Article

A Computerized Treatment Algorithm Trial to Optimize Mineral Metabolism in ESRD

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Summary

Background and objectives Achievement of mineral targets in patients receiving dialysis remains challenging. This study sought to evaluate outcomes for phosphorus, calcium, and parathyroid hormone when a dialysis population was switched from a predominantly active vitamin D analogue treatment regimen to a computerized algorithm incorporating both cinacalcet and active vitamin D as potential first-line therapies.

Design, setting, participants, & measurements This longitudinal prospective trial enrolled 92 patients undergoing maintenance hemodialysis. Baseline measures (the average of the 3 months before computerized algorithm implementation) were compared with the proportion of patients achieving the prespecified targets at 6 and 12 months.

Results After 6 months there was a statistically significant improvement in the percentage of patients achieving the primary and secondary phosphorus targets (primary: phosphorus ≤ 5.5 mg/dl, increase from 41% to 75%, $P<0.001$; secondary: phosphorus 3.0–4.6 mg/dl, increase from 16% to 38%; $P=0.005$). These improvements were sustained at 12 months. There was a statistically significant improvement in the percentage of patients achieving all three prespecified secondary endpoints (an increase from 12.8% to 25.6% at 12 months; $P=0.04$); however, this was mainly driven by improved phosphorus control. The proportion of patients achieving the primary or secondary parathyroid hormone targets did not improve.

Conclusions A greater proportion of dialysis patients achieved improved phosphorus but not parathyroid hormone control by switching from a predominantly active vitamin D analogue–based treatment regimen for mineral and bone disorder to a computer-driven algorithm that incorporated cinacalcet and low-dose active vitamin D analogues as first-line therapy.

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Introduction

In 2009, Kidney Disease Improving Global Outcomes (KDIGO) released guidelines for the management of mineral and bone disorders in CKD (1). These new guidelines recommended achieving normal serum calcium, attempting to achieve normal serum phosphorus, and preventing oversuppression and excessive concentrations of parathyroid hormone (PTH) in patients receiving dialysis. Whether a clinical practice follows the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (2) or the newer KDIGO recommendations (1), achieving control of calcium, phosphorus, and PTH remains challenging in patients with ESRD. Results from the cinacalcet phase III trials as well as postmarketing studies suggest that combination therapy with cinacalcet and active vitamin D analogues allows more patients to reach target than does treatment with active vitamin D alone (3–7). However, these studies were conducted in selected patient populations and may not reflect the results that can be achieved in a general dialysis population.

This study was designed to determine the achievable outcome in a general ESRD facility by moving from a predominantly active vitamin D–based treatment regimen for the management of mineral and bone disorders to a computer-driven treatment algorithm that incorporated both cinacalcet and active vitamin D analogues as both potential first-line therapies and adjunct therapy for the disease management.

Materials and Methods

A Virginia-based dialysis facility affiliated with the University of Virginia was selected for the study on the basis of the following criteria: involved dietitian staff, no integrated (cinacalcet plus active D) protocol, medical officer and practice group with interest in research, and adequate patient numbers.

All patients in the facility were approached for inclusion in the study unless they met one of the following exclusion criteria: low PTH concentration (<150 pg/ml) and not on an active vitamin D analogue or cinacalcet, gross negligence with their dialysis prescription, inability to understand English or give informed consent, scheduled kidney transplantation or change in dialysis modality, hemodialysis frequency more than three times per week, or residence in a nursing home.

The computer algorithm used was written by one author (D.M.S.) and has been used in the University of Colorado outpatient dialysis program since 2004. Although initially designed to achieve KDOQI guidelines, it has been continually modified to achieve optimal management of mineral measures. It primarily focuses on phosphorus and calcium control, with less strict control of PTH in the face of ongoing guideline modifications, known variability in PTH measurements, and

the lack of definitive science. A modified version (designed to reduce the frequency of PTH testing) is available at www. eHealth-Book.com/synapse. Although complex, the algorithm is summarized in Figure 1.

After patients gave written informed consent, baseline data were collected on all patients for the preceding 3 months (months −2 through 0). Following study entry, all changes to cinacalcet and active vitamin D doses were recommended
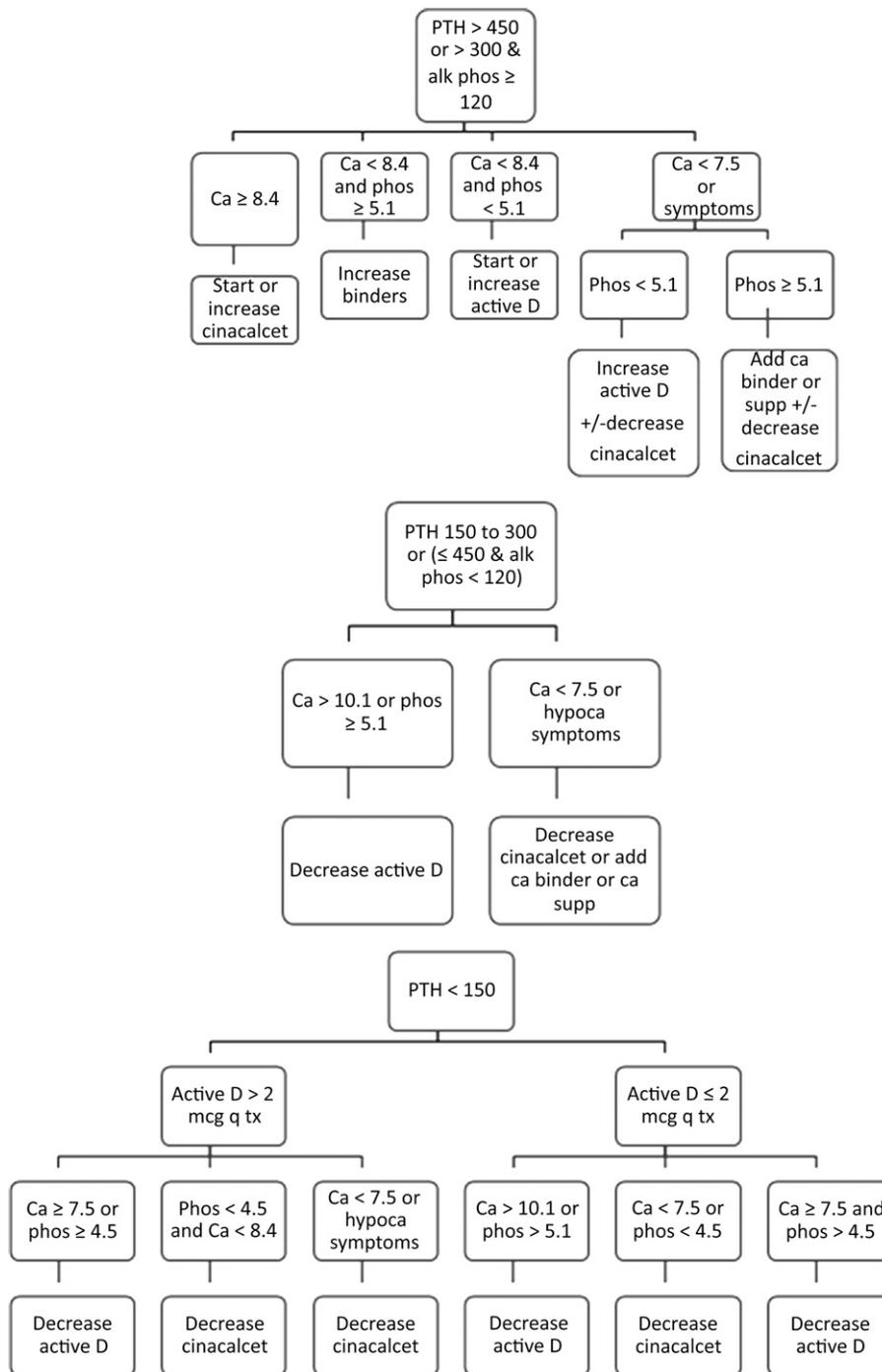

Figure 1. | Outline of mineral and bone algorithm used to adjust active vitamin D analogue and cinacalcet doses. Algorithm shown is a simplified version of complex computer code. alk, alkaline; Ca, calcium; hypoca, hypocalcemia; Phos, phosphorous; PTH, parathyroid hormone; supp, supplement; tx, treatment.

by the computer algorithm and approved by the local nephrologist. Calcium, phosphorus, and PTH, measured monthly as part of routine clinical practice, were used for study purposes, but calcium and phosphorus could be measured more frequently on the basis of clinical circumstances at the direction of the treating nephrologist. During the screening phase and the first month of data collection, laboratory values were measured before dialysis on the first treatment of the week. Because of changes in University of Virginia laboratory practice, chemistries were measured before dialysis at the midtreatment point during the rest of the study. The variation in phosphorus based on dialysis treatment schedule has been evaluated, and the reported difference between the first-of-the-week and midweek serum phosphorus concentrations do not significantly differ (difference, 0.001 mg/dl; M. Lazarus, personal communication).

The primary goal of the computerized algorithm was to achieve near-normal phosphorus (3.0–4.6 mg/dl), near-normal calcium (lower limit adjusted for cinacalcet use: 7.5–10.1 mg/dl), and PTH of ≥150 and ≤450 pg/ml, or ≤300 pg/ml if the total alkaline phosphatase was ≥120 IU/L.

The primary endpoints for the study were the proportion of patients achieving a phosphorus level of ≤5.5 mg/dl at 6 and 12 months compared with baseline and the proportion of patients achieving a PTH level of ≤300 pg/ml at 6 and 12 months compared with baseline. Secondary endpoints were as follows: proportion of patients achieving (1) a phosphorus level of 3.0–4.6 mg/dl at 6 and 12 months, (2) a calcium level of 7.5–10.1 mg/dl at 6 and 12 months, (3) a PTH level of 150–450 pg/ml at 6 and 12 months, and (4) all 3 of these endpoints in comparison with baseline values. For each time period, up to 3 months of data for each patient were averaged. Therefore, the average of months 4, 5, and 6 were considered the 6-month results, and months 10, 11, and 12 (12-month results) were compared with the baseline 3-month average before algorithm initiation.

Cinacalcet was provided free of charge and distributed monthly to the patients on the basis of recommendations from the computer algorithm and local physician approval. During the last 3 months of the study, patients were asked to bring their pill bottles back so that pill counts could be performed for estimation of drug adherence. Patients were categorized as nonadherent if their average prescribed pill intake for those 3 months was less than 75%. Doxercalciferol was the active vitamin D in use at the facility before study initiation and remained in use throughout the study period.

The doses of cinacalcet and doxercalciferol for month 12 were compared with the baseline dose at the time of algorithm initiation. The mean doses of both cinacalcet and doxercalciferol were calculated for patients receiving the medication only.

The McNemar test for paired longitudinal data was used for all statistical analyses to compare 6-month and end-of-study outcomes with baseline values. A P value less than 0.05 was considered to represent a statistically significant difference. This analysis compared patients at the prespecified time points with the same patients from the baseline time period. Although a formal power calculation was not performed, we reasoned that if the algorithm failed to produce clinically meaningful results in a population of close to 100 patients, it did not have clinical relevance (Graphpad Software, Inc., La Jolla, CA).

This study adhered to the principles of the Declaration of Helsinki and was approved by the institutional review boards of the University of Colorado and Centra Health. The trial is registered with ClinicalTrials.gov (identifier: NCT01100723).

Results

One hundred eighty-one patients were treated in the unit for all 3 baseline months. Of these, 65 did not meet enrollment criteria (34 were nursing home residents, 15 had low PTH and were not receiving treatment [9 of these after parathyroidectomy], 10 were unable to give informed consent, and 6 were grossly nonadherent with the dialysis regimen). Of the 116 who met entry criteria, 23 declined to participate and 1 had previously had an adverse event while receiving cinacalcet. A total of 92 patients gave written informed consent and were enrolled in the study. Two were withdrawn early: 1 because of gross nonadherence with the dialysis regimen and the other was diagnosed with sarcoidosis resulting in hypercalcemia. Ten patients died during the year-long follow-up (gross mortality rate, 10.9%). One patient underwent transplantation, and 3 transferred out (2 to other facilities and 1 to daily home hemodialysis). There were 85 patients with at least 1 month of laboratory data for the 6-month analysis and 78 patients with at least 1 month of data for the end-of-study analysis. Results for these patient subsets were compared with their baseline values.

Baseline demographic data are shown in Table 1. The mean age (± SD) was 61.7±11.9 years. Fifty-six percent of patients were male and 74% were black. Figure 2 shows the percentage of patients treated with active vitamin D and cinacalcet and the mean medication dose throughout the study period. At baseline, 80% of patients were receiving intravenous doxercalciferol at an average dose of 9.4±5.3 μg per week. At the end of study 57% of patients were receiving doxercalciferol; the average dose for those receiving the medication had decreased to 4.9±2.7 μg per week. Cinacalcet was prescribed to 41% of patients at baseline; this percentage increased to 84% by the end of study, and the average dose

Table 1. Demographic characteristics for 92 enrolled patients	
Characteristic	Data
Age (yr)	61.7±11.9
Dialysis vintage (yr)	5.2±3.3
Race/ethnicity	
black	68 (73.9)
white	23 (25.0)
other	1 (1.1)
Sex	
male	52 (56.5)
female	40 (43.5)
Cause of ESRD	
diabetes	33 (35.9)
hypertension	23 (25.0)
glomerular disease	28 (30.4)
other	8 (8.7)

Values expressed with a plus/minus sign are the mean ± SD. All other values are the number (percentage) of patients.
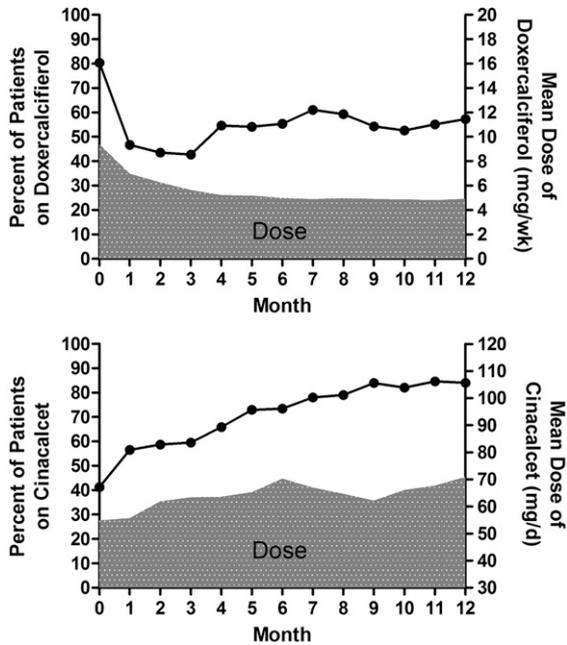
Figure 2. | Medication dosing over the study period. Percentage of patients receiving doxercalciferol (top panel, solid line, left axis) and cinacalcet (bottom panel, solid line, left axis) and the mean dose (right axes).

increased from 55 to 71 mg per day. Prescribed phosphate binder intake did not change significantly over the time period, increasing slightly from a baseline of 7.0±3.4 pills per day to 7.3±4.1 at 6 months and 7.3±4.0 at 12 months.

Figures 3 and 4 show the percentage of patients achieving the primary and secondary study endpoints at 6 and 12 months. The most dramatic improvement was the percentage of patients achieving the phosphorus targets at both 6 and 12 months. The percentage of patients achieving a phosphorus level of ≤5.5 mg/dl increased from 46% at baseline to 68% at 12 months (P=0.003), whereas those achieving a phosphorus level of 3.0–4.6 mg/dl increased from 18% to 37% (P=0.007). The percentage of patients achieving the primary PTH target of ≤300 pg/ml and the secondary calcium or PTH targets did not significantly change. The percentage of patients achieving all three secondary endpoints increased from 12.8% to 25.6% (P=0.04). Figure 5 shows the overall change in phosphorus, albumin-corrected calcium, PTH, and total alkaline phosphatase over the entire study period. Mean phosphorus values decreased over the first 5 months after protocol initiation, from a baseline average of 5.9±1.3 mg/dl, and remained well controlled over the entire study period, with an end-of-study average of 4.9±1.2 mg/dl. The albumin-corrected serum calcium concentrations also decreased over this time period, from 9.2±0.6 to 8.4±0.5 mg/dl. In contrast, mean PTH and total alkaline phosphatase values increased slightly over time, although the proportion of patients achieving the primary or secondary PTH targets did not change significantly (Figures 3 and 4).

During the study, the computer algorithm was run 1003 times (once per patient per month). On 454 of these occasions, the PTH level was greater than 450 pg/ml. In response to the elevated PTH, the algorithm called for an increase in cinacalcet dose 187 times, called for an increase in active

vitamin D dose 101 times, and did not increase the cinacalcet dose because of a calcium concentration less than 8.4 mg/dl 137 times. There were 25 other episodes when the cinacalcet was not increased for various reasons (see later discussion). Table 2 shows the percentage of time the algorithm-generated dosing changes took place by treatment quarter. As the study progressed, the percentage of time cinacalcet could not be increased because of hypocalcemia increased, whereas the number of times the dose was escalated decreased. The percentage of laboratory values that triggered an increase in active vitamin D dose did not change over the study period. PTH variability (defined as a sudden, unexplained increase or decrease in PTH) and decreases in PTH (decrease of >25% from the previous month) that the algorithm interpreted as resulting from the previous months intervention was an infrequent reason for not adjusting the cinacalcet dose when the PTH level was greater than 450 pg/ml, as were problems with medication tolerability or reaching the maximum cinacalcet dose. During the study the cinacalcet dose was decreased or discontinued 22 times for symptomatic or nonsymptomatic hypocalcemia.

Average adherence over the last 3 months of the study was 76%, and individual adherence ranged from less than 10% to close to 100%. For patients who returned their medication bottles, 15.4% were nonadherent (defined as < 75% of medication taken). Sixteen of the 78 patients in the end-of-study analysis would not or continually forgot to bring in their medication bottles. If these patients are considered nonadherent, then the percentage of patients nonadherent with their cinacalcet increased to 35.9%.

Discussion

This study was designed to test the hypothesis that a computer-driven algorithm incorporating both cinacalcet and active vitamin D analogues for the treatment of mineral disorders in ESRD would increase the percentage of patients achieving the predefined target outcomes. We found that when a dialysis facility is moved from a predominantly active D treatment protocol to a combination protocol, serum phosphorus concentrations decrease significantly and there was greater achievement of both the KDOQI phosphorus target and a normal phosphorus value. In addition, the percentage of patients achieving all three secondary endpoints significantly improved, although most of this improvement was due to the improvement in the serum phosphorus concentration.

To our knowledge, this is the first study to report on the prospective implementation of a computer dosing algorithm to manage mineral disorders in ESRD using a combination of cinacalcet and active vitamin D analogue. Although the improvement in phosphorus was significant, there was no overall improvement in PTH control. The primary reasons appear to be both inability to increase the cinacalcet dose because of hypocalcemia and patient nonadherence with oral medication (even though it was provided free of charge). In addition, the reduction in active vitamin D analogue dose may have resulted in the increase in PTH.

These findings are somewhat different from those reported in the cinacalcet phase III data and the postmarketing studies. The phase III trial targeted a PTH level of ≤250 pg/ml, and 43% of the cinacalcet-treated patients achieved this target (3). *Post hoc* data analysis showed that 56% of cinacalcet
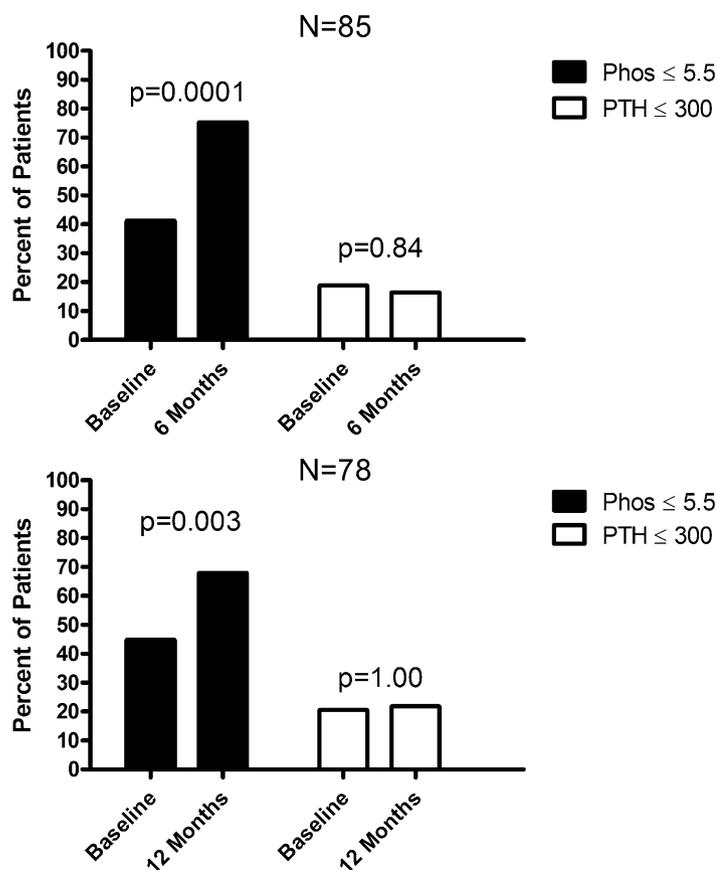
Figure 3. | **Primary outcomes for phosphorus and parathyroid hormone at 6 and 12 months compared with baseline data. N = number of patients included in the analysis.**

recipients met the modified KDOQI target of a PTH concentration of $\leq$300 pg/ml (4). Although our primary endpoint was a PTH level of $\leq$300 pg/ml, this was the treatment goal of the algorithm only if the total alkaline phosphatase level was $\geq$120 IU/L. If the alkaline phosphatase level was less than this value, the algorithm targeted a PTH concentration of $\leq$450 pg/ml. The percentage of patients achieving this target was 43.6%, similar to the percentage of patients meeting the primary PTH endpoint in the phase III trials.

In a trial of patients with PTH values of 300–800 pg/ml, cinacalcet-naive patients were treated with escalating doses of cinacalcet and the vitamin D analogue dose was reduced at study week 2 (5). In that trial, 44% of patients achieved the primary study endpoint of a PTH level of $\leq$300 pg/ml. Again, the percentage of patients achieving the target endpoint in the current study was similar even though a very high PTH level was not an exclusion criterion. A trial with a similar study design enrolled patients with controlled PTH values (150–300 pg/ml) but elevated calcium $\times$ phosphorus product (6). The addition of cinacalcet and reduction in vitamin D analogue dose maintained PTH control and significantly reduced the phosphorus concentration and the calcium $\times$ phosphorus product.

A prospective, randomized European study comparing cinacalcet plus active vitamin D with active vitamin D alone also showed improvement in the achievement of target values for PTH and phosphorus (7). In that study, patients were also

excluded if their PTH level was greater than 800 pg/ml, the cinacalcet dose was titrated every 2 weeks, and the cinacalcet dose could be increased as long as the albumin-corrected serum calcium was at least 8.0 mg/dl (7). Those investigators reported that 71% of the cinacalcet-treated patients achieved the target PTH level of $\leq$300 pg/ml (7). The difference in patient population and patient adherence, along with the lower calcium threshold for cinacalcet dose escalation may have accounted for some of the differences in achieved PTH outcomes.

Overall, there were two major differences between these trials and our current study. This study sought to achieve near-normal phosphorus and therefore used relatively low doses of active vitamin D analogues. More important, the previously published trials enrolled selected patients from multiple centers, whereas the current study sought to enroll all patients within a dialysis facility, excluding only those who were clearly not adherent with their dialysis treatment regimen, had a low PTH and were not receiving treatment, or were unable to give informed consent. Therefore, our data more likely represents results that could be achieved in routine clinical practice.

Austrian data from a multicenter European trial designed to look at the effects of cinacalcet in routine clinical practice reported that when cinacalcet was added to the treatment regimen, the percentage of patients achieving the KDOQI PTH target increased from 3% to 36% and the percentage of
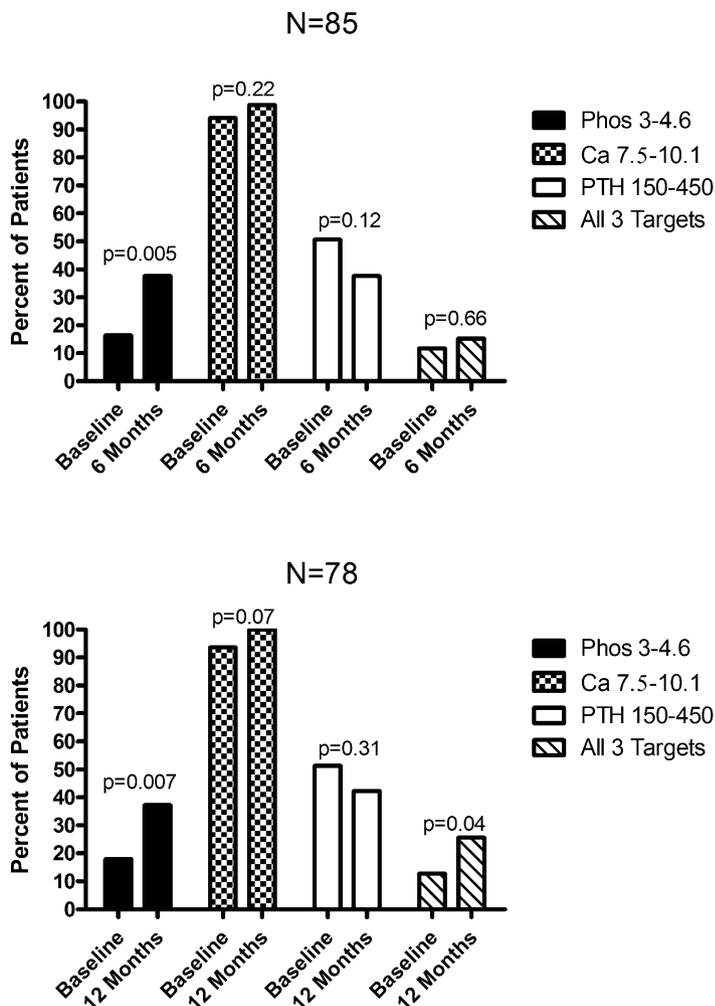
N=85

N=78

Figure 4. | Secondary outcomes for phosphorus (Phos), calcium (Ca), parathyroid hormone (PTH), and all three targets at 6 and 12 months compared with baseline data. *N* = number of patients included in the analysis.

patients achieving the phosphorus target increased from 24% to 39% (8). Italian results showed that the percentage of patients achieving the PTH target increased from 5% to 32% and the percentage achieving the KDOQI phosphorus target increased from 55% to 59% (9). These studies did not mandate a treatment algorithm, but both demonstrate the difficulty in achieving target outcomes in clinical practice even with combination therapy.

Our study has several limitations. It had no control group; therefore, it is possible that the improvements could have been due to a study intervention unrelated to the medication adjustments. The dietitians involved in the trial were actively involved with the patients before study entry, and we tried to mitigate this possibility by having the dietitians continue to provide their routine education and follow-up during the study period. It is possible that some of the changes in the serum phosphorus could have been due to the timing change of monthly chemistries from the beginning-of-the-week laboratory draw to midweek. However, the variation in phosphorus based on dialysis treatment schedule has been evaluated, and the reported difference in first-of-the-week and midweek serum phosphorus concentrations are negligible and could not account for the differences we observed.

Finally, it is possible that the marked decrease in active vitamin D dose recommended by the algorithm improved phosphorus control by decreasing intestinal phosphate absorption but worsened control of PTH. A different treatment algorithm, possibly one more aggressive with active vitamin D or more willing to use large doses of active vitamin D even if the phosphorus or calcium were elevated, could have produced better PTH control. However, we developed our algorithm according to the belief that phosphorus control is critical to the health of patients undergoing dialysis and that the optimal PTH target is less clear. It is also possible that continuing to escalate the cinacalcet dose if the serum calcium level is 8.0 mg/dl or greater, as done in the European trial (7) and is being done in the multicenter Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) study (10), would have produced better PTH control.

In summary, our study demonstrated that switching from a predominantly active vitamin D treatment regimen for the management of mineral disorders in ESRD to a computer algorithm that incorporates both cinacalcet and active vitamin D as first-line therapy significantly improved phosphorus control. The percentage of patients achieving the PTH targets did not improve. Further prospective testing against other
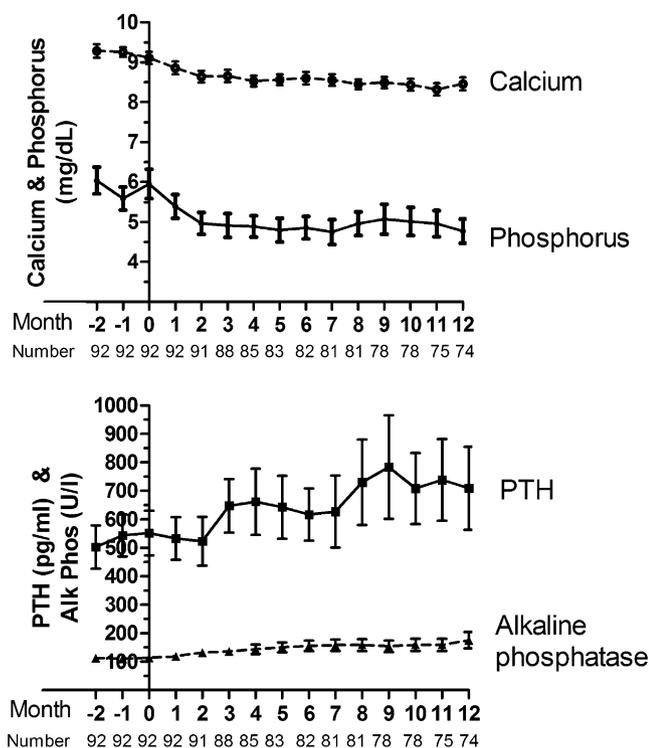
Figure 5. | **Serum calcium, phosphorus, parathyroid hormone, and total alkaline phosphatase over the study period.** *N* = number of patients in the study at each time period.

Table 2. Algorithm's recommendations for parathyroid hormone level greater than 450 pg/ml

Quarter	Increase in Cinacalcet Dose	Increase in Active Vitamin D Dose	Do Not Increase Cinacalcet Dose Because of:					
			Low Calcium	PTH Variability	PTH Decreasing	Intolerance	Off Medication	Maximum Dose
1st	40.2	15.2	23.7	13.6	0	1.6	2.7	3.3
2nd	34.8	23.2	22.5	7.3	3.6	3.6	0.7	4.4
3rd	30.8	16.5	27.1	6.7	6.0	6.0	2.3	4.5
4th	26.7	21.1	30.0	5.6	5.6	6.7	1.1	3.3

Values are percentage of patients who had their medications adjusted as indicated. "Off Medication" indicates that a patient was not taking the prescribed cinacalcet dose and therefore did not have the medication dose increased. "Maximum Dose" indicates that a patient was taking 180 mg of cinacalcet daily. PTH, parathyroid hormone.

protocols is needed to determine the best methods for controlling phosphorus, calcium, and PTH. This study also demonstrates that algorithms with differing endpoints or treatments could be used in randomized prospective trials to evaluate clinically meaningful patient outcomes.

The authors conducted the study independently and had full control of the trial conduct and the analysis and publication of the trial data and results.

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