

Consistent Control of Mineral and Bone Disorder in Incident Hemodialysis Patients

Mark D. Danese,* Vasily Belozeroff,[†] Karen Smirnakis,[†] and Kenneth J. Rothman[‡]

**Outcomes Insights, Inc., Newbury Park, California;* [†]*Amgen, Inc., Thousand Oaks, California;* and [‡]*RTI Health Solutions, Research Triangle Park, North Carolina*

Background and objectives: In 2003, the National Kidney Foundation introduced guidelines for the control of parathyroid hormone, calcium, and phosphorus in hemodialysis patients.

Design, setting, participants, & measurements: A cohort study was conducted of 22,937 incident hemodialysis patients who were identified from a large national provider between July 1, 2000, and June 30, 2002, and followed through June 30, 2004. Consistent achievement was determined (1) as the simultaneous control of multiple markers over time and (2) as the time in target for each marker during the first year of dialysis. Mortality risk was assessed with Cox proportional hazards models.

Results: In the simultaneous control analysis, patients who achieved target for none of the markers had a 51% greater risk for death than those who achieved target for all three markers (reference group). Patients who achieved any target for any single marker had a 35 to 39% higher risk for death, and patients who achieved target for any two of the three markers had a 15 to 21% higher risk for death compared with the reference group. In the time in target analysis, patients with parathyroid hormone in target for 4 quarters had a 25% lower risk for death compared with those who did so for ≤ 1 quarter (reference group). Patients with calcium in target for 4 quarters had a 14% lower risk, and patients with phosphorus in target for 4 quarters had a 38% lower risk.

Conclusions: Consistent control of the markers of bone metabolism and disease within published targets is a strong predictor of survival in hemodialysis patients.

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Mineral and bone disorder (MBD) affects the majority of patients with chronic kidney disease and is characterized by imbalances in serum levels of parathyroid hormone (PTH), calcium (Ca), and phosphorus (P) (1,2). In recognition of the growing body of evidence linking abnormalities of bone and mineral metabolism with adverse clinical outcomes and consistent with their goal of improving the quality of care and outcomes of patients with kidney disease, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) published the Bone Metabolism and Disease treatment guidelines in October 2003 (1). These guidelines contain specific treatment targets for PTH (150 to 300 pg/ml), Ca (within the normal range, particularly the lower end from 8.4 to 9.5 mg/dl), P (3.5 to 5.5 mg/dl), and Ca-P product ($\text{Ca} \times \text{P}$; $<55 \text{ mg}^2/\text{dl}^2$) (3). Although elevations in each of these biochemical markers, as well as elevations in $\text{Ca} \times \text{P}$ have been associated with increased morbidity and mortality in dialysis patients, the authors of the guidelines acknowledge that additional evidence from epidemiologic studies, including randomized trials, is needed to inform future revisions to these guidelines (3–10).

The percentage of patients who met the KDOQI targets

around the time of their introduction in 2003 ranged from 21 to 26% for PTH, 29 to 49% for Ca, 39 to 55% for P, and 54 to 73% for $\text{Ca} \times \text{P}$ (10–13). Most concerning was that only 5 to 7.3% of dialysis patients simultaneously met all four targets (PTH, Ca, P, and $\text{Ca} \times \text{P}$). According to one study that evaluated target achievement both before and after the KDOQI treatment guidelines were introduced, a majority of patients remained outside at least some of the target ranges even after implementation (6.6 and 10.9% met all for targets in 2003 and 2004, respectively) (12). Another study evaluated the effects of guideline-induced changes in non-calcium-containing phosphate binders, vitamin D use, and dialysate calcium levels and found that serum P and serum PTH levels increased in association with a modest reduction in serum Ca (14).

One of the difficulties in achieving multiple KDOQI targets consistently is that most existing treatment approaches reflect a compromise between controlling PTH and controlling Ca and P (14). Some newer therapies (*e.g.*, Renagel [Genzyme Corporation, Cambridge, MA], Sensipar [Amgen, Inc., Thousand Oaks, CA]), as well as combinations of therapeutic agents, may make it easier to achieve consistent control of multiple MBD parameters (15). Currently, there is no information to assist physicians in understanding the tradeoffs being made by achieving one target at the expense of another. Similarly, although one recent study suggests that short-term control of these markers is associated with lower mortality, no study has investigated the significance of long-term control of these parameters (16). The goal of our study was to determine whether more consistent

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Correspondence: Dr. Mark Danese, 4737 Via Canada, Newbury Park, CA 91320. Phone: 805-498-0034; Fax: 805-715-8106; E-mail: mark@outins.com

control of PTH, Ca, and P (or $\text{Ca} \times \text{P}$) within the KDOQI target ranges was associated with better survival compared with less consistent control, where consistency was defined as either the number of markers in target at one time or the duration of time in target for each marker.

Materials and Methods

Patient Population

The study was conducted among 24,803 adults who were randomly selected from a pool of patients who initiated hemodialysis at Fresenius Medical Care–North America (Lexington, MA) facilities between July 1, 2000, and June 30, 2002. Patients were included in the study when they survived >3 mo after initiation of hemodialysis. Patients' demographic (age, race, gender, body mass index, and vitamin D use) and clinical (primary cause of renal disease and dialysis initiation date) characteristics, as well as follow-up data through June 30, 2004, were extracted from the centralized database. Available follow-up data included average monthly values for serum Ca, P, albumin, hemoglobin, transferrin saturation, predialysis systolic and diastolic BP, and dialysis adequacy (*i.e.*, urea reduction ratio) and average quarterly values for PTH. All laboratory assessments for Fresenius Medical Care–North America were conducted using a central laboratory, which improved consistency of the measurements. Total Ca was corrected for serum albumin when <4.0 g/dl [corrected Ca = total Ca + $0.8 \times (4 - \text{albumin})$], and all analyses that included Ca (including $\text{Ca} \times \text{P}$) were conducted and reported using corrected Ca. Patient deaths were recorded and entered into the database by individual facilities.

Descriptive Analysis: Proportion Meeting KDOQI Targets

We estimated the proportion of patients who achieved each KDOQI target in each calendar quarter across the first 2 yr of follow-up. To be included in this analysis, patients must have survived a minimum of 2 yr after initiating dialysis.

Simultaneous Control Analyses

To examine the effects of simultaneous achievement of the PTH, Ca, P, and $\text{Ca} \times \text{P}$ targets on mortality, we constructed two models. Exposures for model 1 included PTH, Ca, and P, and exposures for model 2 included PTH and $\text{Ca} \times \text{P}$. We modeled Ca and P separately from $\text{Ca} \times \text{P}$ because patients who meet both Ca and P, by definition, meet the $\text{Ca} \times \text{P}$ target; hence, a model with Ca, P, and $\text{Ca} \times \text{P}$ cannot be fit. The following mutually exclusive patient exposure categories were defined for model 1: No parameters within targets, PTH only, Ca only, P only, PTH and Ca, PTH and P, Ca and P, and all three within target (*i.e.*, PTH, Ca, and P). Mutually exclusive exposure categories for model 2 were as follows: Neither PTH nor $\text{Ca} \times \text{P}$ within targets, PTH only in target, $\text{Ca} \times \text{P}$ only in target, and both in target (*i.e.*, PTH and $\text{Ca} \times \text{P}$). The reference group in each model was the group that met the targets for all MBD laboratory parameters. The primary outcome measure was time to death during the entire follow-up period.

In our time-to-event analyses, we used Cox proportional hazards regression with time-dependent covariates to estimate effects of target achievement in each calendar quarter on the risk for death in the subsequent quarter. Patients began accruing risk time after the first 3 mo of hemodialysis and were followed until death or censored at the earliest of June 30, 2004, loss to follow-up (*i.e.*, no additional data), or kidney transplantation (identified by *International Classification of Diseases, Ninth Revision* code V42.0). For each 3-mo interval beginning with the initiation of dialysis, patients were assessed for attainment of KDOQI targets on the basis of mean laboratory values for each interval and then classified with respect to being within the PTH, Ca, P, and

$\text{Ca} \times \text{P}$ target ranges. The primary analysis evaluated the association between being in target in one 3-mo period and death in the subsequent 3-mo period. Consequently, patients were required to have survived the first 3-mo period to be included in the analyses.

The model was adjusted for the potential confounding effects of factors that may be associated with levels of PTH, Ca, or P and mortality, including age, gender, race, diabetes, body mass index, and albumin. In addition, because patients who are in target for MBD measures may be more likely to be in target for other measures associated with risk for death, we adjusted the model for hemoglobin and both systolic and diastolic BP. Similarly, we included transferrin saturation because it can affect hemoglobin levels and hence the ability to achieve a hemoglobin level.

Excess Fraction Analyses

We assessed the potential effect on mortality of moving the entire population into simultaneous control for PTH, Ca, and P by estimating the population excess fraction (also known as the population attributable fraction) (17). Because the hazard ratios (HR) estimated from a proportional hazards model are not appropriately weighted to the population for use in estimating excess fractions, we combined the proportional hazards model with a stratified approach to estimate standardized mortality ratios (SMR) for each KDOQI target group. From the SMR, we estimated the excess fraction for each target group and combined these to obtain the population excess fraction (17,18).

To obtain the SMR, we used the full model results from model 1 to calculate a risk score for each patient assuming that he or she had achieved target for all three markers. (The KDOQI target variables were included in the calculation, but in estimating the expected relative risk (RR) for death, each person was assumed to have achieved target for all three markers [19,20].) We then stratified patients into deciles of mortality risk on the basis of this score to control for confounding from the other risk factors in the proportional hazards model. For each decile of risk score, we obtained an expected number of deaths for each of the eight KDOQI target group categories. The expected number of deaths in each target group was estimated by multiplying the probabilities of death in each of the risk deciles from the "all in target" group by the number of patients in each risk decile in each of the other target groups. Subtracting the expected number of deaths from the observed number of deaths in each category of the target group and then summing that excess over all strata yielded the overall number of excess deaths in the study population. Dividing this number by the total number of deaths in the study population gives the proportion of all observed deaths that might be prevented by achieving targets for all three markers simultaneously (*i.e.*, the excess fraction). See the Discussion section for the limitations of this analysis.

Time-in-Target Analyses

We evaluated time in target over the first 12 mo of hemodialysis as another measure of consistent control. The exposure of interest was the number of quarters in which a patient was within the KDOQI target ranges for PTH, Ca, or P. In the model, each of the three markers was incorporated using three categorical variables: ≤ 1 quarter, 2 quarters, 3 quarters, or 4 quarters (reference group). The primary outcome measure was time to death over the entire follow-up period.

The construction of the model was identical to that used in the simultaneous control analyses, except that time-dependent covariates were handled differently. In the time-in-target model, information for the 12-mo baseline period was used to evaluate risk during the follow-up period. To account for nonproportionality of hazards, we added time-dependent covariates by including product interaction terms be-

tween time and the categorical variables indicating calendar quarters in target for PTH, Ca, and P (21).

Sensitivity Analysis

Because we hypothesized that vitamin D is on the causal pathway between our exposures and the outcome of interest, we did not include it in our final models. As a sensitivity analysis, however, we fit models that included the number of months of vitamin D use to assess the magnitude of potential confounding by vitamin D assuming that it was not in the causal path that we are studying. All analyses were conducted in SAS 9.1.3 (SAS Institute, Cary, NC).

Results

Baseline characteristics for all patients in both regression analyses are described in Table 1.

Proportion in Target

The percentage of patients who achieved each KDOQI target throughout the 2-yr follow-up period is shown in Figure 1. After the first quarter, results were consistent over time with the fewest patients achieving the PTH target and the most achieving the Ca × P target.

Simultaneous Control

The simultaneous control analyses included 22,937 patients who survived at least 3 mo and 42,036 person-years of follow-up. During the follow-up interval, there were 7083 deaths.

The proportions of patients who were in each of the mutually exclusive groups defined by our models at baseline are provided in Figures 2 and 3. For patients in model 1 (with PTH, Ca,

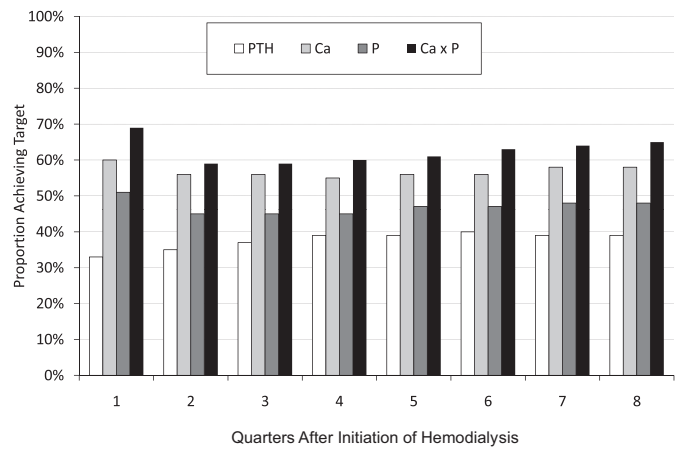


Figure 1. Proportion of patients who met target by calendar quarter over 2 yr (n = 13,015). Bars show the percentage of patients who met Kidney Disease Outcomes Quality Initiative (KDOQI) targets for parathyroid hormone (PTH), calcium (Ca), phosphorus (P), and Ca-P product (Ca × P) for each quarter after beginning hemodialysis. Only patients who survived for a minimum of 2 yr after hemodialysis initiation are included.

and P), meeting only the PTH target and meeting only the PTH and P targets were the least common groups (5 or 6% of patients, respectively). Meeting the Ca target only and meeting both the Ca and P targets were the most common groups (19% of patients each).

Figure 2 also shows the RR for death for each of the mutually

Table 1. Baseline demographic information^a

Variable	Simultaneous Control Analyses (n = 22,937)		Time-in-Target Analyses (n = 17,828)	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Continuous				
age (yr)	61 (15)	63 (51, 73)	60 (15)	62 (50, 72)
PTH (pg/ml)	288 (270)	215 (118, 371)	283 (257)	216 (132, 345)
Ca (mg/dl)	9.2 (0.7)	9.2 (8.9, 9.6)	9.3 (0.7)	9.3 (9, 9.7)
P (mg/dl)	5.4 (1.5)	5.2 (4.4, 6.3)	5.7 (1.5)	5.5 (4.6, 6.6)
Ca × P (mg ² /dl ²)	49.8 (13.4)	48 (41, 58)	53.1 (14)	51.6 (43.2, 61.4)
albumin (g/dl)	3.6 (0.48)	3.6 (3.3, 3.9)	3.8 (0.4)	3.9 (3.6, 4.1)
Hb (g/dl)	11.1 (1.3)	11.1 (10.2, 12)	11.8 (1.2)	11.8 (11.1, 12.5)
DBP (mmHg)	76.4 (12.9)	76 (67, 85)	77.5 (13.7)	77 (68, 86)
SBP (mmHg)	148.7 (22.4)	148 (133, 164)	150.8 (23.5)	150 (135, 166)
TSAT (%)	23.1 (9.8)	21 (17, 27)	28.7 (11)	27 (21, 34)
URR (%)	67 (9.3)	68 (62, 73)	71 (7.2)	72 (67, 76)
Categorical (%)				
male		53		53
black (versus all other)		33		36
BMI ≥30 kg/m ²		33		34
diabetes		42		43

^aAge and categorical demographic variables are based on values at the start of hemodialysis. BMI, body mass index; Ca, calcium; DBP, diastolic BP; Hb, hemoglobin; IQR, interquartile range (25%, 75%); P, phosphorus; PTH, parathyroid hormone; SBP, systolic BP; TSAT, transferrin saturation; URR, urea reduction ratio.

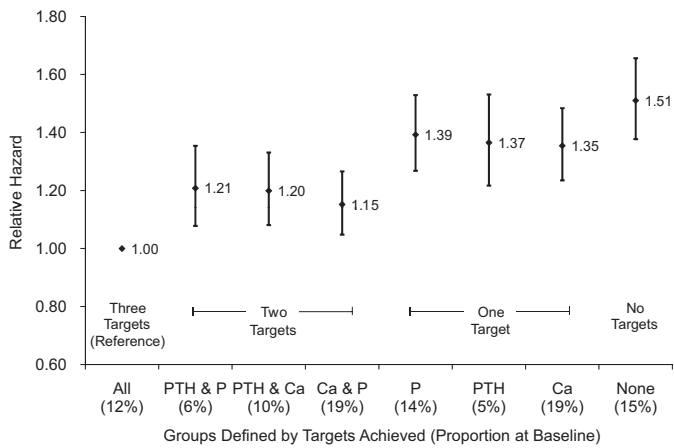


Figure 2. Simultaneous control: Relationship between KDOQI targets achieved and risk for death (model 1). Hazard ratios (HR) and 95% confidence intervals (CI) for various combinations of achieving KDOQI target values for PTH, Ca, and P are shown. Values in parentheses represent the proportion of patients in each category at baseline.

exclusive groups using model 1. The reference group contains patients who achieved targets simultaneously for all three markers. Meeting target for none of the three markers was associated with a 1.51-fold increased risk for mortality (95% CI 1.38 to 1.66). There seemed to be an association between the number of markers in target and the risk for death. Patients who met only one target (Ca, PTH, or P) had between a 1.35- and 1.39-fold higher risk for death compared with patients who simultaneously met all three targets, whereas patients who met any two targets (Ca and P, PTH and Ca, or PTH and P) had between a 1.15- and 1.21-fold higher risk for death compared with those who achieved all three targets.

In model 2, which includes only PTH and Ca \times P, at baseline, 9% of the population met the only the PTH target, whereas 46% met only the Ca \times P target. The RR for death are given for model 2 in Figure 3. The reference group contains patients who achieved target levels for both PTH and Ca \times P simultaneously. Patients who achieved target for neither marker had the highest RR for death (HR 1.31; 95% CI 1.22 to 1.41). The RR associated with achieving target for either marker alone were similar (HR 1.20 and 1.24).

Excess Fraction

The excess fraction results are provided in Table 2. We estimated the population excess fraction (the proportion of deaths associated with patients' not being in control for all three laboratory markers simultaneously) to be 20%.

Time in Target

This analysis included 17,828 patients who survived at least 12 mo and 26,879 person-years of follow-up (excluding the first year of hemodialysis). During the follow-up interval, there were 4410 deaths.

As part of the evaluation of the model, we tested the proportional hazards assumption by adding interaction terms with

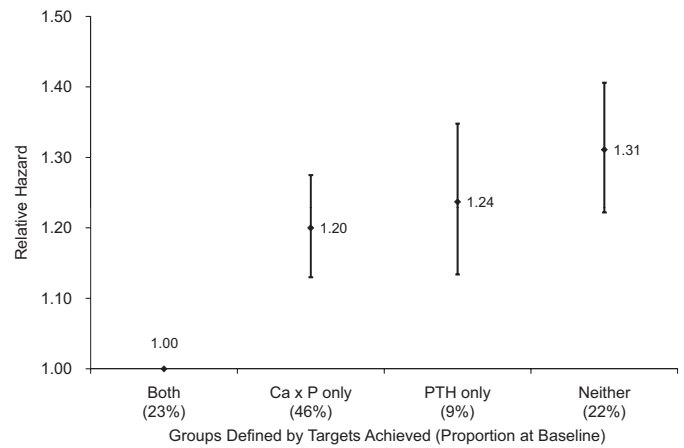


Figure 3. Simultaneous control: Relationship between KDOQI targets achieved and risk for death (model 2). HR and 95% CI for various combinations of achieving KDOQI target values for PTH and Ca \times P. Values in parentheses represent the proportion of patients in each category at baseline.

time as described already (see the Materials and Methods section). Although these improved the model fit, the effects of nonproportionality did not substantively alter the inferences from the initial model (initial model results not provided). Virtually all of the coefficients for interactions with time were >1.0 , suggesting that the association between consistently meeting targets during the first year of hemodialysis and death was attenuated during the follow-up period. The PTH terms were attenuated the most.

RR for mortality for various durations of time within target for PTH, Ca, and P are displayed in Figure 4 for the model with interaction terms. For each marker, patients who achieved target values for ≤ 1 quarter had the highest risk for death compared with those who did so for all 4 quarters. In particular, patients with a PTH in target for ≤ 1 quarter had a 34% higher risk for death (HR 1.34; 95% CI 1.11 to 1.61) than those in target for all 4 quarters (the reference group). Patients with Ca in target for ≤ 1 quarter had a 16% higher risk for death (HR 1.16; 95% CI 1.02 to 1.33) than the reference group. Finally, patients with P in target for ≤ 1 quarter had a 62% higher risk for death (HR 1.62; 95% CI 1.39 to 1.90) than the reference group.

Sensitivity Analysis

When we included the number of months of vitamin D use per quarter in the simultaneous control analyses, there was virtually no change in the RR estimates. We found similar results in the time-in-target analyses.

Discussion

Previous studies have reported the effects of elevated Ca, P, Ca \times P, and PTH levels on mortality in hemodialysis patients (4–9). Elevated serum P levels (>6.5 mg/dl) have been associated with increased mortality (4–6). Similarly, higher mortality has been associated with elevated Ca \times P levels, particularly above 70 mg/dl (5,6). Increased mortality was also reported in patients with elevated Ca levels, although this relationship is

Table 2. Excess fractions by exposure groups and overall^a

KDOQI Targets Achieved	Proportion of Deaths in Each Group (%)	SMR	Population Excess Fraction (%)
None	18	1.39	28
Ca only	18	1.31	24
PTH only	7	1.37	27
P only	16	1.30	23
Ca and P only	15	1.14	12
PTH and Ca only	10	1.31	24
PTH and P only	7	1.16	14
All three (PTH, Ca, and P)	10	1.00 (reference)	0
Total	100	1.25	20

^aKDOQI, Kidney Disease Outcomes Quality Initiative; SMR, standardized mortality ratio.

more controversial (5,7,8). In addition, increased mortality was linked with higher PTH levels, particularly in the highest PTH categories (5–7). Some studies have also demonstrated increased mortality with low PTH levels (22,23) and low Ca levels (10), suggesting that these relationships may be complex. A time-dependent survival analysis reported that P and Ca × P levels above the upper thresholds published by KDOQI were associated with increased all-cause mortality in hemodialysis and peritoneal dialysis patients (10). Finally, a recent analysis of consistent control showed that PTH, Ca, and P values within the KDOQI target range during a 90-d period are associated with lower mortality (16).

The findings from our two survival analyses support this body of previous research and, importantly, extend our knowledge by demonstrating that consistent achievement of the KDOQI targets over time is associated with improved survival. In the analyses to evaluate the simultaneous control of PTH, Ca, and P, we identified the importance of meeting as many of the targets as possible at a given time. In the analyses of time in target, we showed the importance of the duration of time that patients are within the PTH, Ca, and P target ranges. In addition,

we showed that relatively few patients either simultaneously met published targets for PTH, Ca, and P (12%) or met any target for 4 consecutive quarters (10 to 27% depending on target and 1% for all three targets) at baseline. Last, we demonstrated that PTH, Ca, and P outside the KDOQI target ranges may account for as much as 20% of deaths in dialysis patients. When taken together, these results suggest that there is a need for more consistent achievement of the KDOQI mineral metabolism targets and that meeting this need may result in improved survival for incident hemodialysis patients.

Addressing this need is challenging. The use of current treatment options often requires a tradeoff between controlling PTH and controlling Ca and P. This tradeoff was highlighted by recent studies that reported that even after implementing the KDOQI treatment guidelines, a majority of patients still failed to meet target ranges for PTH, Ca, and P (12,14). Although the proportion of patients who achieved the Ca target increased in these studies and the mean Ca levels improved, there were no benefits in P levels in the population. Furthermore, achievement of the PTH goal was worse and the mean PTH level increased in the population. The effect of these changes on patient mortality is unknown.

The analyses presented here have several strengths. They were conducted using a large incident cohort of hemodialysis patients with detailed information that allowed for adjustment of potential confounding and for reliable ascertainment of mortality status. Nevertheless, the study has several limitations. One potential concern is whether target guidelines can be evaluated before they are introduced. Most of our data on target achievement are based on a period before the KDOQI target guidelines were in place. Consequently, in our data, the proportion of patients out of target may be higher or distributed differently among exposure groups than patients in current clinical practice. Conversely, an advantage to evaluating target ranges before they are introduced is that the data capture a wider range of exposure values, which may provide information that is more stable statistically for modeling the effects of these exposures on survival. This analysis, however, did not address the question of whether the introduction of the guidelines or a change in guideline achievement favorably affects

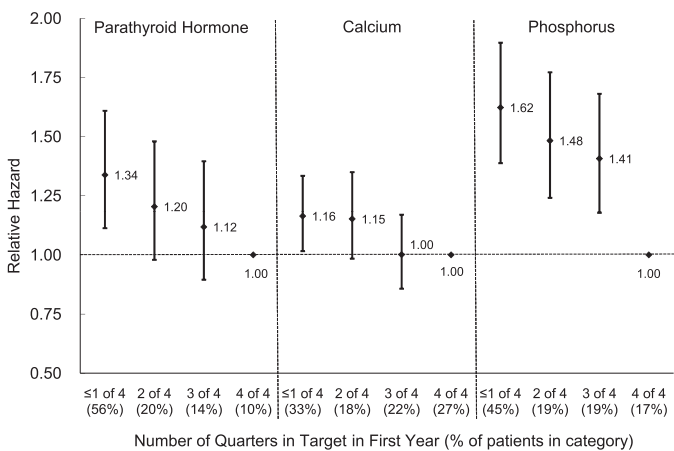


Figure 4. Time in target: Relationship between quarters in target and risk for death. HR and 95% CI for number of quarters in target PTH, Ca, and P. Values in parentheses represent the proportion of patients in each category at baseline.

mortality. Another limitation is that we had quarterly data only for PTH, and we were not able to use a more frequent updating of the laboratory information in our models (*e.g.*, monthly in the simultaneous control analyses) or smaller intervals of time (*e.g.*, number of months in target). Furthermore, we did not exhaustively evaluate all possible combinations of groups, and we did not compare being above a target *versus* being below target. Nevertheless, as discussed, several previously published studies showed that mortality risk varies across the levels of PTH, Ca, and P in a continuous manner; therefore, we elected not to repeat these analyses.

We could not incorporate information about MBD treatments, including vitamin D, phosphate binders, or calcimimetics into our analyses because our exposures (PTH, Ca, and P) are hypothesized to be on the causal pathway between these treatments and the mortality outcome. Although the effects of these medications on PTH, Ca, and P are implicitly captured in the model because they are commonly used, any effects of these medications that are mediated through other pathways (*i.e.*, outside of alterations in PTH, Ca, or P levels) would not have been identified in these models. We further evaluated this possibility by conducting sensitivity analyses using the available active vitamin D data. Our results indicate that conditioning on vitamin D use does not change the RR estimates. This finding may seem counterintuitive because previous studies showed an association between vitamin D use and a reduction in mortality, even for patients within the KDOQI targets at particular points in time (24–26). Our study differed from previous analyses, however, in that it focused on effects of consistent target achievement, rather than on simply whether single measurements of PTH, Ca, P, or vitamin D were associated with mortality. Because active vitamin D decreases PTH and increases Ca and P, it would not be expected to facilitate simultaneous control or time in control and should not have any apparent confounding effect, as was indeed the case in our sensitivity analyses.

In addition to assessing risk with statistical models, we attempted to estimate the hypothetical effect of simultaneously achieving all of the KDOQI targets on mortality at the population level. We estimated that 20% of the deaths could be avoided in this hemodialysis population if all uncontrolled patients were moved into the recommended KDOQI target ranges for PTH, Ca, and P simultaneously and remained there for their remaining lifetimes. This result, however, must be evaluated in the context of the assumptions required to estimate it. First, we assumed that the results from our analyses, which evaluated mortality in incident dialysis patients from one large US dialysis provider, estimated causal effects that would apply to the broader population of hemodialysis patients. Second, we assigned patients to a single group on the basis of targets achieved at one point in time, whereas patients typically fluctuate among our mutually defined categories over time. Third, we could not take into account any additional effects of the treatments used to move people into target. Furthermore, this analysis did not address the effort required to achieve simultaneous control of all targets, which may not be realistic in clinical practice. Despite these limitations, these

results provide a quantitative estimate of the importance of controlling PTH, Ca, and P in the hemodialysis population and suggest a boundary for the mortality benefit that could be achieved.

Conclusions

Simultaneous control of the all three bone and mineral metabolism markers within the target ranges recommended by KDOQI guidelines is associated with improved survival compared with controlling fewer markers. Furthermore, there is a monotonic relationship between the number of targets achieved and the mortality risk that is observed. In addition, sustained achievement of each target over time is associated with improved survival. It is possible that maintenance of the KDOQI targets for PTH, Ca, and P could reduce mortality in hemodialysis patients by as much as 20%.

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Disclosures

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