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ORIGINAL ARTICLE

Achievement of 2009 and 2017 Kidney Disease: Improving Global Outcomes mineral and bone targets and survival in a French cohort of chronic kidney disease Stages 4 and 5 non-dialysis patients

Denis Fouque[1], Hubert Roth[2], Bernadette Darné[3], Jean-Louis Bouchet[4], Eric Daugas[5], Tilman B. Drüeke[6], Thierry Hannedouche[7], Guillaume Jean[8] and Gérard M. London[9], for the French Calcium and Phosphate Observatory

[1]Department of Nephrology, CH Lyon Sud, Univ Lyon, Lyon, France, [2]Department of Nephrology, Centre de Recherche en Nutrition Humaine Rhône-Alpes, Pôle Recherche CHU-Grenoble, Inserm U1055-Bioénergétique, Université J. Fourier, Grenoble, France, [3]Monitoring Force Group, Maisons-Laffitte, France, [4]Centre de Traitement des Maladies Rénales Saint-Augustin, Bordeaux, France, [5]HU-Paris Nord site Bichat, Paris, France, [6]Inserm U1018, CESP, Université Paris-Saclay, Université Paris-Sud, UVSQ, Villejuif, France, [7]Service de Néphrologie, Hôpitaux Universitaires de Strasbourg & Faculté de Médecine, Strasbourg, France, [8]NephoCare, Tassin-Charcot, Sainte-Foy-lès-Lyon, France and [9]Hôpital Manhes, Fleury-Mérogis, France

Correspondence and offprint requests to: Denis Fouque; E-mail: denis.fouque@univ-lyon1.fr; Twitter handle: @denisfouque1

ABSTRACT

Background. The aim of the third French Phosphorus and Calcium Observatory (Photo-Graphe® 3) was to assess the achievement of international Kidney Disease: Improving Global Outcomes (KDIGO) recommendations on optimal serum phosphate, calcium and parathyroid hormone (PTH) levels and possible associations with mortality in patients with chronic kidney disease (CKD).

Methods. This was a prospective, observational study conducted with nephrologists in France who were selected using a clustering approach. Adult patients with non-dialysis Stage 4 or 5 CKD and no kidney graft history were eligible. Data about clinical events, serum biochemistry and treatment were collected every 6 months for 2.5 years and 12 months thereafter. The Kaplan–Meier method was used for survival analysis and Cox proportional hazards model for identification of factors associated with survival.

Results. Overall, 566 CKD Stage 4 patients (men, 56%) and 153 CKD Stage 5 patients (men, 62%) were included. In Stage 4, only 14–15% patients achieved the three main 2009 KDIGO targets during the first 2 years and 22% at 2.5 years. In Stage 5 patients, the proportion remained <6% throughout. The percentages of patients achieving the three main 2017 KDIGO targets were slightly higher at each time point. Overall, 14% of Stage 4 and 10% of Stage 5 patients died in the observation period. Only age and haemoglobin level were significantly associated with risk of all-cause mortality.

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Conclusions. Few CKD patients achieved KDIGO mineral targets. Increased mortality risk was linked to older age and lower haemoglobin level, but not to serum calcium, phosphate or PTH targets.

Keywords: calcium, chronic kidney disease, KDIGO, phosphate, survival

INTRODUCTION

Advanced chronic kidney disease (CKD) is a powerful risk factor for all-cause and cardiovascular (CV) mortality [1]. A systematic review of 35 studies, published in 2009, showed that a significant part of the excessive risk of mortality (CV and all-cause mortality) and of CV events was associated with the mineral and bone disorder of CKD (CKD–MBD) [2]. This issue was mainly studied and reported in dialysis patients [2, 3].

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in the USA for CKD–MBD were published in 2003 [4]. The KDOQI guidelines focused and recommended to maintain serum phosphate, calcium and parathyroid hormone (PTH) within narrow ranges, although adherence to the recommended target ranges has proved challenging [5–8]. Six years later, the international Kidney Disease: Improving Global Outcomes (KDIGO) guideline for CKD–MBD became available, with serum phosphate, calcium and PTH targets different from those of the KDOQI guidelines [3]. However, the evidence supporting these guidelines has been challenged subsequently as it was mainly based on retrospective observational studies [9, 10]. Of particular concern is the fact that for non-dialysis-dependent CKD Stages 3–5, even observational evidence has remained scarce.

The 2009 KDIGO clinical practice guideline on the management of CKD–MBD was updated in 2017 and is intended to assist the practitioner caring for adults and children with CKD Stages 3–5, on long-term dialysis therapy, or with a kidney transplant [3, 11]. This guideline has been endorsed in Europe since 2010 [12]. However, effective management of CKD–MBD includes a substantial effort on the part of patients to be adherent with dietary restrictions, thrice daily doses of oral phosphate binders, and, for many patients, regular use of several other oral medications [13, 14]. Following the release of the 2009 KDIGO guideline, several studies have estimated the percentage of patients achieving 2009 KDIGO targets for CKD–MBD [15]. A recent report based on a large international sample of chronic haemodialysis patients showed that the treatment approaches for secondary hyperparathyroidism had changed between 1996 and 2011 and that serum PTH levels had increased in most countries [15]. To the best of our knowledge, no information is available on the proportion of patients who reach KDIGO target ranges in CKD Stages 3–5 before the initiation of renal replacement therapy [16, 17].

The main objective of the observational Photo-Graphe® 3 study in France was to estimate the percentage of CKD Stages 4–5 and 5D patients (patients with CKD requiring dialysis) who achieved the target ranges suggested by the 2009 KDIGO guideline. A secondary objective was to investigate the relationship between the control of mineral metabolism and patient outcomes. We report here the results of the study in non-dialysis CKD Stages 4–5 patients regarding the 2009 and 2017 KDIGO guidelines.

MATERIALS AND METHODS

Population

The French Phosphorus and Calcium Observatory (Photo-Graphe® 3) is a prospective, multicentre, epidemiological observational study undertaken by nephrologists in France. The primary objective of the study was to estimate the percentage of CKD patients achieving 2009 KDIGO recommendations for the three main, routinely measured parameters of calcium and phosphate metabolism [serum phosphate, serum calcium and serum intact PTH (iPTH)] over a 3.5-year follow-up period (once every 6 months for 2.5 years and then 12 months thereafter). Nephrologists working in public, private and community centres were invited to participate. A total of 70 active nephrologists included 736 subjects out of the theoretical sample size of 1328 non-dialysis patients. The theoretical sample size was calculated to obtain a 2.5% precision of a 95% confidence interval of the prevalence of patients achieving 2009 KDIGO recommendations. Nephrologists were selected using a clustering approach, where clusters (nephrologists) were randomly drawn, in respect of geographical distribution and type of practice. The study was proposed to nephrologists in chronological order in the drawn list, until the number of required clusters was reached. Patients were selected within each cluster in chronological order.

All adult patients referred for the first time to the nephrologist and with Stage 4 or 5 CKD who were not yet receiving dialysis therapy, and had no kidney graft history, were eligible.

Data collection

Clinical events, serum biochemistry data and information on the treatment of CKD patients were collected at the above fixed time points. The following data were retrieved: laboratory parameters [serum levels of C-reactive protein, phosphate, calcium, iPTH, alkaline phosphatase both total and bone-specific enzymes], 25-hydroxyvitamin D [25(OH)D], albumin, low-density lipoprotein cholesterol, ferritin, transferrin saturation, blood haemoglobin (Hb) concentration, glycated Hb level, demographics, blood pressure, CV and valvular calcifications, current treatments {medications to control serum phosphate, vitamin D [oral or intravenous (IV) route], erythropoiesis stimulating agent (ESA), IV iron, hypolipidaemic drug, antihypertensive, oral anticoagulant and anticonvulsive}, history of parathyroidectomy, hospitalizations, bone fracture and CV events. Patient status (on dialysis, dead, lost to follow-up, moved to another centre and kidney transplantation) was also recorded during follow-up. All laboratory evaluations were performed locally.

Patients were prospectively enrolled between October 2010 and October 2012. Data were collected every 6 months between October 2010 and April 2013 and then lastly in April 2014. Therefore, seven data collections were available for some patients included in October 2010, whereas patients included in October 2012 had a maximum of three data collections.

Data were entered in an electronic case report system (Photo-Graph™ software developed by Genzyme S.A.S. then Sanofi France). Data collected in each region were anonymized at each patient level and then centralized by regional coordinators. After regional data collection was completed, 19 regional electronic files were transferred after centre anonymization to the national coordinating centre for data processing. Thus, data collection was performed with respect to patient's anonymity at the regional and national levels. Inconsistencies were checked after consolidation of national data. The national coordinator

might ask for data correction or deletion. As data were handled in an anonymous way, data source verification was not planned. This study was conducted according to French regulatory rules and good clinical practices.

Statistical analysis

Statistical analyses were performed using SAS/STAT 14.1 (SAS Institute Inc., Cary, NC, USA). Statistical analysis is at the patient level. Patients who discontinued the study after the baseline visit were excluded from all survival analyses. Patients who started dialysis therapy or were transplanted or lost to follow-up were included in analyses to the point of study discontinuation. Statistical analyses were independently performed in each population (CKD Stage 4 and CKD Stage 5) except survival analysis.

Standard descriptive statistics were used for demographic, biological and clinical data, to determine mean and standard deviation for normally distributed data, and median and 25th and 75th percentile values for non-normally distributed data. No replacement of missing data was performed and, therefore, the number of patients with documented laboratory data may change according to the time point.

The percentage of patients achieving the three KDIGO targets, according to the 2009 and 2017 guideline, respectively, was estimated at inclusion and at each following determination (abnormal PTH value was defined as an iPTH value above the upper normal limit of the assay kit). The evolution of the percentage of patients achieving the main three KDIGO targets was evaluated using a generalized estimating equation (GEE) model on available data with a binomial distribution and a logit function. As the study was performed at the time of the 2009 KDIGO guideline, this analysis was restricted to the 2009 KDIGO targets. Furthermore, for serum phosphate and calcium levels and, at each data collection, patients were classified into three groups according to normal laboratory ranges: patients below, within and above normal ranges. Normal ranges were 2.15–2.55 and 0.9–1.4 mmol/L for serum calcium and phosphate, respectively.

In addition, for the analysis of the comparison with the 2017 KDIGO guidelines and starting from the 6-month time point, abnormal PTH was defined as two consecutive values above the upper normal limit of the laboratory kit or >5% increase in the second consecutive PTH determination compared with the previous one, whatever the interval between two time points. Modifiable factors were hyperphosphataemia and hypocalcaemia at the time of the second PTH determination.

The survival curves were plotted using the Kaplan–Meier method and the differences in survival were determined using a log-rank test. A Cox proportional hazards model was used to identify the factors measured at baseline and significantly associated with survival using a backward selection method. The backward selection was started with all variables significant at the 0.20 threshold level in univariate analysis and after the proportional hazards assumption has been checked. The significance level for removing an explanatory variable from the model was set at 0.10, with comparison between two adjacent models using Akaike's information criterion. Interactions between two variables were tested on the final model. All tested factors were recorded at inclusion.

RESULTS

Patient population

Overall, 566 CKD Stage 4 patients and 153 CKD Stage 5 patients were included. More than half of the patients were males: 316 (56%) CKD Stage 4 patients and 95 (62%) CKD Stage 5 patients. Patient characteristics at inclusion are shown in Table 1. After inclusion and whatever the time point, serum 25(OH)D was available in few patients and was not included in further analyses.

Achievement of KDIGO targets

The evolution of serum calcium and serum phosphate over time is displayed in Figure 1. The percentage of patients achieving the three main 2009 KDIGO targets remained between 14% and 15% during the first 2 years and slightly increased thereafter, reaching a maximum of 22% at 2.5 years in CKD Stage 4 patients, and remained <6% throughout the study in CKD Stage 5 patients. Slightly more patients fulfilled the three mains 2017 KDIGO targets whatever the time (Table 2).

In Stage 4, the percentage of patients achieving 2009 KDIGO targets for serum phosphate decreased over time ($P = 0.0001$), while no significant trend was observed over time either for calcium ($P = 0.90$), PTH ($P = 0.36$) or the three parameters combined ($P = 0.12$). In Stage 5, no significant trend was reported over time for serum phosphate ($P = 0.80$), calcium ($P = 0.47$), PTH ($P = 0.77$) or the three parameters combined ($P = 0.66$).

As expected, at each data collection and in both CKD stages, 2009 KDIGO targets were not fulfilled most often because serum calcium and phosphate levels were below and above KDIGO targets, respectively (Table 3).

Using the 2017 KDIGO guideline, abnormal PTH level corresponded mainly to two consecutive iPTH above the upper normal limit of the assay kit (Table 4). Whatever the time, >50% of the patients have an abnormal iPTH value. Moreover, >30% of the Stage 4 patients and >50% of the patients with abnormal iPTH have concomitant hyperphosphataemia and/or hypocalcaemia whatever the time (Table 4).

CKD–MBD-directed therapies at each data collection time point are displayed in Table 5. The number of patients receiving various treatments decreased over time for most drugs: any vitamin D sterol, any phosphate binder and any calcium salt; in contrast, cinacalcet slightly rose. However, for some time periods, the effective of patients is very low, precluding any reasonable interpretation.

Survival analysis

Median duration of follow-up was 23 (6; 36) months in CKD Stage 4 patients and 8 (3; 18) months in CKD Stage 5 patients. Over the study period, 34 (6%) patients with CKD Stage 4 and 41 (27%) with CKD Stage 5 started dialysis, and 16 (3%) patients with CKD Stage 4 patients and 7 (5%) patients with CKD Stage 5 underwent kidney transplantation. Overall, 81 (14%) patients with CKD Stage 4 and 15 (10%) patients with CKD Stage 5 died during the observation period. In addition, 126 (22%) patients with CKD Stage 4 and 31 (20%) patients with CKD Stage 5 were lost to follow-up at the end of the study. The 157 patients lost to follow-up were significantly older (median age 77 versus 73 years, $P < 0.001$) and less often patients with diabetes (10% versus 35%, $P < 0.0001$) than the other patients. No statistically significant differences in gender and glomerular filtration rate were observed between patients lost to follow-up and the others.

No statistically significant difference in survival was observed between the two CKD stages ($P = 0.10$) (Figure 2).

Age, history of CV disease, Hb and albumin levels, treatment with an ESA, IV iron and classes of serum phosphate and

Table 1. Characteristics of the patients at inclusion

Variables	CKD Stage 4 ($n = 566$)		CKD Stage 5 ($n = 153$)	
	n		*n*	
Male		316 (55.8)		95 (62.1)
Age (years)	566	74 (63; 81)	153	73 (59; 81)
Body mass index (kg/m^2)	355	26.5 (23.9; 30.1)	106	27.3 (23.2; 30.8)
Systolic blood pressure (mmHg)	447	142 (130; 156)	133	140 (134; 158)
Diastolic blood pressure (mmHg)	447	80 (70; 85)	133	80 (70; 86)
Estimated GFR (mL/min/1.73 m^2)[a]	566	22.4 (18.9; 25.8)	153	12.1 (10.5; 13.7)
Serum albumin (g/L)	455	38 (35; 41)	128	38 (35; 41)
Hb (g/dL)	506	12.1 (1.4)	142	11.4 (1.2)
Serum 25(OH)D (ng/mL)	457	61.0 (32.5; 90.0)	121	60.0 (39.0; 95.0)
Smoker	566		153	
Former		105 (18.6)		34 (22.2)
Current		36 (6.4)		20 (13.1)
Associated risk factors and disease	566		153	
Arterial hypertension		362 (64.0)		111 (72.6)
Diabetes mellitus		168 (29.7)		45 (29.4)
History of CV disease		234 (41.3)		57 (37.3)
Any CKD–MBD-directed therapy	566		153	
Active vitamin D		64 (11.3)		26 (17.0)
Native vitamin D		282 (49.8)		83 (54.3)
Calcium-free phosphate binder		17 (3.0)		23 (15.0)
Calcium-based phosphate binder		123 (21.7)		43 (28.1)
Any calcium salt		135 (23.9)		61 (39.9)
Cinacalcet		2 (0.4)		5 (3.3)
Other drug treatments	566		153	
ESA		129 (22.8)		64 (41.8)
IV iron		24 (4.2)		9 (5.9)
Antihypertensive drug		472 (83.4)		130 (85.0)

Continuous data are presented as mean ± standard deviation or median (25%; 75%); categorical data are presented as *n* (%) patients.
[a]GFR = glomerular filtration rate calculated using the modification of the diet in renal disease formula.

calcium at inclusion were associated with survival in univariate analysis (Table 6). In multivariable analysis, only two of those parameters were selected by the backward selection method: older age and lower blood Hb level were associated with an increased risk of overall mortality over the study period (Table 6).

DISCUSSION

This is the first study showing that it is quite difficult to achieve KDIGO CKD–MBD targets in patients with Stages 4 and 5 CKD. Patients with CKD are stratified using five stages based on glomerular filtration rate [3, 18], and taking into account the degree of albuminuria as well [18]. The CKD staging system is useful in many regards, including the prediction of the associated comorbidities [18]. A review of data from 19 general-population studies from 13 European countries showed considerable differences in both CKD Stages 1–5 and CKD Stages 3–5 prevalence across European study populations. The adjusted CKD Stages 1–5 prevalence varied between 3.31% in Norway and 17.3% in Northeast Germany. The adjusted CKD Stages 3–5 prevalence varied between 1.0% in Central Italy and 5.9% in Northeast Germany [19]. In this context, the Photo-Graphe® 3 is one of the most recent and largest European prospective studies, specifically aimed at assessing disturbances of phosphate, calcium and PTH metabolism.

The present analysis confirms that adherence to the recommended target ranges for serum PTH, phosphate and calcium remains challenging despite several therapeutic advances. In particular, the proportion of patients who achieved the individual 2009 KDIGO target, after 2 years and 3.5 years, for serum PTH was ∼25% and ∼10% in Stage 4 CKD and Stage 5 CKD, respectively. Note that the 2009 KDIGO guideline suggested not to routinely prescribe vitamin D supplements or vitamin D analogues, in the absence of suspected or documented deficiency, for the control of elevated PTH concentrations in people with CKD not on dialysis [20]. This could explain the high percentage of patients receiving no vitamin D supplement at inclusion in the present study.

The proportion of patients achieving the individual 2009 KDIGO target for serum phosphate decreased significantly from 74% at inclusion to 61% after 3.5 years in CKD Stage 4 and was mainly related to the increase in the percentage of patients with serum phosphate above the target range. This fact, not unexpected since the CKD progression leads to a further impairment in renal phosphate excretion, might have been limited through a more intensive control, including phosphate binders prescription. No significant trend over time was observed for that parameter in CKD Stage 5 patients. As to serum calcium, no significant trend was observed over time in the proportion of CKD patients who achieved the individual 2009 KDIGO target. However >80% of the patients, both in CKD Stage 4 and Stage 5, achieved the 2009 KDIGO calcium targets after 2 years of follow-up. With regards to serum PTH, <30% of patients in CKD Stage 4 and <20% of patients in CKD Stage 5 achieved the 2009 KDIGO targets at each time point.

Even if the 2017 KDIGO guideline had been used the conclusions regarding achievement of KDIGO objectives would have

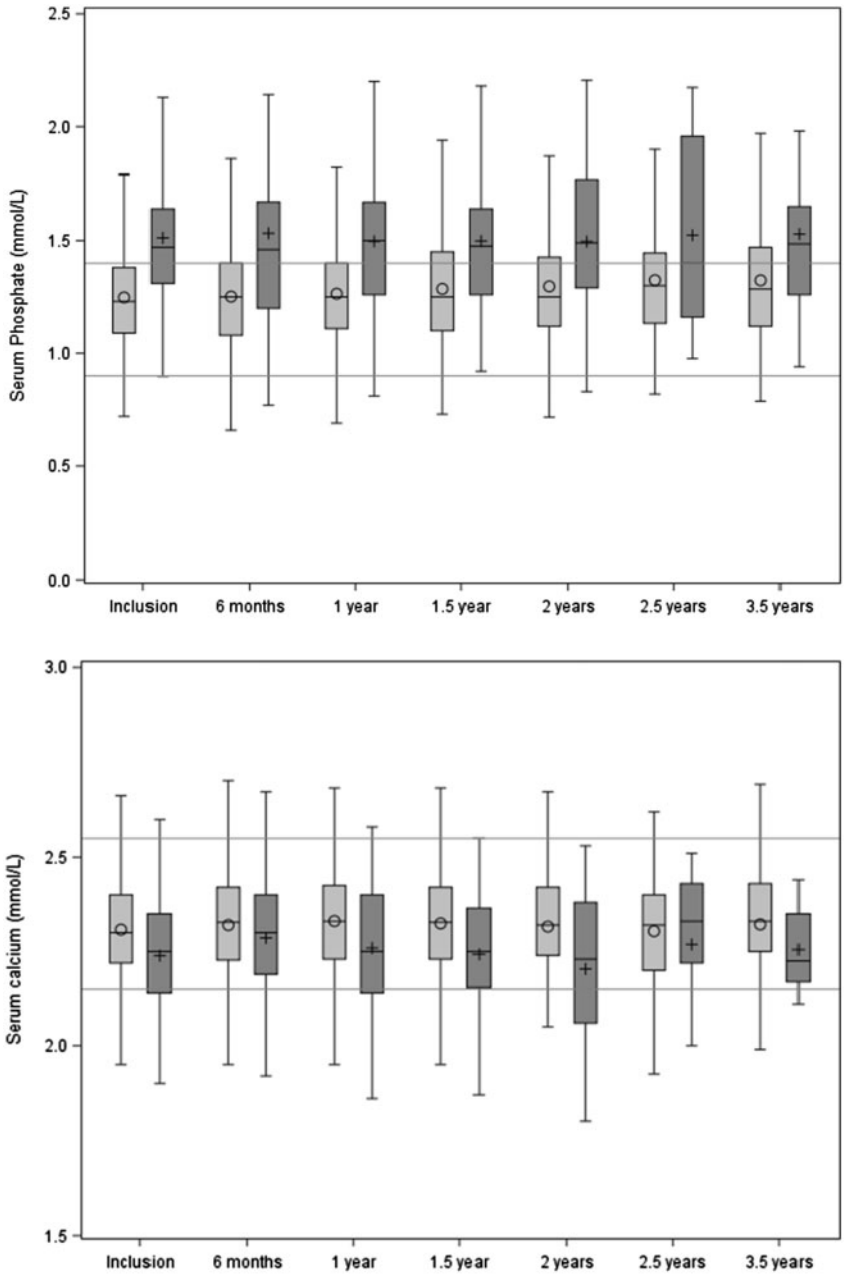

FIGURE 1: Serum phosphate and calcium levels over time. Horizontal lines correspond to lower and upper limit levels of normal. O indicate stage 4 CKD; + indicate stage 5 CKD.

likely been the same. Clearly, more studies are needed in order to understand the reason why so many CKD patients failed to achieve the KDIGO targets and to find out how guideline compliance can be improved, or to realize that the guideline may not be appropriate for very advanced stages of CKD.

Information obtained on 25(OH)D seems of interest. At inclusion, nearly 80% of CKD patients were assessed for serum concentration. However, the mean serum 25(OH)D was 60 ng/mL whatever the stage, quite below the 75 ng/mL minimal value, indicating that >60% of patients were vitamin D deficient. This is to be paralleled to the number of patients receiving a vitamin D supplement (50% at Stage 4 and 54% at Stage 5). Altogether, these data may suggest some improvement in care at these predialysis stages.

The longitudinal analysis of CKD–MBD-directed therapy reported a decrease in most prescribed drugs (Table 5). This is interesting to note because at the same time, the control for serum calcium, PTH and phosphorus could have been improved. It is important to point out this fact since these data have been obtained through a well-designed prospective longitudinal study, which further suggests that in the real life, results might have been even poorer.

As expected, more Stage 5 patients started dialysis than Stage 4 patients and underwent kidney transplantation over the

Table 2. Percentage of patients achieving the three main KDIGO targets of calcium and phosphate metabolism

Data collection	Inclusion	6 months	1 year	1.5 year	2 years	2.5 years	3.5 years
CKD Stage 4							
n patients with documented data	469	327	286	246	194	136	127
Patients achieving the three 2009 KDIGO targets (%)	67 (14.3)	50 (15.3)	41 (14.3)	36 (14.6)	28 (14.4)	30 (22.1)	23 (18.1)
Patients achieving the three 2017 KDIGO targets[a] (%)	84 (17.9)	59 (18.0)	53 (18.5)	42 (17.1)	31 (16.0)	33 (24.3)	26 (20.5)
CKD Stage 5							
n patients with documented data	139	83	57	35	21	14	9
Patients achieving the three 2009 KDIGO targets (%)	2 (1.4)	1 (1.2)	3 (5.3)	2 (5.7)	0	0	0
Patients achieving the three 2017 KDIGO targets[a] (%)	5 (3.6)	3 (3.6)	5 (8.8)	2 (5.7)	0	0	0

n (%) patients with available data. Starting from the third determination, the time between two determinations is 6 months or 1 year depending on time of patient inclusion in the study.

[a]Achievement defined as serial assessment and the three parameters less than the upper normal limit, for serum iPTH upper normal limit of the assay kit.

Table 3. Numbers (proportion) of patients within normal range for calcium and phosphate metabolism at each data collection time point

Data collection	Inclusion	6 months	1 year	1.5 year	2 years	2.5 years	3.5 years
CKD Stage 4							
Serum phosphate (mmol/L)							
Value unavailable	21	165	197	192	190	142	185
Hypo ≤0.9 (%)	31 (5.7)	27 (6.7)	25 (8.0)	15 (5.4)	14 (6.3)	6 (3.9)	9 (6.2)
Normal (%)	404 (74.1)	280 (69.8)	218 (70.1)	180 (65.0)	148 (66.4)	103 (67.8)	89 (60.9)
Hyper >1.4 (%)	110 (20.2)	94 (23.5)	68 (21.9)	82 (29.6)	61 (27.3)	43 (28.3)	48 (32.9)
Serum total calcium (mmol/L)							
Value unavailable	19	162	194	193	187	141	185
Hypo ≤2.15 (%)	69 (12.6)	54 (13.4)	37 (11.8)	37 (13.4)	27 (11.9)	22 (14.4)	17 (11.6)
Normal (%)	455 (83.2)	334 (82.7)	259 (82.5)	221 (80.1)	185 (81.9)	127 (83.0)	125 (85.6)
Hyper >2.55 (%)	23 (4.2)	16 (3.9)	18 (5.7)	18 (6.5)	14 (6.2)	4 (2.6)	4 (2.7)
Serum iPTH							
Value unavailable	90	233	220	221	216	156	201
≤ upper normal limit of the assay kit (%)	108 (22.7)	80 (24.0)	69 (24.0)	60 (24.2)	45 (22.8)	41 (29.7)	33 (25.4)
CKD Stage 5							
Serum phosphate (mmol/L)							
Value unavailable	2	56	67	84	83	67	78
Hypo ≤0.9 (%)	4 (2.6)	2 (2.1)	2 (3.3)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)
Normal (%)	54 (35.8)	42 (43.3)	22 (36.1)	16 (40.0)	8 (34.8)	8 (50.0)	4 (40.0)
Hyper >1.4 (%)	93 (61.6)	53 (54.6)	37 (60.6)	24 (60.0)	14 (60.9)	8 (50.0)	6 (60.0)
Serum total calcium (mmol/L)							
Value unavailable	2	56	67	84	83	68	78
Hypo ≤2.15 (%)	44 (29.1)	24 (24.7)	18 (29.5)	10 (25.0)	7 (30.4)	3 (20.0)	2 (20.0)
Normal (%)	102 (67.6)	65 (67.0)	42 (68.9)	30 (75.0)	16 (69.6)	12 (80.0)	8 (80.0)
Hyper >2.55 (%)	5 (3.3)	8 (8.3)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serum iPTH							
Value unavailable	14	70	70	88	85	69	79
≤ upper normal limit of the assay kit (%)	15 (10.8)	9 (10.8)	9 (15.5)	5 (13.9)	2 (9.5)	1 (7.1)	1 (11.1)

n (%) patients with documented data.

study period (27% versus 6% and 5% versus 3%, respectively). Overall, 81 (14%) patients with CKD Stage 4 and 15 (10%) patients with CKD Stage 5 died within 3.5 years. In the 20th century, CKD replaced infection and malnutrition as leading causes of mortality in the general population [21]. Individuals with CKD have an increased risk of all-cause mortality, mainly from CV disease [2, 22]. Somewhat surprisingly, the 1- and 2-year survival rates (68% and 47%) among CKD Stage 5 patients aged >75 years and not undergoing dialysis were found to be lower than survival rates of patients receiving dialysis therapy (84% and 76%), suggesting a selection bias in patients referred to maintenance dialysis [23]. However, even early CKD patients have poorer survival than people of comparable age in the general population, with ∼25% among them dying before reaching end-stage kidney disease [24].

The present study has several limitations. First, centres that participated on a voluntary basis were likely to be more interested in correcting CKD–MBD in their patients than those who did not join the study group. On the other hand, the high number of unavailable CKD–MBD laboratory parameters suggests that even in that population, compliance to the guidelines for the management of those patients is low. Secondly, the percentage of patients lost to follow-up over 3.5 years was 22% in patients with CKD Stage 4 and 20% in patients with CKD Stage 5.

Table 4. Numbers (proportion) of patients with abnormal iPTH levels (KDIGO 2017) at each follow-up

Data collection	6 months	1 year	1.5 year	2 years	2.5 years	3.5 years
CKD Stage 4						
n evaluable patients	333	288	248	197	138	130
Above the upper normal limit of the laboratory kit (%)	208 (62.5)	156 (54.2)	150 (60.5)	124 (62.9)	71 (51.5)	75 (57.7)
>5% increase (%)	44 (13.2)	53 (18.4)	33 (13.3)	24 (12.2)	33 (23.9)	25 (19.2)
Not abnormal (%)	81 (24.3)	79 (27.4)	65 (26.2)	49 (24.9)	34 (24.6)	30 (23.1)
Modifiable factors[a]						
Hyperphosphataemia (%)	47 (18.7)	40 (19.1)	38 (20.8)	30 (20.3)	20 (19.6)	29 (29.3)
Hypocalcaemia (%)	23 (9.2)	16 (7.7)	10 (5.5)	8 (5.4)	7 (6.9)	7 (7.1)
Both (%)	11 (4.4)	8 (3.8)	17 (9.3)	8 (5.4)	8 (7.8)	5 (5.1)
CKD Stage 5						
n evaluable patients	83	58	36	21	14	9
Above the upper normal limit of the laboratory kit (%)	68 (81.9)	40 (69.0)	25 (69.4)	16 (76.2)	9 (64.3)	6 (66.7)
>5% increase (%)	5 (6.0)	3 (5.2)	4 (11.1)	1 (4.8)	3 (21.4)	0
Not abnormal (%)	10 (12.1)	15 (25.8)	7 (19.4)	4 (19.0)	2 (14.3)	3 (33.3)
Modifiable factors[a]						
Hyperphosphataemia (%)	26 (35.6)	17 (39.5)	11 (39.3)	5 (29.4)	3 (25.0)	3 (50.0)
Hypocalcaemia (%)	3 (4.1)	2 (4.7)	3 (10.1)	1 (5.9)	0	1 (16.7)
Both (%)	16 (21.9)	13 (30.2)	6 (21.4)	6 (35.3)	3 (25.0)	1 (16.7)

n (%) patients; abnormal iPTH: two consecutive determinations above the upper normal limit of the assay kit or >5% increase in the second consecutive PTH determination compared with the previous one.

[a]On the subgroup of patients with abnormal iPTH. Hyperphosphataemia or hypocalcaemia at the time of the second PTH determination.

Table 5. CKD–MBD-directed therapy at each data collection time point

Data collection	Inclusion	6 months	1 year	1.5 year	2 years	2.5 years	3.5 years
Stage 4							
Number of patients	566	566	508	469	413	294	331
Any vitamin D sterol (%)	313 (55.3)	245 (43.3)	202 (39.8)	189 (40.3)	153 (37.1)	106 (36.1)	103 (31.1)
Any phosphate binder (%)	152 (26.9)	118 (20.9)	90 (17.7)	83 (17.7)	72 (17.4)	48 (16.3)	53 (16.0)
Any calcium salt (%)	135 (23.9)	107 (18.9)	80 (15.8)	71 (15.1)	64 (15.5)	38 (12.9)	42 (12.7)
Cinacalcet (%)	2 (0.4)	3 (0.5)	3 (0.6)	6 (1.3)	5 (1.2)	5 (1.7)	8 (2.4)
Stage 5							
Number of patients	153	153	128	124	106	83	88
Any vitamin D sterol (%)	97 (63.4)	61 (39.9)	45 (35.2)	32 (25.8)	17 (16.0)	12 (14.5)	6 (6.8)
Any phosphate binder (%)	84 (54.9)	53 (34.6)	38 (29.7)	26 (21.0)	13 (12.3)	10 (12.1)	8 (9.1)
Any calcium salt (%)	61 (39.9)	40 (26.1)	26 (20.3)	17 (13.7)	8 (7.6)	6 (7.2)	6 (6.8)
Cinacalcet (%)	5 (3.3)	3 (2.0)	4 (3.1)	2 (1.6)	2 (1.9)	1 (1.2)	1 (1.1)

n (%) patients receiving the corresponding therapy at each data collection time point.

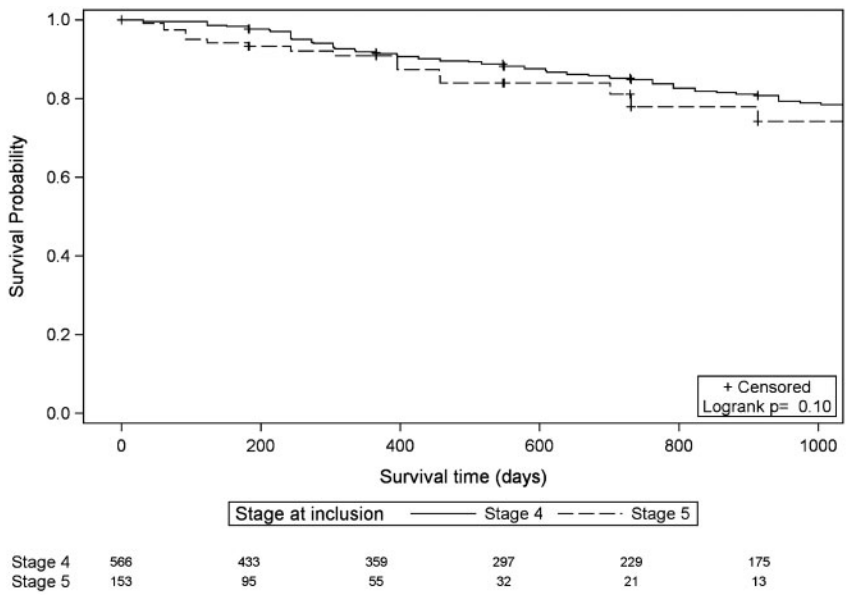

FIGURE 2: Survival of patients with CKD Stages 4 and 5. Product-limit survival estimates with number of subjects at risk in in each CKD stage.

Table 6. Univariate and multivariate Cox proportional analysis with overall mortality

		Univariate analysis			Multivariate analysis		
Variable	Number of observations used	Hazard ratio	95% CI	P-value	Hazard ratio	95% CI	P-value
Female sex	719	0.74	0.49–1.10	0.13			
Age (years)	719	1.08	1.06–1.10	$<10^{-4}$	1.09	1.06–1.11	$<10^{-4}$
History of CV disease: yes	719	2.24	1.49–3.35	$<10^{-4}$			
Hb (g/dL)	648	0.82	0.71–0.95	$<10^{-2}$	0.78	0.67–0.92	$<10^{-2}$
Serum albumin (reference ≥39.5 g/L)							
Serum albumin ≤33	583	2.49	1.35–4.59	$<10^{-2}$			
Serum albumin (33.1–36.9)	583	1.63	0.84–3.16	0.15			
Serum albumin (37.0–39.4)	583	1.42	0.75–2.69	0.28			
Diabetes mellitus: yes	719	1.27	0.86–1.89	0.23			
Serum phosphate, 2009 KDIGO classes	696			0.10			
Phosphate (mmol/L) ≤ 0.9		0.51	0.16–1.63	0.26			
Phosphate (mmol/L) > 1.4		1.43	0.94–2.18	0.09			
Serum total calcium, 2009 KDIGO classes	698			0.03			
Calcium (mmol/L) ≤ 2.15		1.85	1.16–2.96	0.01			
Calcium (mmol/L) > 2.55		0.88	0.28–2.78	0.83			
Serum iPTH: achieved 2009 KDIGO target (≤ upper normal limit of the assay kit)	615	0.89	0.54–1.48	0.66			
ESA: yes	719	1.97	1.34–2.91	$<10^{-3}$			
IV iron: yes	719	2.10	1.06–4.16	0.03			
Hypertension: yes	719	1.31	0.80–2.14	0.28			

All variables are variables measured at inclusion. CI, confidence interval.
Backward selection was started with all variables significant at the 0.20 threshold level in univariate analysis. The significance level for removing an explanatory variable from the model was set at 0.10, with comparison between two adjacent models using Akaike's information criterion. Interactions between two variables were tested on the final model.

Such relatively high rates may have biased our interpretation of the results; loss to follow-up of ≤10% would have been desirable. Patients lost to follow-up were significantly older than those who remained in the study. Missing information on them was probably mainly due to deaths unknown to the treating physician. Because of the small number of deaths, the power of the survival analysis was low, but the survival curves are in favour of no real difference in all-cause mortality risk between CKD Stage 4 and CKD Stage 5 patients.

In conclusion, the present study shows that only few patients eventually achieved the 2009 KDIGO targets. In the present study older age and lower blood Hb levels, but abnormal serum calcium, phosphate or PTH, were not associated with an increased risk of all-cause mortality.

With the inherent limitation of its small size and the possibility that some patients have been lost to follow-up because of death, this study does not support that the achievement of KDIGO CKD–MBD targets is associated with better survival in patients with CKD Stage 4 or 5.

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CONFLICT OF INTEREST STATEMENT

Sanofi did not interfere with the statistical analysis. D.F. served as national coordinator and received honoraria from Sanofi for travel and lectures. H.R. reports personal fees from Sanofi during the conduct of the study and grants from Genzyme outside the submitted work. E.D. declares having served as consultant for Amgen, Sanofi, Shire and Astra Zeneca, and having received speaker honoraria from Amgen and Sanofi, and having received travel grants from Sanofi, Roche, Shire and Alexion. T.B.D. declares having served as consultant for Amgen, F. Hoffman-La Roche, FMC, Sanofi-Genzyme and Vifor, and having received speaker honoraria from Amgen, Kyowa Hakko Kirin and Sanofi-Genzyme. B.D., T.H., G.M.L., G.J. and J.-L.B declared no competing interests.

LIST OF COORDINATORS

B. Dallaporta, B. Vendrely, C. Delcroix, D. Joly, E. Daugas, E. Laruelle, G. Choukroun, G. Jean, H. Leray Moragues, L. Azzouz, M. Essig, M. Hammadi, M. Kessler, M. Touam, P. Bories, P. Brunet, P. Henri, P. Zaoui, R. Azar, S. Delbes, T. Hannedouche, V. Esnault.

LIST OF PHYSICIANS

A. Abbassi, M. Abtahi, C. Achard Hottelart, H. Adda, G. Al Chahin, B. Al Jalaby, I. Al Moubarak, M. Al Rifai, M. Aladib, N. Albeiriss, S. Albitar, J. Aldigier, F. Alenabi, A. Amaouche, C. Araujo, U. Assogba, L. Azeroual, D. Babici, B. Ball, S. Bally, E. Barga, F. Basse, N. Bassilios, J. Batho, C. Baudeau, M. Bauwens, D. Bazin, B. Ben Taarit, S. Benarbia, J. Bendini, F. Berge, P. Bernadet, J. Bertheleme, F. Besson, S. Billion, A.

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Blanpain, C. Bonniol, C. Boriceanu, J. Bosc, B. Bouali, K. Boubenider, L. Boudier, J. Bouet, M. Bouiller, M. Boukelmoune, Z. Boukhalfa, R. Boula, H. Boulanger, J. Bourdenx, F, Bourdon, F. Bournerias, E. Bourry, P. Bouvier, M. Bouzernidj, M. Brahimi, B. Branger, M. Brucker, I. Brunak, S. Burtey, E. Caniot, J. Cardozo, M. Catoliquot, L. Chalabi, F. Chantrel, L. Chenine, P. Choulet, G. Cimarelli, M. Ciobotaru, K. Clabault, P. Clavel, O. Coldefy, J. Cridlig, C. Dabot, A. Dahmani, S. Darre Plat, D. Daubresse, J. De Fremont, R. De La Faille, V. De Precigout, F. Dehais, M. Dehina, C. Delclaux, P. Deleaval, S. Deleuze, C. Denicola, C. Deprele, T. Dervaux, J. Devaux, A. Diddaoui, C. Diet, Y. Dimitrov, V. Drouillat, P. Dubot, J. Dueymes, A. Duhem, A. Duveault, F. Easy, N. El Esper, K. El Nasser, C. Epron, B. Fadel Babba, J. Faucon, A. Faure, M. Fen Chong, H. Fessi, M. Ficheux, D. Fleury, M. Fodil, D. Fouque, P. Fournier, B. Franko, L. Frantzen, R. Fraoui, F. Frejate, L. Fromentin, H. Gaid, A. Ganea, C. Gaudry, J. Gaultier, E. Gauthier, M. Gavard, R. Genin, T. Ghafari, N. Ghali, A. Ghazali, B. Gilson, P. Giraud, A. Girault Lataste, P. Grimal, C. Guedon, B. Guery, C. Guibergia, M. Guimont, C. Hacen, S. Haddad Lekhal, A. Haddj El Mrabet, M. Hadj Abdelkader, A. Hafi, P. Halin, P. Hallonet, N. Hamdini, M. Hanoy, S. Helou, P. Hiernaux, D. Hristea, M. Isnard, D. Jacq, M. Jamali, D. Jaubert, C. Jolimoy, A. Jolivot, A. Karame, S. Kaysi, A. Keller, E. Kernaonet, R. Khayat, Z. Koochaki Pour, N. Kossari, F. Kriaa, C. Lamotte, B. Lamy Cavalerie, P. Lan Yue Wah, I. Landru, A. Laradi, N. Larroumet, R. Latif, F. Lavainne, O. Lavelle, B. Legallicier, N. Legros, M. Leteif, H. Lokmane, A. Lyon, M. Maaz, S. Mailliez, H. Maiza, G. Majdalani, E. Maksour, E. Marcu, M. Marraoui, S. Martin, V. Masson Charmoille, F. Maurice, D. May, B. Mayor, O. Mazouz, H. Mehamha, S. Mehrbanian, H. Merault, G. Messier, P. Michaut, C. Michel, P. Michel, O. Milioto, H. Mohey, R. Monkam, O. Moranne, I. Mpio, B. Muniz, E. N Sembani, F. Nemmar, S. Neuville, F. Ngopa, P. Nicoud, J. Nogaro, J. Ollier, J. Ottavioli, M. Ouziala, B. Painchart, P. Palacin, A. Pardon, C. Passeron, F. Perrin, P. Pointet, A. Pommereau, J. Poux, V. Pradier, O. Puyoo, W. Qin Guillon, C. Quere Maurouard, M. Rabec, N. Rabot, A. Rachi, M. Reberolle, H. Renaud, E. Renaudineau, F. Reynaud, E. Ricard Sutra, S. Richter, P. Rieu, M. Rince, A. Robert, C. Rosati, J. Rottembourg, S. Roueff, P. Rousseau, A. Sahar, F. Saidani, S. Saksi-Ahriz, D. Sarret, T. Sawadogo, F. Schott Moussion, P. Sebahoun, E. Semjen, P. Seris, T. Serrato, R. Sharobeem, M. Shenouda, D. Simonin, K. Sirajedine, A. Skandri, M. Smati, N. Soltani, A. Stolz, T. Tanquerel, D. Teboulle, B. Temperville, P. Thomas, A. Tifoura, D. Touzard, L. Tricot, P. Urena Torres, J. Valentin, H. Van Der Pijl, M. Vanel, C. Vela, J. Verdier, D. Verhelst, I. Vernier, G. Vernin, C. Verove, S. Vido, E. Villar, B. Viron, F. Vocila, F. Von Ey, J. Wauquier, B. Wehbe, M. Wong-Fat, D. Yousfi, M. Youssef.

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