iPTH, using the main adjustment model. The lowest risk range (HR≤1.1) is indicated with vertical dashed lines. HR below and above the lowest risk range in comparison to the lowest risk range as the reference (HR=1) are shown with horizontal dash-dotted lines.

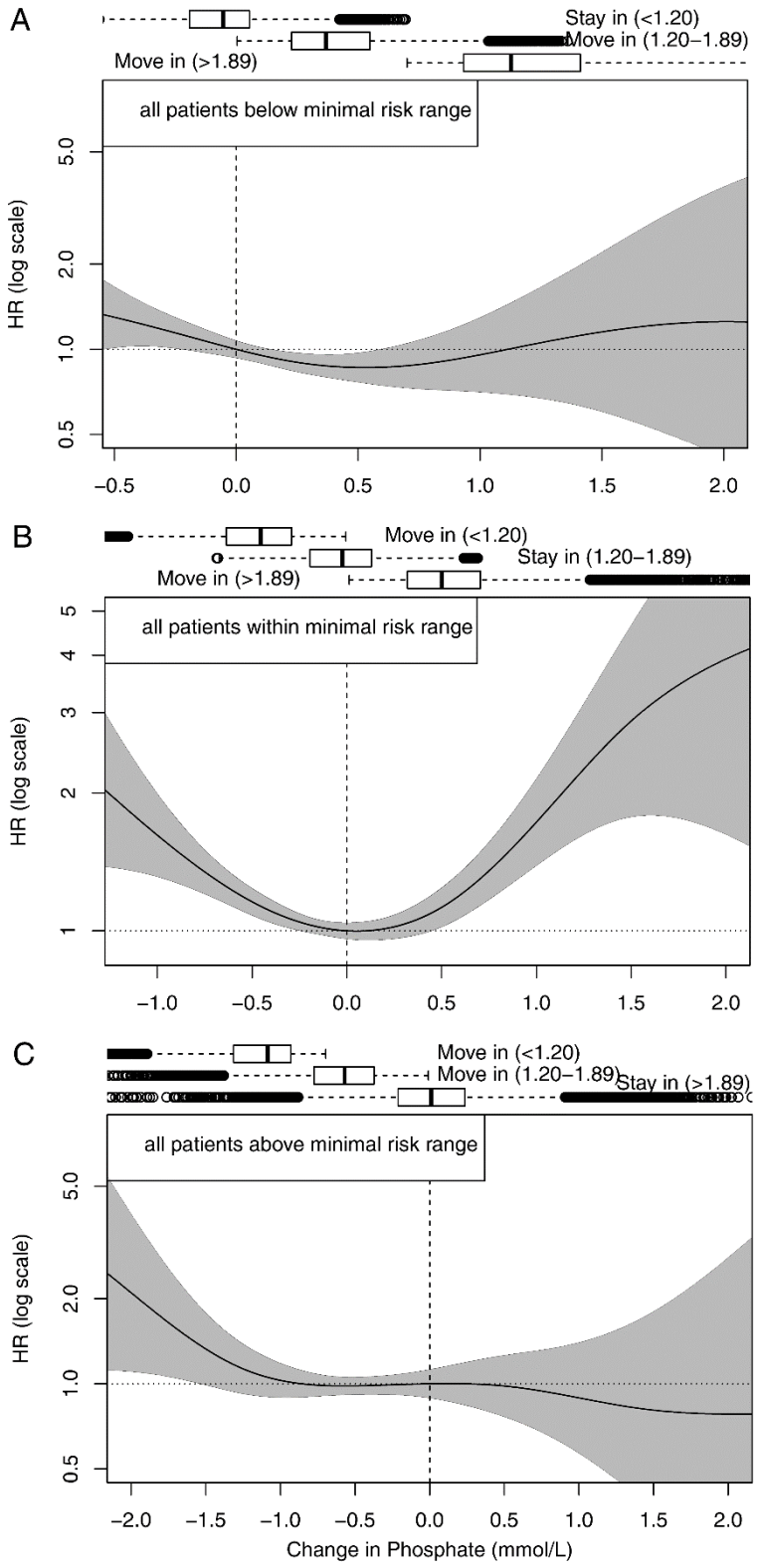

Figure 2: Relative risk of all-cause mortality for change in phosphate compared with the baseline (averaged over Months 3–6) for those patients (A) below the minimal risk range (phosphate <1.20), (B) within the minimal risk range (phosphate 1.20–1.89) and (C) above the minimal risk range (phosphate >1.89) at baseline. The main adjustment model was used and no change to baseline was set as the reference (HR=1). Boxplots represent the distribution of changes, separated for the three different risk categories.

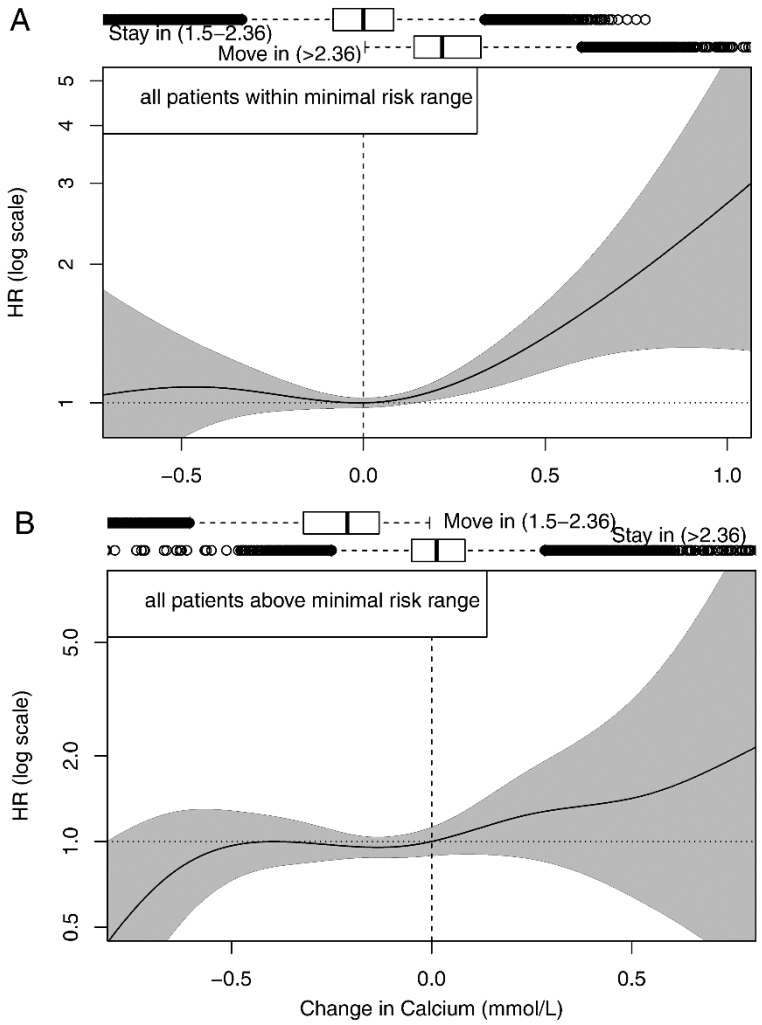

Figure 3: Relative risk of all-cause mortality for change in calcium compared with the baseline (averaged over Months 3–6) for those patients (A) within the minimal risk range (calcium ≤2.36) and (B) above the minimal risk range at baseline (calcium >2.36). The main adjustment model was used and no change to baseline was set as the reference (HR=1). Boxplots represent the distribution of changes separated for the two different risk categories.

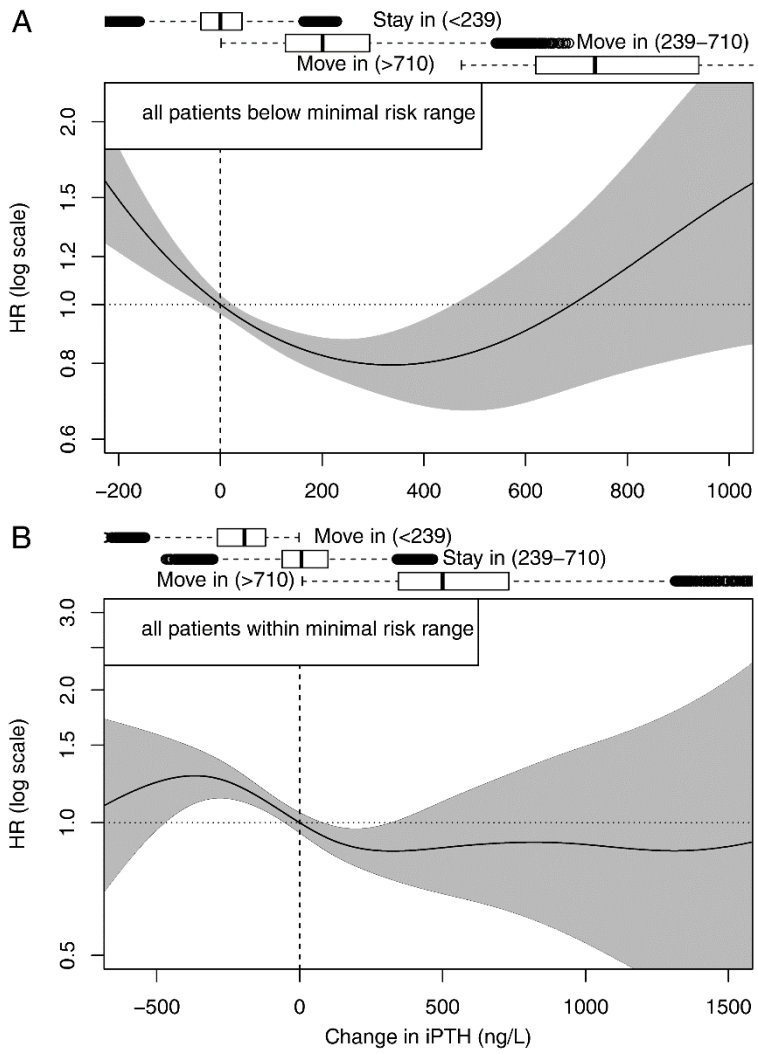

Figure 4: Relative risk of all-cause mortality for change in iPTH compared with the baseline (averaged over Months 3–6) for those patients (A) below the minimal risk range (iPTH <239) and (B) within the minimal risk range (iPTH 239–710) at baseline. The main adjustment model was used and no change to baseline was set as the reference (HR=1). Boxplots represent the distribution of changes separated for the three different risk categories. For iPTH above the minimal risk range, no plot is given, since models based on absolute changes were numerically unstable due to low sample size within this category.