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ORIGINAL ARTICLE

Achievement of Kidney Disease: Improving Global Outcomes mineral and bone targets between 2010 and 2014 in incident dialysis patients in France: the Photo-Graphe3 study

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Abstract

Background: Abnormal serum phosphate, calcium and parathyroid hormone (PTH) levels in patients with chronic kidney disease (CKD) undergoing haemodialysis have been associated with poor survival. The French Phosphorus and Calcium Observatory (Photo-Graphe® 3) aimed to estimate the percentage of CKD patients achieving the three Kidney Disease: Improving Global Outcomes (KDIGO) targets about optimal serum phosphate, calcium and PTH over a 3.5-year follow-up period.

Methods: This was a prospective, multicentre, epidemiological observational study conducted with nephrologists in France, selected using a clustering approach. Eligible patients were adults undergoing intermittent haemodialysis or haemodiafiltration therapy started within the preceding 12 months. Data about clinical events, serum biochemistry and treatment were collected once every 6 months for 2.5 years and 12 months thereafter.

Results: Overall, 9010 incident patients were included (men, 63%; median age, 71 years) of whom 7515 (83.4%) were treated by haemodialysis and 1495 (16.6%) by haemodiafiltration. None had a history of fracture or revascularization while 89 (1%) patients had a history of parathyroidectomy >6 months. Overall, 874 (10%) patients received a kidney graft, 2183 (24%) died and 1148 (13%) were lost to follow-up. The proportion achieving the three KDIGO targets increased significantly from 11% to 16% ($P < 0.0001$) until Year 2, but remained stable afterwards. The percentage of incident dialysis patients with normal serum phosphate ($P < 0.0001$) or normal serum calcium ($P < 0.0001$) levels increased significantly over time, while no significant change was observed for those with controlled PTH.

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Conclusion: Less than 20% of patients achieved the KDIGO recommendations although their proportion increased slightly over time.

Key words: calcium, haemodialysis, KDIGO, parathyroid hormone, phosphate, survival

Introduction

As kidney function declines the maintenance of mineral homeostasis becomes increasingly difficult, with a disruption of normal serum and tissue concentrations of phosphate and calcium, and abnormal circulating and tissue levels of hormones and growth factors [1].

Abnormalities of mineral and bone metabolism—the so-called 'CKD–MBD' for 'chronic kidney disease–mineral and bone disorder'—are common in haemodialysis patients and have been associated with poor survival [2–5]. The bulk of evidence shows that both high and low levels of serum phosphate, calcium and parathyroid hormone (PTH), as well as high levels of fibroblast growth factor-23 (FGF23) and low levels of α-Klotho, are associated with an increased risk of cardiovascular morbidity and mortality [6–10].

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in the USA for bone metabolism and disease in CKD were published in 2003 [11]. The KDOQI guidelines recommended to maintain serum phosphate, calcium and PTH within narrow ranges, although adherence to the recommended target ranges has proved to be challenging [12–16]. Six years later, the international Kidney Disease: Improving Global Outcomes (KDIGO) guideline for CKD–MBD became available, with serum phosphate, calcium and PTH targets being different from those of the KDOQI guidelines [3] (Table 1). The KDIGO clinical practice guideline of 2009 suggested to maintain serum calcium within the normal range, to lower elevated serum phosphate levels toward the normal range and to maintain serum PTH in the range of two to nine times the upper normal limit of the various assays used for its measurement. The evidence supporting these two guidelines has, however, been challenged subsequently as it was mainly based on retrospective observational studies.

The 2009 KDIGO clinical practice guideline on the management of CKD–MBD is intended to assist the practitioner caring for adults and children with CKD Stages 3–5, on maintenance dialysis therapy, or with a kidney transplant [3]. This guideline has been endorsed in Europe since 2010 [17]. However, effective management of CKD–MBD includes a substantial effort on the part of patients to adhere to dietary restrictions, thrice-daily doses of oral phosphate binders and, for many patients, regular use of several other oral medications [18, 19]. Following the release of the KDIGO guideline, several studies have estimated the percentage of patients achieving KDIGO targets for CKD–MBD [6, 20]. A large international sample of chronic haemodialysis patients showed that PTH levels had subsequently increased in most countries, and that the treatment approaches of secondary hyperparathyroidism had changed between 1996 and 2011 [19]. In France, <20% of the prevalent patients receiving intermittent haemodialysis therapy between July 2007 and December 2009 were within the KDIGO target ranges of serum phosphate, calcium and PTH [6]. However, this analysis was related to data available before the implementation of the 2009 KDIGO guideline. Furthermore, data on CKD–MBD in incident dialysis patients are sparse, and to the best of our knowledge, no information is available on the proportion of such patients reaching KDIGO target ranges.

The main objective of the observational Photo-Graphe® study in France was to estimate the percentage of CKD Stages 4–5 and 5D patients achieving the newly recommended target ranges as defined by the KDIGO guideline [9]. Data recorded in incident dialysis patients are presented here.

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 dialysis CKD patients achieving KDIGO recommendations for the three main routinely assessed parameters of calcium and phosphate metabolism (serum phosphate, calcium and intact PTH) 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 230 active nephrologists contributed to attain the required sample size of 6813 dialysis. The sample size was calculated to obtain a 2.5% precision of a 95% confidence interval (CI) of the prevalence of patients achieving KDIGO recommendations. Nephrologists' selection was done using a clustering approach, where clusters (nephrologists) were randomly drawn, in respect of geographical distribution and type

Table 1. Comparison of the KDOQI (2003) and KDIGO (2009) targets for the three main circulating parameters of calcium and phosphate metabolism

	KDOQI (2003) [11]	KDIGO (2009) [3]
Phosphate (mmol/L)	1.13–1.78	Reduce elevated phosphate levels towards the normal range (usually 0.90–1.40)
Total calcium (mmol/L)	2.10–2.37 (corrected for serum albumin level)	Maintain in the normal range (usually 2.15–2.55, uncorrected for albumin level)
iPTH (pg/mL)	150–300 (based on second generation Allegro® kit)	CKD Stages 4 and 5: maintain below the upper limit of normal for the assay Dialysis: maintain in the range of approximately two to nine times the upper normal limit for the assay

iPTH, so-called 'intact' parathyroid hormone.

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 adults who started dialysis within the preceding 12 months were eligible. There were no exclusion criteria.

Data collection

Clinical events, serum biochemistry data and information on the treatment of incident dialysis patients were collected at the above fixed time points. When available, the following data were recorded: serum levels of C-reactive protein, phosphate, calcium, PTH, alkaline phosphatases (both total and bone specific enzymes), 25-hydroxy vitamin D (25-OH Vit D), albumin, low-density lipoprotein cholesterol, ferritin, transferrin saturation, blood haemoglobin (Hb) concentration, glycated haemoglobin (HbA1c) level, demographics, blood pressure, cardiovascular and valvular calcifications, current medications to control serum phosphate, history of parathyroidectomy, hospitalizations, bone fracture, cardiovascular events and dialysis modality. 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. Serum PTH values were used both as raw values and after adjustment to account for variation in calibration between local PTH assay kits, as described previously [9, 21].

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, a maximum of seven data collections over a time period of 3.5 years was available for patients included in October 2010, whereas patients included in October 2012 had a maximum of three data collections with a follow-up of only 1.5 years.

Data were entered in an electronic case report system (Photo-Graphe™ 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 then 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.

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 were transplanted or lost to follow-up were included in analyses to the point of study discontinuation.

Standard descriptive statistics were used, for demographic, biological and clinical data, to determine mean and standard deviation (SD) for normally distributed data and, median and 25th and 75th percentile values for non-normally distributed data. The percentage of patients achieving the three KDIGO targets was estimated at inclusion and at each following determination with the corresponding 95% CI. The evolution of the percentage of patients achieving the main three KDIGO targets or of the percentage of patients receiving a CKD–MBD-directed therapy was evaluated using a generalized estimating equation (GEE) model. Quartiles were used to test the association between continuous parameters and the evolution of the percentage of patients achieving the main three KDIGO targets. Furthermore, for phosphate and calcium levels, and at each data collection time, patients were classified into three groups according to KDIGO recommendations: (i) patients controlled within the recommended ranges; (ii) patients beyond the upper limit of recommended ranges; and (iii) patients below the lower limit of recommended ranges.

Results

Patient population

Overall, 9010 incident patients were included. More patients were males than females, with 5665 (63%) being of male gender. Patient characteristics at inclusion are shown in Table 2.

A total of 1495 (16.6%) patients were treated by intermittent haemodiafiltration and 7515 (83.4%) patients by intermittent haemodialysis. Median (interquartile range) dialysis time at first recording was 4.0 months (2.0 months; 7.0 months). The vast majority (89.1%) of patients underwent three dialysis sessions per week. No patient had a history of fracture or revascularization. A history of parathyroidectomy >6 months was reported in 89 (1%) patients. Medical history and comorbid conditions upon inclusion are summarized in Figure 1.

Follow-up

Median duration of follow-up was 17.9 months. Overall, 874 (10%) patients underwent kidney graft, 2183 (24%) died and 1148 (13%) were lost to follow-up during the study period. Figure 2 shows the percentage of deaths and kidney grafts at each data collection.

Achievement of KDIGO targets

The percentage of patients achieving the three main KDIGO targets increased significantly over time ($P < 0.0001$), from 11% up to 16%, until Year 2. Thereafter, the percentage remained stable (Table 3). Overall, 936 patients achieved the three main KDIGO targets at inclusion: among the 663 patients with KDIGO targets determined 6 months after inclusion, 196 (28%) patients still achieved the three KDIGO targets and, among the 161 patients with KDIGO targets determined at 3.5 years, 39 (24.2%) patients

Table 2. Characteristics of the patients at inclusion

Variables	All
Patients (*n*)	
Male	5665 (62.9)
Age (years)	71 (59; 80)
Body mass index (kg/m^2)	24.9 (21.8; 28.7)
Systolic blood pressure (mmHg)	137 ± 23
Diastolic blood pressure (mmHg)	70 ± 15
Serum albumin (g/L)	35 ± 5
Haemoglobin (g/dL)	11.1 ± 1.5
Smoker	
No	6285 (69.8)
Former	1712 (19.0)
Current	982 (10.9)
Unknown	31 (0.3)

Continuous data are presented as mean ± SD or median (25%; 75%); categorical data are presented as *n* (%).

still achieved the three KDIGO targets. The corresponding proportions among the patients not achieving the three main KDIGO targets at inclusion were 10.6% (566/5347) and 15.2% (180/1182) after 6 months and 3.5 years, respectively.

The percentage of incident dialysis patients with serum levels of phosphate ($P < 0.0001$) or calcium ($P < 0.0001$) within the normal range increased significantly over time while no statistically significant trend was observed for the percentage of patients with 'controlled' PTH ($P = 0.19$) (Table 4). In parallel, the percentage of patients with no available data for these three parameters tended to increase with time (Table 3). CKD–MBD-directed therapy at each data collection time point is displayed in Table 5. The percentage of patients receiving cinacalcet increased over time ($P < 0.0001$) while the percentage of patients receiving other CDK–MBD therapies decreased significantly (Table 3). Few patients received bisphosphonates.

Parameters significantly associated with lower achievement of the three main KDIGO targets were a younger age ($P < 0.0001$ for patients ≤59.3 years, $P < 0.01$ for patients between 59.3 and 71.3 years old) and an Hb level ≤10.1 g/dL at inclusion ($P < 0.0001$). Gender ($P = 0.61$), type of dialysis ($P = 0.28$) and body mass index ($P = 0.59$) at inclusion were not significantly associated with the achievement of the three KDIGO targets.

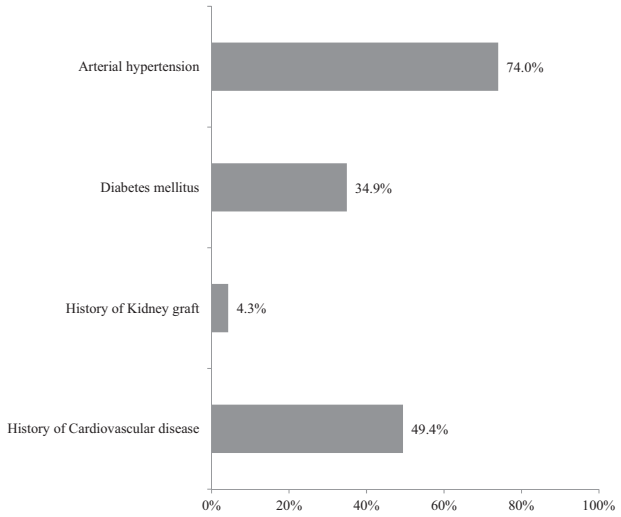

Fig. 1. Medical history and comorbid conditions at inclusion.

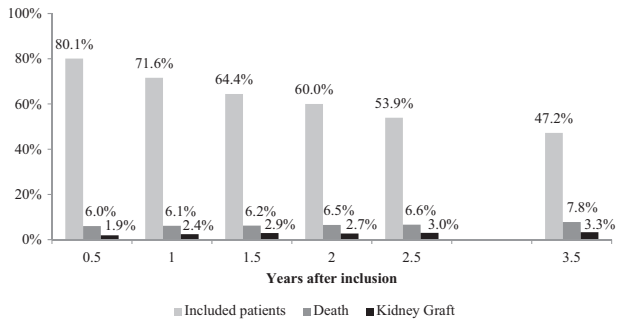

Fig. 2. Patient status at each follow-up, among the 9010 included incident haemodialysis patients. Follow-up to death, kidney graft or change of centre, if any.

Discussion

The French Phosphorus and Calcium Observatory (Photo-Graphe3) is the most recent and largest European prospective study that specifically aimed to assess disturbances of phosphate, calcium and PTH metabolism and their relationships with the outcome in incident patients undergoing haemodialysis or haemodiafiltration. A previous analysis of Photo-Graphe3 showed that a low PTH status was an independent risk factor for cardiovascular death in haemodialysis patients [9]. High dialysate calcium was an important contributor to PTH oversuppression, and continuous use was associated with increased cardiovascular mortality. In patients on haemodialysis, both low and high serum PTH levels have been associated with a higher mortality rate [6, 22, 23].

Based on evidence from observational studies, high serum phosphate levels have been linked with increased mortality risk both in the general population and in patients with CKD–MBD [13, 24–26]. Similarly, serum calcium levels were found to be associated with all-cause mortality in dialysis patients, including cardiovascular mortality, and progression of aortic calcification [27]. Therefore, it has been suggested that the correction of abnormal serum levels of phosphate, calcium and PTH might improve the survival of haemodialysis patients [28].

The present analysis confirms that adherence to the recommended target ranges for serum phosphate, calcium and PTH remains challenging in spite of several therapeutic advances. Nearly 90% of the patients failed to attain the three main KDIGO targets at inclusion, that is a short time after the start of dialysis. A poor control of CKD–MBD could have motivated the start of dialysis in at least some of the patients. Adherence to the recommended target ranges slightly increased after dialysis onset, but nearly 85% of the patients failed to attain the three main KDIGO targets 2 years later. However, compliance with MBD targets seems higher in France than in Spain, where only 6% of the patients consistently achieved the three main KDIGO targets over a 1-year follow-up period [29].

Except cinacalcet, the percentage of patients taking any other CKD–MBD-directed therapies tended to decrease with time. In the previous French Photo-Graphe study, which evaluated prevalent cases, ∼12% among them were within the KDIGO guideline ranges for all three parameters [6], a percentage consistent with the percentage observed at inclusion in the present study. In this

Table 3. Percentage and 95% CI of patients achieving the three main KDIGO targets of calcium and phosphate metabolism

	Inclusion	6 months	1 year	1.5 years	2 years	2.5 years	3.5 years
Patients (*n*)	9010	9010	7120	6475	4903	3587	3224
Patients with documented data (*n*)	8211	6492	4610	3851	2717	1826	1428
Patients achieving the three KDIGO targets, *n* (%)	936 (11.4)	811 (12.5)	648 (14.1)	574 (14.9)	433 (15.9)	296 (16.2)	226 (15.8)
95% CI	(10.7–12.1)	(11.7–13.3)	(13.1–15.1)	(13.8–16.0)	(14.6–17.3)	(14.5–17.9)	(13.9–17.7)

Patients were followed up to death, kidney graft or change of centre, if any.

Table 4. Number and percentage of patients achieving the three KDIGO targets of calcium and phosphate metabolism at each data collection time point

Data collection	Inclusion	6 months	1 year	1.5 years	2 years	2.5 years	3.5 years
Number of patients	9010	9010	7120	6475	4903	3587	3224
Serum phosphate (mmol/L)							
Hypo ≤0.9	772 (8.8)	587 (8.6)	428 (8.8)	372 (9.2)	259 (9.0)	172 (9.1)	146 (9.7)
Normal	3218 (36.6)	2649 (38.7)	1971 (40.6)	1663 (41.2)	1189 (41.5)	793 (41.8)	624 (41.8)
Hyper >1.4	4795 (54.6)	3609 (52.7)	2457 (50.6)	2004 (49.6)	1420 (49.5)	931 (49.1)	723 (48.4)
Missing values	225	2165	2264	2436	2035	1691	1731
Serum total calcium (mmol/L)							
Hypo ≤2.15	3580 (40.7)	2566 37.4)	1627 (33.4)	1402 (34.7)	955 (33.2)	670 (35.3)	559 (37.1)
Normal	4957 (56.3)	4107 (59.9)	3073 (63.0)	2522 (62.4)	1824 (63.5)	1186 (62.4)	912 (60.5)
Hyper >2.55	262 (3.0)	185 (2.7)	175 (3.6)	116 (2.9)	94 (3.3)	43 (2.3)	36 (2.4)
Missing values	211	2152	2245	2435	2030	1688	1717
Serum corrected PTH[a]							
Hypo	2517 (30.2)	2125 (32.2)	1454 (31.0)	1146 (29.3)	764 (27.6)	495 (26.7)	373 (25.7)
Normal	4945 (59.4)	3835 (58.0)	2743 (58.5)	2296 (58.)	1669 (60.3)	1121 (60.5)	900 (61.9)
Hyper	865 (10.4)	647 (9.8)	492 (10.5)	467 (12.0)	333 (12.0)	237 (12.8)	181 (12.4)
Missing values	683	2403	2431	2566	2137	1734	1770

[a]With correction factors to account for the laboratory kit (see Materials and methods). Data are *n* (%) patients. Patients were followed up to death, graft or change of centre, if any.

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

Data collection	Inclusion	6 months	1 year	1.5 years	2 years	2.5 years	3.5 years	P*
Number of patients	9010	9010	7120	6475	4903	3587	3224	
Active vitamin D	1304 (14.5)	1013 (11.2)	725 (10.2)	636 (9.8)	471 (9.6)	354 (9.9)	291 (9.0)	$<10^{-4}$
Native vitamin D	4755 (52.8)	4476 (49.7)	3124 (43.9)	2811 (43.4)	2042 (41.7)	1449 (40.4)	1195 (37.1)	$<10^{-4}$
Calcium-free phosphate binder	3433 (38.1)	3282 (36.4)	2450 (34.4)	2006 (31.0)	1470 (30.0)	964 (26.9)	763 (23.7)	$<10^{-4}$
Calcium salt	3915 (43.5)	3086 (34.3)	2137 (30.0)	1766 (27.3)	1301 (26.5)	881 (24.6)	693 (21.5)	$<10^{-4}$
Cinacalcet	548 (6.1)	660 (7.3)	572 (8.0)	592 (9.1)	484 (9.9)	380 (10.6)	346 (10.7)	$<10^{-4}$
Bisphosphonates	27 (0.4)	17 (0.3)	8 (0.2)	14 (0.4)	6 (0.3)	10 (0.6)	6 (0.5)	0.28

Number (%) of patients receiving the corresponding therapy at each data collection time point.
*P-value of time trend (GEE model).

more recent photograph study, the higher percentage of patients within the KDIGO guideline ranges, observed during the follow-up period, may reflect an improvement in patient management and compliance to guidelines. In 2004, in a US study, more biochemical markers were out of target in prevalent patients who were younger or had a longer time on dialysis (i.e. longer vintage) when in the present study adherence increased over time [5].

Adherence to two among the three CKD–BMD parameters taken separately was better and, except for serum PTH, improved significantly over time. Nevertheless, the best adherence was observed for PTH throughout the follow-up time period since nearly 62% of the patients achieved the KDIGO PTH target versus 60.5% for calcium during the extended follow-up period of 3.5 years. The lowest adherence rate was observed for phosphate, for which >50% of the patients failed to attain the target range even after 3 years. Except for intact PTH, KDIGO individual targets do not appear to be better achieved in our study compared with an observational study conducted in the same settings over 1744 patients (prevalent dialysis) and monitored for 3 years in Serbia. In the latter, the percentage of patients achieving individual KDIGO targets was 42.8% for intact PTH, 44.4% for phosphate and 76.7% for calcium [27]. In contrast, our findings of guideline adherence tend to be better than those of a retrospective study carried out in 44 haemodialysis patients who were continuously monitored for 32 months in a hospital in Spain. In this study, permanent compliance within KDIGO targets was achieved in only one patient for PTH, 46% for phosphate and 52% for calcium [30].

Patients with CKD can be educated to control their hyperphosphataemia through phosphate binders, dialysis and diet. On one hand, patient education is essential for the successful use of phosphate binders, which need to be taken properly and consistently with meals and snacks to be effective. On the other hand, dietary counselling should encourage the patients to consume foods with the least amount of inorganic phosphate, low phosphate-to-protein ratios and adequate protein content [31]. In the present study, the percentage of patients receiving a phosphate binder decreased over time. This may be due to a reduction in appetite and/or protein–phosphorus intake with age and dialysis duration.

The present study has some limitations. First, we cannot exclude that centres which participated on a voluntary basis were more interested by the correction of CKD–MBD in the care of their patients than those who did not join the study group. However, the baseline characteristics of our patients were comparable to those of the global French National Registry (REIN) [32]. Secondly, the percentage of patients lost to follow-up over 3 years was 13%. This percentage is lower than the 17% observed in the previous Photo-Graphe study [6]. Yet, the rate of 13% may render interpretation of the results more difficult.

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Certainly, a loss to follow-up of ≤10% would have been more appropriate.

The serum calcium, phosphate, 25-OH vitamin D and PTH targets of KDIGO have been recently questioned for their pertinence to predict morbidity and mortality across time and countries [33]. Given the complete absence of randomized controlled trials assessing the control of hyperphosphataemia, the guidelines have been established on epidemiological observations alone. However, KDIGO did not recommend precise threshold values for serum phosphate. It only advised an attempt to aim for 'normal' laboratory values or, as in the case of intact PTH, the rather wide range of two to nine times the upper limit of normal (which generally differs from one PTH kit to another), a recommendation endorsed by the European nephrology community. The present study shows that although the percentage of adherent patients slightly increased over time, only very few patients eventually achieved the KDIGO targets.

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Conflict of interest statement

Sanofi France did not interfere with the statistical analysis. D.F. served as national coordinator. B.D. performed the statistical analyses and drafted the article. E.D. declares having served as consultant for Amgen, Sanofi, Shire and Astra Zeneca. T.B.D. declares having served as consultant for Amgen, F. Hoffman-La Roche, FMC, Sanofi-Genzyme and Vifor. T.H., G.M.L., G.J. and L.J.-B. declared no conflict of interests.

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