Achievement of NKF/K-DOQI Recommended Target Values for Bone and Mineral Metabolism in Incident Hemodialysis Patients: Results of the FARO-2 Cohort

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Key Words

Mineral Bone Disorders · NKF/K-DOQI · Incident haemodialysis · Survival

Abstract

Background: Mineral Bone Disorders (MBD) is prevalent in hemodialysis (HD) patients and associated with increased cardiovascular mortality. The FARO-2 study evaluated the achievement of the NKF/K-DOQI guidelines on recommended target values for serum calcium (Ca), phosphorous (P) and intact parathyroid hormone (PTH) levels on survival in incident HD patients. **Methods:** Data were collected by questionnaire from 568 incident HD patients followed prospectively over a 3-year period from 26 Italian dialysis units. The cumulative probability of time-to-death for CKD-MBD treatment characteristics was determined by the Kaplan-Meier curves. **Results:** Serum PTH levels (median values at

6 months vs. 36 months; 225 vs. 254 pg/ml), Ca (8.8 vs. 8.9 g/dl) and P (5.1 vs. 4.8 mg/dl) were not significantly different at 6 months versus follow-up. The majority of incident HD patients (60–70%) who were followed up for 36 months did not achieve the NKF/K-DOQI recommended target values. Survival rates were higher in patients on target for three parameters versus patients off target (survival at 24 months: at target 95.7% (95% CI: 84.0–98.9) versus not on target 71.1% (95% CI: 66.3–75.4, $p < 0.01$)). The 30.1% of patients on target for three MBD parameters at least once during the follow-up period had better survival rates compared to those not reaching these targets (survival at 24 months: at least once 88.0% (95% CI: 81.9–92.1); 67.7% (95% CI: 61.9–72.8, $p < 0.01$)). **Conclusion:** Our findings indicate that incident HD patients who achieved target levels (for three MBD parameters) for at least one visit have a lower risk of mortality.

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Introduction

Despite therapeutic advances, mortality rates remain high among patients with chronic kidney disease (CKD), particularly those undergoing hemodialysis (HD) [1, 2]. The main cause of mortality in these patients is attributed to cardiovascular-related diseases [2]. However, patients with CKD are also affected by mineral and bone disorders (CKD-MBD), resulting in abnormalities in serum calcium (Ca), phosphorous (P) and parathyroid hormone (PTH) [3]. Changes in mineral metabolism have also been associated with higher rates of both all-cause and cardiovascular-related mortality [3–15]. The majority of HD patients are also deficient in the endogenous hormone, 1,25-dihydroxyvitamin D (calcitriol) often contributing to increased secondary hyperparathyroidism (SHPT) and consequently abnormal levels of Ca, P and PTH [16].

In 2003, the US National Kidney Foundation implemented The Kidney Disease Outcomes Quality Initiative (K/DOQI) international guidelines to establish target levels for serum PTH, Ca and P in an effort to help lower secondary hyperparathyroidism (SHPT)-related mortality [17]. Unfortunately, evidence suggests that these restrictive guidelines are difficult to achieve, especially over the long term [18, 19]. Since these guidelines were implemented, there has been an increased awareness of SHPT, in addition to the introduction of newer treatment options in clinical practice. Furthermore, clinical guidelines are available for optimal levels of serum markers of CKD-MBD, but target parameters are not achieved in many HD patients [20].

Among these, synthetic vitamin D receptor activators (VDRAs) have been developed, that are less hypercalcaemic and hyperphosphataemic compared to exogenous administration of calcitriol and other vitamin D metabolites, and are efficacious in treating patients with CKD-MBD [21, 22], and are now considered the standard therapy for CKD patients [23]. The use of VDRAs, such as calcitriol or the selective VDR activator paricalcitol, is also associated with improved survival in HD patients [15, 24–31].

Although several studies have examined the association between mineral levels and the impact of achievement of K/DOQI mineral target ranges on mortality rates in HD patients [3–6, 8–15, 19, 31, 32], only a few studies have been conducted to date on incident HD patients [33, 34]. Furthermore, evidence indicates that in incident HD patients, mortality rates are higher in the early stages (first 3–4 months) of dialysis, warranting studies in this setting

[35]. Therefore, the aim of this analysis of the FARO-2 study, a sub-group of the original FARO study [31, 36], was to assess SHPT management and alignment with K-DOQI target ranges [17, 37], on mortality rates on a subgroup of incident HD patients from the FARO study [31, 36].

Materials and Methods

Study Design

FARO-2 was undertaken in 26 dialysis centers across Italy. This observational study was performed on a subgroup of incident HD patients who participated in the FARO study (conducted between 2006 and 2007) [31, 36]. Subjects who started dialysis treatment during the FARO study, that is, those who had vintage dialysis of ≤ 8 months were included. Data were collected retrospectively through the use of 6 questionnaires (4 questionnaires were collected during the original FARO study between 2006 and 2007) and 2 additional questionnaires were collected during 2008 in the present study (FARO-2). Data are presented by semester from the beginning of dialysis (irrespective of the moment in which the patient entered into the FARO study). The follow-up period for each subject is a variable and ranged from a minimum of 6 months to a maximum of 3 years. All patients provided written informed consent and the study was approved by all local ethic committees.

Achievement of MBD K-DOQI Recommended Target Values

For patients with stage 5 CKD undergoing HD, the 2003 guidelines of the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation were used [17]. The 2009 Kidney Disease – Improving Global Outcomes (KDIGO) guidelines were not yet available at the time this study was undertaken [38].

Statistical Analysis

The proportion of patients achieving K-DOQI ranges for any one of the biochemical parameters (PTH, Ca or P) was calculated every 6 months; the proportion of patients achieving target K-DOQI ranges for all three parameters (tri-target) was also calculated likewise; the proportion of patients achieving tri-target at least once, was calculated over the entire follow-up period. Differences in the proportion of patients achieving target values over the study period were assessed by chi-squared for trend.

The Kaplan-Meier (KM) method was used to estimate the cumulative probability of all-cause mortality in all patients. KM survival estimates were also performed to assess the effect of achievement of K-DOQI target values on all-cause mortality. The KM survival analysis was performed at 24-month due to the low number of patients included in the last 12 months of observation. Given that the achievement of K-DOQI targets (for 'tri-target' and for 'at least once' on target) varies during the follow-up period, the risk time was divided into specific time contributions depending on when the K-DOQI target was achieved. Thus, survival curves were adapted to take into account this time-dependent variation of variables. In the case of the 'at least once' achievement, when this was achieved at a specific visit, then the patient remained in this group for all subsequent visits. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS (version 8.2 for Windows™, Cary, N.C., USA) and STATA (version 8.0, College Station, Tex., USA) software.

Table 1. Patient clinical characteristics

Clinical characteristic	Total (n = 568)	Females (n = 179)	Males (n = 389)	p value
General				
Age, years	65.5±15.2	65.5±15.8	65.5±15	>0.99
Height, cm	166.6±8.5	159.7±7.3	169.8±7	<0.0001
Body weight, kg	67.9±15	61.8±15.1	70.7±14.1	<0.0001
BMI, kg/m ²	24.4±4.9	24.4±5.7	24.4±4.5	>0.99
Dialysis vintage, months	3.3±1.7	3.4±1.7	3.3±1.8	0.53
Comorbid diseases				
Hypertension, n (%)	438 (77.1)	141 (78.8)	297 (76.3)	0.59
Ventricular hypertrophy, n (%)	314 (55.3)	102 (57)	212 (54.5)	0.64
Cardiovascular disease, n (%)	226 (39.8)	60 (33.5)	166 (42.7)	0.048
Vascular disease, n (%)	143 (25.2)	43 (24)	100 (25.7)	0.75
Coronary artery disease, n (%)	134 (23.6)	30 (16.8)	104 (26.7)	0.013
Diabetes, n (%)	134 (23.6)	47 (26.3)	87 (22.4)	0.36
Peripheral artery disease, n (%)	106 (18.7)	27 (15.1)	79 (20.3)	0.17
Dyslipidemia, n (%)	104 (18.3)	34 (19)	70 (18)	0.86
Cerebrovascular disease, n (%)	71 (12.5)	28 (15.6)	43 (11.1)	0.16
Biochemical parameters				
iPTH, pg/ml	284.9±265	330.7±354.6	264.7±211.4	0.0061
Serum phosphorus, mg/dl	5.2±1.4	5.3±1.4	5.1±1.4	0.11
Serum calcium, mg/dl	8.8±0.8	8.9±0.8	8.8±0.8	0.17
Hemoglobin, g/dl	10.9±1.2	10.8±1.3	10.9±1.2	0.37
Serum albumin, g/dl	3.5±0.7	3.5±0.7	3.5±0.7	>0.99

Data presented as mean ± SD or number and %. BMI = Body mass index; iPTH = intact parathyroid hormone. p values represent differences between male and female patients.

Results

Baseline Clinical Characteristics

Of the 610 subjects who were eligible for participation in the FARO-2 study, 7 subjects were excluded because they were referred to centers that did not adhere to the project, while 35 were excluded because they had an HD start date earlier than 8 months of the date of study enrollment, therefore not meeting the inclusion criteria. The total sample size was 568 subjects. Of the 568 patients who were included in the first survey (follow-up of 6 months), 128 patients (22.5%) were observed up to 36 months.

Patient demographic and clinical characteristics at baseline are presented in table 1. At the start of HD, the average age was 65.5 and 68% of patients were male. The average duration of HD recorded at study entry was 3 months. The majority of subjects (83.1%) had HD sessions 3 times per week. Most frequent comorbid diseases were hypertension (77%), ventricular hypertrophy (55.3%) and cardiovascular disease (39.8%). Significant

differences were observed between male and female patients for some parameters. Besides expected anthropometric differences (height and body weight), male patients had a greater prevalence of cardiovascular disease (42.7% vs. 33.5%, $p = 0.048$) and coronary artery disease (26.7% vs. 16.8%, $p = 0.013$) compared to females. In contrast, female patients were observed to have significantly higher baseline serum PTH levels compared to male patients (330.7 ± 354.6 vs. 264.7 ± 211.4 , $p = 0.0061$).

Levels of MBD Biochemical Parameters

Levels of serum PTH, Ca and P did not significantly change in patients over the 6 visits (table 2). However, analysis of patients who attended all 6 visits ($n = 128$) revealed a significant increase in serum calcium levels between 6 months and 36 months (8.9 ± 0.91 vs. 8.98 ± 0.64 , $p = 0.028$) (fig. 1a) and concomitant reduction in serum P levels (5.35 ± 1.51 vs. 4.91 ± 1.3 , $p = 0.005$) (fig. 1b). No significant change in serum PTH levels was noted (fig. 1c).

Table 2. Levels of PTH, P and Ca

Follow-up time, months	PTH, pg/ml			P, mg/dl			Ca, mg/dl		
	n	median	IQR	n	median	IQR	n	median	IQR
6	523	225	118–380	563	5.1	4.3–6.0	562	8.8	8.4–9.3
12	507	197	105–324	514	5.2	4.3–6.0	513	8.9	8.5–9.3
18	444	201	118–332	452	5.0	4.2–5.8	452	8.9	8.5–9.3
24	319	212	119–315	323	4.9	4.1–5.8	323	9.0	8.5–9.3
30	182	247	137–375	191	4.9	4.0–5.9	191	9.0	8.5–9.3
36	117	254	138–371	119	4.8	4.1–5.7	120	8.9	8.6–9.3

Ca = Serum calcium; P = serum phosphorus; PTH = parathyroid hormone; IQR = interquartile range.

Fig. 1. Levels of biochemical parameters at baseline and follow-up. Levels of Ca (a), P (b) and PTH (c) are shown for patients who attended all visits (n = 128). Levels of biochemical parameters are compared between 6 months and 36 months. p values denote statistically significant differences. **Fig. 2.** Proportion of patients achieving target ranges of PTH, P and Ca at 6 months versus 36 months. p values denote statistically significant differences.

MBD Biochemical Parameters and Achievement of K-DOQI Target Values

The proportion of patients achieving target ranges for PTH, Ca or P increased from the first visit (6 months) to the final visit (36 months), attaining statistical significance for Ca (fig. 2). The proportion of patients achieving the recommended targets for PTH, Ca and P (all three parameters on target) increased from 8.3% at baseline to 13.3% at the end of the follow-up period (36 months), this increase just failing to reach statistical significance ($p = 0.086$, table 3). When all semesters were considered together, the proportion of patients increased in a time-dependent manner over the course of the follow-up period (semester 1–6) (Chi-squared for trend = 5.6, $p = 0.018$). We next analyzed the proportion of patients who achieved levels of three biochemical parameters on target at least once during follow-up period. A significant increase was observed in the propor-

Table 3. Patients with three biochemical parameters on target (tri-target)

Follow-up time, months	Yes		No		Total, n
	n	%	n	%	
6	47	8.3	521	91.7	568
12	60	10.6	507	89.4	567
18	51	10.3	445	89.7	496
24	41	12.0	302	88.0	343
30	28	13.1	186	86.9	214
36	17	13.3	111	86.7	128

Table 4. Patients with three biochemical parameters on target at least once during follow-up

Follow-up time, months	Yes		No		Total, n
	n	%	n	%	
6	171	30.1	397	69.9	568
12	171	30.2	396	69.8	567
18	164	33.1	332	66.9	496
24	132	38.5	211	61.5	343
30	83	38.8	131	61.2	214
36	54	42.2	74	57.8	128

Fig. 3. The Kaplan Meier curve showing the survival rate of patients: tri-target. Survival estimates (all-cause mortality) for FARO-2 patients with three biochemical parameters on target. HD = Hemodialysis.

Fig. 4. The Kaplan Meier curve showing the survival rate of patients: tri-target. Survival estimates (all-cause mortality) for FARO-2 patients with three biochemical parameters on target at least once during the 36 months. HD = Hemodialysis.

tion of patients increasing from baseline to follow-up (30.1 vs. 42.2%, $p = 0.011$) and this increase was observed across all 6 semesters (Chi-squared for trend = 15.1, $p = 0.0001$) (table 4).

Survival in Patients on Target for MBD Biochemical Parameters

The survival rate at the end of the study was higher in incident HD patients on target for the three MBD parameters (tri-target) compared to patients off target (survival at 24 months: at target 95.7% (95% CI: 84.0–98.9) versus not at target 71.1% (95% CI: 66.3–75.4, $p < 0.01$))

(fig. 3). The time course presented in figure 3 shows that the event curves for patients on target for the three MBD parameters compared with those patients not on target had already separated as early as 6 months (clearly separating at 1 year), and continued to further diverge for the duration of the study. The proportion of patients on target for the three MBD parameters (30.1%) at least once during the 36 months of follow-up (see table 4) showed a better survival rate compared to those that never reached these targets (survival at 24 months: at least once 88.0% (95% CI: 81.9–92.1); 67.7% (95% CI: 61.9–72.8, $p < 0.01$)) (fig. 4).

Discussion

Previous studies have examined the effects of elevated Ca, P and PTH levels on mortality in hemodialysis patients [3–6, 8–15, 19, 31, 32, 39]. Although this analysis has also been extended to incident hemodialysis patients [33, 34], only a few studies have been conducted to date and none of these have been performed in Italy.

In this analysis of the FARO-2 study, we show that mortality rates at 24 months are associated with a reduction by as much as 25% in patients who achieved target ranges for three of the bone and mineral parameters (Ca, P and PTH) according to K/DOQI guidelines. Moreover, by attaining target ranges for the three parameters at least once over the survey, survival rates were still 20% greater than those never achieving the K/DOQI targets. The findings from our survival analysis support these previous studies and more importantly, extend our knowledge by demonstrating that the achievement of KDOQI targets over time is associated with a significant improvement in survival.

In our original FARO study [36], approximately two-thirds of all patients failed to achieve target PTH levels and nearly 90% failed to achieve the combined target of PTH, P, and Ca levels according to K/DOQI guidelines [17]. Likewise, in this analysis of the FARO-2 study, approximately 90% of patients failed to achieve combined and sustained target ranges. Although survival analysis emerging from our study underline that sustained achievement of combined target ranges over time is not essential to overall survival improvement (20% vs. 25%), collectively, these data indicate that the achievement of K/DOQI target ranges may be difficult for many CKD patients with SHPT. With this in mind, we also performed a retrospective analysis to determine how patients fared in terms of achievement of target ranges according to the newer KDIGO guidelines [38]. It is important to underline that while the target ranges for Stage 5 CKD HD patients for iPTH concentrations are 150–300 pg/ml according to K/DOQI guidelines [17], the newer KDIGO guidelines recommend maintaining PTH levels 2–9-fold the upper normal limit [38], corresponding to a range of 130–600 pg/ml [40]. As we would have expected, by following KDIGO guidelines the number of patients on target was increased. While only 35.9% of patients were on target for PTH levels according to K/DOQI guidelines, this proportion increased to 63% when KDIGO guidelines were adopted (see online suppl. table 1; for all online suppl. material,

see www.karger.com/doi/10.1159/000365386). Likewise, the proportion of patients with three biochemical parameters on target (tri-target) at least once was higher for KDIGO (46%) compared to K/DOQI guidelines (30.1%) and in patients who attained tri-target for all 6 visits (25.8% for KDIGO vs. 13.3% for K/DOQI; online suppl. table 2). Since KDIGO guidelines are less restrictive, a greater proportion of patients will likely have more severe hyperparathyroidism. Therefore, it was not surprising that our analysis also revealed a higher mortality rate in those patients who were never on target according to KDIGO ranges (46%) compared to K/DOQI (29.7%). Our findings indicate that while a reassessment of K/DOQI target ranges may be warranted to determine if they are perhaps too strict, tentative evidence from our retrospective analysis suggests that the newer KDIGO guidelines, particularly for the PTH range, are possibly too relaxed. Actually, a recent prospective observational study performed on 8,377 prevalent patients receiving intermittent hemodialysis therapy in France examined the association between mortality and serum concentrations of phosphate, calcium and PTH through KDIGO target ranges [41]. They concluded that a 'grey zone' exists where the precise biochemical targets are difficult to define, with the exception of avoiding extreme values. KDIGO did not recommend precise threshold values, but rather 'normal' laboratory values, which may differ from one PTH kit to another. This study also confirmed the relative risk of low iPTH values, as proposed by KDIGO recommendations [41–52].

One of the difficulties in achieving multiple K/DOQI targets consistently is that the majority of treatment approaches reflect a compromise between controlling PTH and controlling Ca and P [42]. Although newer therapies such as paricalcitol [43–47], as well as combined calcimimetic and VDRA therapy have been shown to enhance the ability of patients reaching KDOQI target values for biochemical parameters [48], their long-term safety and efficacy, and ultimately mortality rates, still needs to be verified in randomized controlled trials. The IMPACT study, a randomized controlled trial performed on 272 patients with SHPT on maintenance HD was recently undertaken with the aim of examining the efficacy and safety of paricalcitol compared to cinacalcet [49]. In this 28-week, multicenter, open-label Phase 4 study, participants received paricalcitol or cinacalcet plus low-dose vitamin D. Findings from this study revealed overall superiority of paricalcitol (56%) over cinacalcet (38.2%; $p = 0.01$) in the proportion of patients achieving PTH 150–300 pg/ml

[49]. Long-term randomized controlled trials are still needed to determine the extent that these therapies, administered in combination or as monotherapy provide survival benefit.

Two other studies have been performed to date that have examined the achievement of K/DOQI guidelines on incident HD patients [33, 34]. Although both studies had a large sample size (7,076 and 22,937 respectively), the follow-up period was only for 2 years. The proportion of patients achieving K/DOQI target ranges for individual mineral parameters was marginally less than what we observed for FARO-2 and these differences may be attributed to the difference in the follow-up period, heterogeneous population (75% of patients were incident HD in study by Tangri) [33] and a substantial proportion of patients were managed prior to 2003 K/DOQI updates.

One finding that emerged from our analysis was that female subjects had significantly elevated serum PTH levels at the first visit compared to their male counterparts. It is recognized that osteoporosis is more prevalent among women than among men and abnormalities in iPTH secretion play an important role in bone loss. Thus, hypersecretion of iPTH might be expected to be more pronounced in women than in men. An observational study by Haden and colleagues (2000) [50] demonstrated that the levels of serum PTH were higher in elderly women compared to elderly men. Although this study was performed on a healthy control population, perhaps these findings could be extended to patients with CKD. Indeed, in young healthy females, serum vitamin D levels can be lower than male subjects; this may be attributed to the differences in factors such as hormonal, muscle mass and bone density [51]. Interestingly, additional analysis of survival rates stratified by gender did not reveal any significant difference. This would imply that survival benefit in terms of patients attaining K/DOQI target ranges is distributed equally by gender, regardless of differences in biochemical parameters at baseline.

Study Limitations

Although findings from this analysis of the FARO-2 study provide clinical insights on the importance of attaining target ranges in incident HD patients, some weaknesses of this study do need to be addressed. Even though the number of patients at baseline was relatively large ($n = 568$), only a fraction of this population (one-quarter) attended all visits during the entire follow-up period ($n = 128$). Our analysis was based on all patients and as such

does not correct for changes in characteristics of patients who entered or left the study. However, we have also performed additional sub-analysis on patients attending all visits and observed a similar proportion of patients achieving K/DOQI target ranges. For some parameters (e.g., PTH), values were missing for some patients during the follow-up period as they were not requested by the nephrologist to be present or they were absent from the CRF. Target ranges for biochemical parameters were based on the 2003 guidelines of the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation [17], since the 2009 Kidney Disease – Improving Global Outcomes (KDIGO) guidelines were not yet available when this study was undertaken [38]. Despite the availability of the newer KDIGO guidelines, the majority of clinical practice still employs the KDOQI recommendations, thus maintaining the clinical relevance of the present findings. Visits were conducted every 6 months. More frequent visits (e.g., monthly) may have provided more detailed information with regard to associations between therapeutic management and changes in biochemical and mineral parameters. Regardless of these study limitations, several strengths of the FARO-2 study are worth highlighting. Our survey was based on an observation over a long period of time (36 months) on incident CKD patients undergoing HD treatment and to our knowledge is the longest follow-up period conducted to date examining the achievement of K/DOQI targets on survival. Second, FARO-2 was a multicentric study, ensuring our findings are representative of the entire Italian HD population.

Conclusion

Findings from FARO-2 indicate that control of the three bone and mineral metabolism markers PTH, P and Ca within target ranges recommended by KDOQI guidelines is associated with improved survival in incident HD patients, compared with controlling fewer markers. Although only 8% of patients were able to achieve K/DOQI targets for all three bone and mineral metabolism markers (30% achieved K/DOQI targets at least once over the study period), this equated to a notable 25% increase in survival after 2 years. However, considering the limitations of this observational design, the benefit of achieving K/DOQI targets, and the more recent KDIGO targets, on survival in incident HD patients still remains to be confirmed in long-term prospective randomized clinical trials.

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