



# International and Racial Differences in Mineral and Bone Disorder Markers and Treatments Over the First 5 Years of Hemodialysis in the Dialysis Outcomes and Practice Patterns Study

Kevin Chan, Angelo Karaboyas, Hal Morgenstern, Bruce M. Robinson, Friedrich K. Port, Stefan H. Jacobson, Masafumi Fukagawa, Yvonne Meier, Philipp A. Csomor, and Ronald L. Pisoni

**Rationale & Objective:** Normalization of parathyroid hormone (PTH), serum calcium, and phosphorus levels may prevent coronary and bone disease in hemodialysis (HD) patients. We describe the trajectory of these mineral bone disorder parameters and treatments during the first 5 years of HD by international region and race.

**Study Design:** Prospective cohort study.

**Setting & Participants:** 33,517 US black/African American, US non-black/African American, European, and Japanese HD patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 4 to 5 (2009-2015).

**Predictor:** Time since HD initiation.

**Outcomes:** Monthly cross-sections of mineral bone disorder parameters (PTH, serum calcium, and phosphorus) and medications (cinacalcet, active vitamin D, and phosphate binders).

**Results:** Mean PTH levels declined precipitously during the first 4 months of HD in all 4 groups, then steadily increased during the next 4.5 years in the United States/Europe but not in Japan. 3 years after HD initiation (month 36), mean PTH level

was highest in US black/African Americans (496 pg/mL), despite greater prescription of cinacalcet (23%) and active vitamin D (85%), and lowest in Japan (151 pg/mL). Mean serum calcium and phosphorus levels increased during the first 4 months of HD. By month 36, the mean calcium level was lower in Japan (8.8 mg/dL) than United States/Europe (9.0-9.1 mg/dL), while the mean phosphorus level was lower in Europe (4.8 mg/dL) than United States/Japan (5.1-5.3 mg/dL).

**Limitations:** Lack of data for medication dosages; most patients were not followed from HD onset.

**Conclusions:** Large differences exist in the levels, trajectories, and therapies for PTH, calcium, and phosphorus by country and race in the first 5 years of HD. Higher PTH levels were observed in the United States, especially among black/African American patients, despite greater use of cinacalcet and active vitamin D than in Japan or Europe. Potential contributors to differences in PTH levels should be explored to study their impact on PTH management strategies and consequent bone and cardiovascular complications.

Complete author and article information provided before references.

Correspondence to R.L. Pisoni (ronald.pisoni@arborresearch.org)

Kidney Med. 1(3): 86-96. Published online May 10, 2019.

doi: 10.1016/j.xkme.2019.04.004

© 2019 The Authors. Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Optimal management of calcium, phosphorus, and parathyroid hormone (PTH) levels may prevent coronary artery calcification progression and subsequently decrease cardiovascular mortality in the maintenance dialysis population.<sup>1,2</sup> Findings from several studies suggest mineral and bone disorder (MBD) management to be insufficient regardless of sex, race, vintage, or nationality where less than half the patients achieve all nationally recommended MBD target values.<sup>3,4</sup> This is likely because MBD management is complex, requiring the interdependent titration of phosphate binders, active vitamin D, and cinacalcet to achieve pharmacotherapeutic equilibrium. Furthermore, patient characteristics, diet, and environmental factors additionally complicate the response to therapy and the achievement of therapeutic targets.<sup>5,6</sup>

The average life expectancy of a US dialysis patient after initiating dialysis is almost 5 years.<sup>7</sup> Although there are MBD studies that compare calcium, phosphorus, and PTH level management in a limited cohort of dialysis patients, few studies provide longitudinal data for MBD practice patterns and how these biochemical factors change in the

period after dialysis initiation and during the lifetime of a dialysis patient in relation to race, geography, and drug treatment.<sup>8</sup> This information is important if we are to understand the gaps in care and opportunities for us to improve MBD globally.

In this study, we aim to describe serum calcium, phosphorus, and PTH levels in conjunction with cinacalcet, active vitamin D, and phosphate binder use in monthly cross-sections during the first 5 years of hemodialysis (HD). We do this in a large international HD cohort to uncover MBD differences among incident and prevalent HD populations across different countries and races to characterize contemporary practices and quality indicators.

## METHODS

### Data Source

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is an international multiphase cohort study involving HD patients from 21 countries, ongoing since

1996. HD patients 18 years or older are recruited from randomly selected dialysis facilities within each participating country.<sup>9,10</sup> Patients are followed prospectively for detailed data collection of demographics, comorbid conditions, hospitalizations, deaths, laboratory measures, prescribed medications, dialysis prescriptions, and other practices. The DOPPS data coordinating center is based in Ann Arbor, MI, and manages the multinational data collection through uniform and standardized data collection tools and processes.

For this study, we followed HD patients from 9 countries in DOPPS phase 4 (2009–2011) and phase 5 (2012–2015). This included data from the United States, Japan, and 7 European countries: Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom. Institutional review board (IRB) study approval (#98004 from Ethical & Independent IRB #2-IRB0007807) and patient consent were obtained to meet national and local ethics committee regulations.

### Statistical Methods

In our primary analysis, we modeled mean values of PTH, serum phosphorus, and calcium in monthly cross-sections by dialysis vintage, using locally weighted regression (LOESS). LOESS fits parametric functions to localized subsets of the data using weighted least squares regression, resulting in a “smoothed” moving average and allowing for maximum flexibility in modeling the trajectory of the mean values.<sup>11</sup> All available monthly data were included in each model; model outcomes were the values of individual laboratory measurements or an indicator (yes/no) for the medication prescription, and exposure was the time since HD initiation at which this information was obtained. Separate models were used for each of 4 race/region groups: US black/African American, US non-black/African American, Japan, and Europe. Similarly, we used LOESS to model how the proportion of patients prescribed MBD medications (cinacalcet, active vitamin D, and phosphate binders) changed with dialysis vintage. Although not all DOPPS participants were enrolled in the study at HD initiation and no individual patients were followed within a study phase for more than 40 months, we used repeated cross-sections from overlapping periods to obtain trajectories in MBD parameters and treatments during the first 5 years of HD.

In secondary analyses, we reported distributions of MBD laboratory values and prescription prevalence at 2 cross-sections: the first (month 1) and 36th (month 36) month after initiating HD therapy. Numbers of patients available for analysis were 7,328 in month 1 and 6,548 in month 36. We also reported a descriptive summary of patient characteristics in the month 1 cohort.

We noted that the trajectory of PTH, serum calcium, and phosphorus levels substantially changed at about 4 months. We thus executed sensitivity analyses by reproducing LOESS curves, excluding patients who died or

switched modality in the first 4 months of dialysis to assess whether the high competing incident mortality risk at dialysis initiation could explain the sudden inflection of the trajectories.<sup>12,13</sup>

All results were stratified into the following 4 groups by region and race: US black/African Americans, US non-black/African Americans, Japan, and Europe. Analyses were conducted using SAS software, version 9.4 (SAS Institute).

## RESULTS

### Summary of Patient Characteristics at HD Initiation

Table 1 summarizes patient characteristics among the 7,328 patients who enrolled in DOPPS at HD initiation, although additional patients contributed to the subsequently described trajectory analyses. Black/African American patients in the United States were much younger than European, Japanese, and non-black/African American US patients. Catheter use was highest in the United States (60%–65%), slightly lower in Europe (47%), and much lower in Japan (6%). Hemoglobin, serum albumin, and C-reactive protein levels were lower in Japan than other regions. The prevalence of many comorbid conditions varied widely across regions.

### Description of Global HD Population

We followed 33,517 HD patients over 41,240 patient-years to describe longitudinal changes in PTH, serum calcium, and serum phosphorus levels along with the prevalence of cinacalcet, active vitamin D, and phosphate binder prescription among US black/African Americans, US non-black/African Americans, Japanese, and European groups. Numbers of patients analyzed were 7,123 (8,957 patient-years) for US black/African Americans, 14,642 (17,523 patient-years) for US non-black/African Americans, 2,745 (4,588 patient-years) for Japan, and 9,007 (10,172 patient-years) for Europe. The median time that each patient contributed to the analysis was 12 (interquartile range [IQR], 6, 22) months, and median number of laboratory measurements per patient was 11 (IQR, 5, 20) for phosphorus, 11 (IQR, 5, 20) for calcium, and 5 (IQR, 3, 10) for PTH.

### Variation in PTH Levels

Marked variations in the level and trajectory of PTH values were noted among the 4 study groups by dialysis vintage (Fig 1A). In all groups, PTH levels were high at HD initiation and then declined sharply. In the first 4 months of HD, PTH levels decreased by 118 pg/mL in US black/African Americans, 58 pg/mL in US non-black/African Americans, 31 pg/mL in Europe, and 66 pg/mL in Japan. From 4 to 12 months after HD start, PTH levels increased in Europe and the United States. However, in Japan, PTH levels instead declined throughout the first year of HD, to a nadir of about 140 pg/mL, and then

**Table 1.** Patient Characteristics at HD Start by Region and Race

Patient Characteristics	Europe	Japan	US Non-Black/African American	US Black/African American
No. of patients	1,691	541	3,525	1,571
Age, y	66.6 ± 14.5	66.2 ± 12.9	65.3 ± 14.7	60.2 ± 15.1
Male sex	1,112 (66%)	377 (70%)	2,022 (57%)	851 (54%)
BMI, kg/m <sup>2</sup>	26.7 ± 5.5	22.4 ± 3.6	28.6 ± 6.9	28.5 ± 7.4
Catheter use	465 (47%)	26 (6%)	1,214 (62%)	490 (63%)
Systolic BP, mm Hg	142 ± 22	148 ± 22	144 ± 23	148 ± 23
Hemoglobin, g/dL	10.0 ± 1.4	9.4 ± 1.3	10.2 ± 1.4	10.0 ± 1.5
Serum albumin, g/dL	3.4 ± 0.6	3.2 ± 0.6	3.4 ± 0.5	3.4 ± 0.5
C-Reactive protein, mg/L	7.3 [3.1, 19.1]	1.2 [0.6, 6.6]	NA	NA
Comorbid conditions				
Coronary artery disease	503 (30%)	110 (21%)	634 (24%)	197 (17%)
Cancer (nonskin)	316 (19%)	65 (12%)	220 (7%)	50 (4%)
Other cardiovascular disease	473 (28%)	84 (16%)	383 (14%)	107 (9%)
Cerebrovascular disease	233 (14%)	50 (9%)	114 (4%)	22 (2%)
Congestive heart failure	335 (20%)	112 (21%)	860 (29%)	339 (26%)
Diabetes	707 (42%)	294 (55%)	2,189 (69%)	959 (68%)
Gastrointestinal bleeding	61 (4%)	21 (4%)	58 (2%)	31 (3%)
Hypertension	1,490 (89%)	457 (86%)	2,377 (77%)	1,134 (83%)
Lung disease	225 (13%)	20 (4%)	289 (11%)	92 (8%)
Neurologic disease	175 (10%)	47 (9%)	122 (5%)	41 (4%)
Psychiatric disorder	215 (13%)	20 (4%)	638 (23%)	211 (18%)
Peripheral vascular disease	432 (26%)	52 (10%)	488 (16%)	141 (11%)
Recurrent cellulitis, gangrene	99 (6%)	11 (2%)	114 (4%)	23 (2%)

Note: Values expressed as mean ± standard deviation, median [interquartile range], or number (percent). The patients described in this table are only those who enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) at HD start. C-Reactive protein data not routinely collected in the United States. Abbreviations: BMI, body mass index; BP, blood pressure; HD, hemodialysis; NA, not applicable.

remained low through the following 5 years after HD start.

In month 1 of HD (Fig 1B), US black/African Americans had a mean PTH level of 496 pg/mL, which was considerably higher than both their non-black/African American US counterparts (345 pg/mL) and European patients (303 pg/mL). Even at month 36, US black/African Americans had the highest mean PTH level of 496 pg/mL, which still remained considerably higher than the non-black/African American US (367 pg/mL) and European (316 pg/mL) patients. Japanese patients had the lowest mean PTH value in months 1 (238 pg/mL) and 36 (151 pg/mL) of HD.

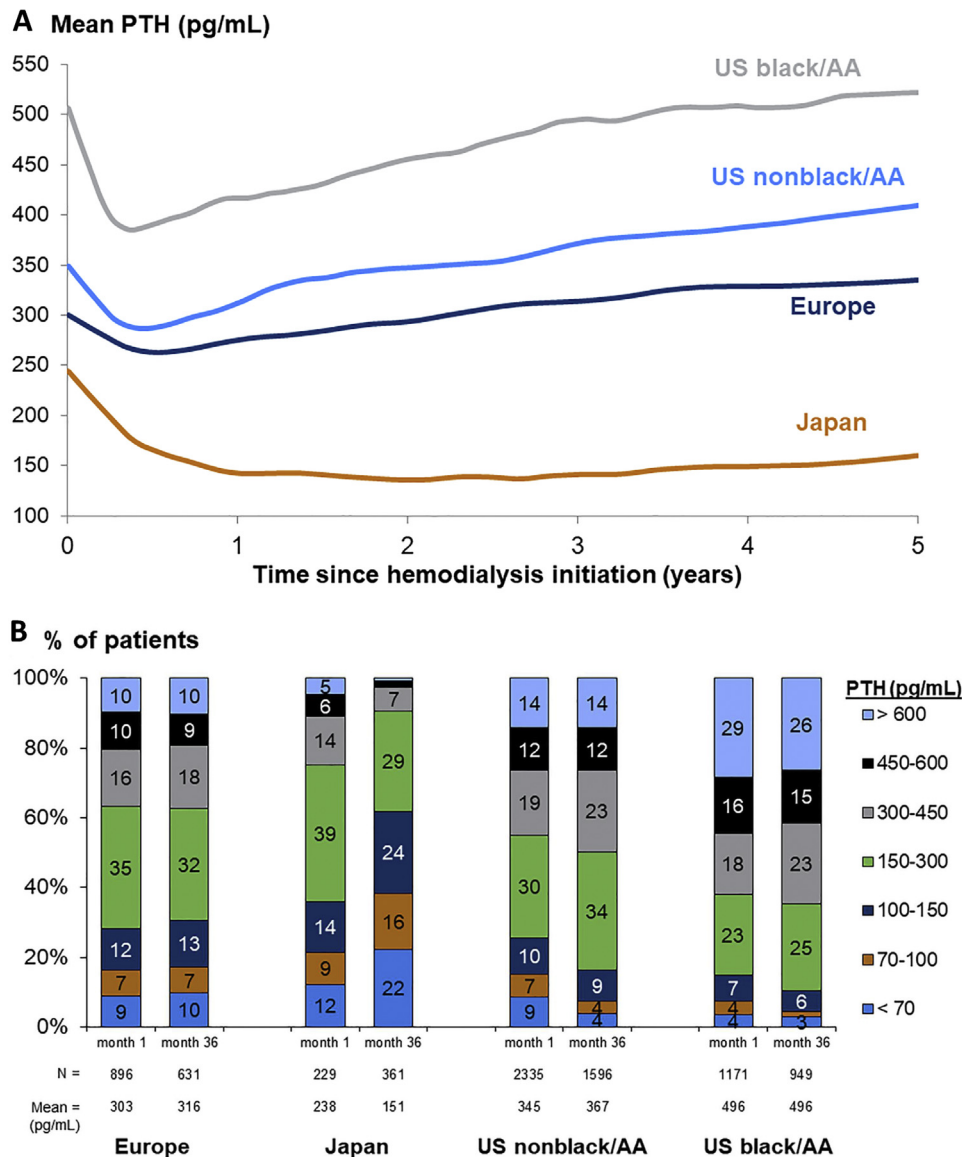
### Variation in Cinacalcet and Active Vitamin D Prescription

Cinacalcet prescription, used to suppress PTH, increased linearly during the 5 years after patients initiated HD, from <5% at HD start to 15% to 35% after 5 years (Fig 2A). Active vitamin D prescription increased rapidly among Americans and Japanese in the first 4 months from about 35% to 50% at HD start to 50% to 70% at 4 months and then 70% to 85% at 5 years (Fig 2B). In Europe, the proportion of patients prescribed active vitamin D increased more gradually, from 44% at HD start to only 57% after 5 years on HD. In month 36, the proportion of patients prescribed neither cinacalcet nor active vitamin D ranged from 13% in US black/African Americans to 40%

in Europe (Fig 2C). When restricted to patients with elevated PTH levels (>300 pg/mL), the proportion prescribed neither treatment was 9% in US non-black/African Americans, 10% in US black/African Americans, 24% in Japan, and 33% in Europe (Fig 2D).

### Variation in Serum Calcium Levels, Phosphorus Levels, and Phosphate Binder Prescription

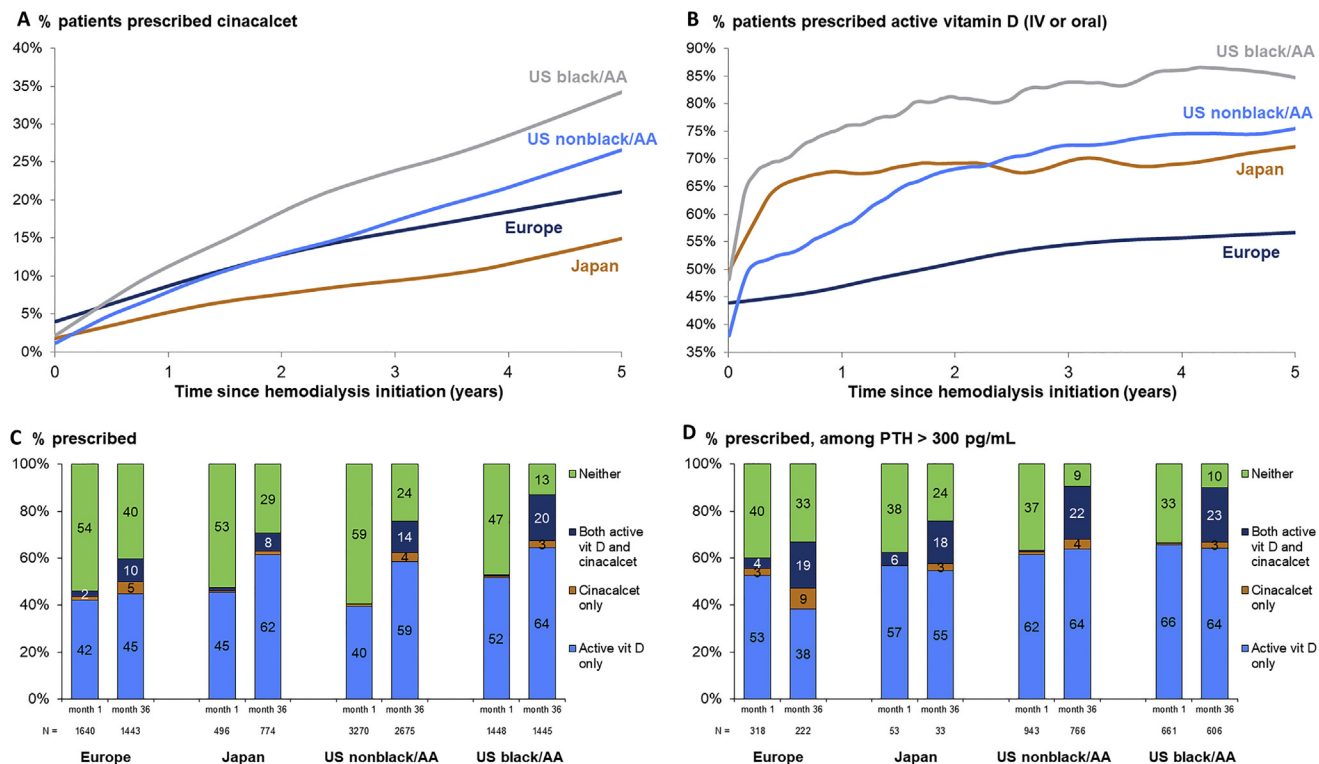
Calcium levels in all groups increased precipitously by 0.3 to 0.5 mg/dL in the first 4 months of HD before achieving a steady state. Serum calcium levels were consistently lowest among Japanese HD patients (Fig 3A) at all vintages. In month 1, mean serum calcium level was 8.1 mg/dL in Japanese patients, which was considerably lower than the mean calcium level of 8.6 to 8.7 mg/dL observed in Europe and the United States (Fig 3B). Even in month 36, Japanese patients continued to have the lowest serum calcium levels (8.8 mg/dL) when compared with European and US patients despite the fact that Japanese patients: (1) were prescribed the most calcium-based phosphate binders (Fig S1), which increases serum calcium levels; (2) were prescribed the least cinacalcet (Fig 2C), which lowers serum calcium levels; and (3) were prescribed higher dialysate calcium baths (vs the United States), which increases serum calcium levels. Mean dialysate calcium concentration was 2.85 mEq/L in Japan, 2.84 mEq/L in Europe, 2.46 mEq/L in US non-black/African Americans, and 2.45 mEq/L in US black/African Americans.



**Figure 1.** (A) Mean parathyroid hormone (PTH) levels in US black/African American (AA), US non-black/African American, European, and Japanese hemodialysis (HD) populations over the first 5 years of HD. Locally weighted regression (LOESS) model includes 253,909 PTH measurements from 31,986 patients. (B) Distribution of PTH levels at months 1 and 36 after initiating HD in US black/African American, US non-black/African American, European, and Japanese HD populations.

Serum phosphorus levels increased dramatically in the first few months after HD initiation, then continued to increase gradually in Japan and the United States, but decreased in Europe (Fig 4A). In month 1, mean phosphorus levels were highest among Japanese and Europeans (4.8 mg/dL) while lower in US non-black/African Americans and US black/African Americans (4.5 mg/dL). By month 36, mean phosphorus levels in Europe had decreased back to 4.8 mg/dL, substantially lower than in Japan (5.3 mg/dL), US non-black/African Americans (5.2 mg/dL), and US black/African Americans (5.1 mg/dL; Fig 4B).

The prevalence of phosphate binder prescription in Europe was in the same range as Japan and the United States throughout the first 5 years of HD (Fig 5A); however, phosphate binder type differed by group. Calcium-based phosphate binders were more common in Japan than in Europe and the United States (Fig S1). When restricting the analysis to patients with hyperphosphatemia, defined as phosphorus level > 5.5 mg/dL, the proportion of patients who were not using a phosphate binder in month 1 ranged from 27% in Europe to 53% in Japan. These proportions declined in all 4 groups in month 36 to a low of 14% in Europe



**Figure 2.** (A) Prevalence of cinacalcet prescription in US black/African American (AA), US non–black/African American, European, and Japanese hemodialysis (HD) populations during the first 5 years of HD. Locally weighted regression (LOESS) model includes 480,237 months of data from 32,625 patients. (B) Prevalence of active vitamin (vit) D prescription in US black/African American, US non–black/African American, European, and Japanese HD populations during the first 5 years of hemodialysis. LOESS model includes 477,507 months of data from 32,505 patients. (C) Prevalence of cinacalcet and active vitamin D prescription at months 1 and 36 after initiating HD in US black/African American, US non–black/African American, European, and Japanese HD populations. (D) Prevalence of cinacalcet and active vitamin D prescription at months 1 and 36 after initiating HD in US black/African American, US non–black/African American, European, and Japanese HD populations, among patients with parathyroid hormone (PTH) levels > 300 pg/mL in the prior month.

and Japan and a high of 21% in US black/African Americans (Fig 5B).

### Sensitivity Analyses

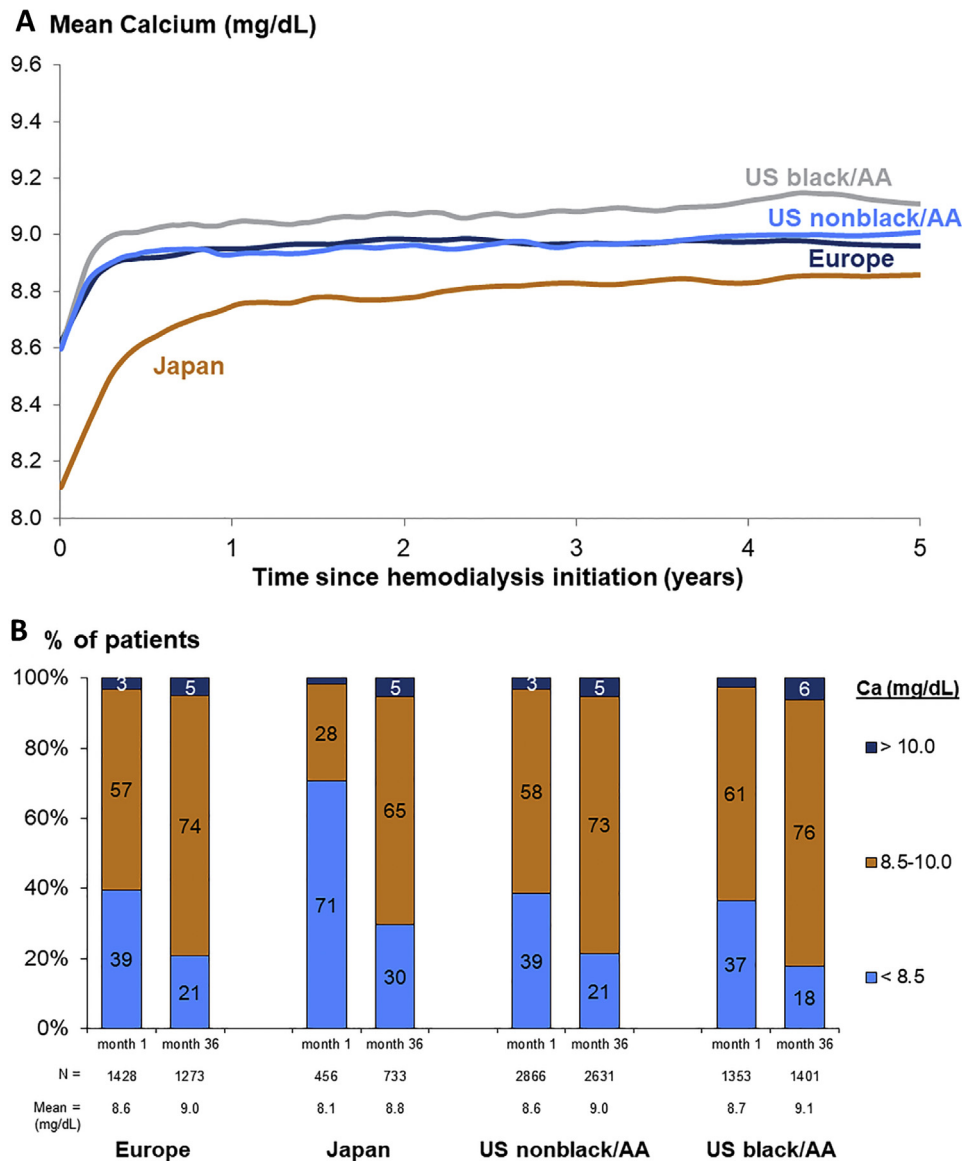
As a sensitivity analysis, we reproduced longitudinal PTH, calcium, and phosphorus curves after excluding patients who died or switched modality in the first 4 months to verify that the sudden inflection in the LOESS curves could not be attributed to the high competing incident mortality risk.<sup>12,13</sup> The level and trajectory of the curves did not change even after excluding the 224 patients who died or 49 patients who switched modality within 4 months of starting HD.

### DISCUSSION

This large international study has revealed wide variations in achieved levels of some MBD markers by international region and race during the first 5 years of maintenance HD therapy. In some cases, these differences did not appear to reflect differences in MBD management practices; for example, higher PTH levels in the United States

despite more patients treated with active vitamin D and cinacalcet.

Active vitamin D appeared to be the first-line therapy for managing PTH levels in all 3 international regions (Europe, Japan, and the United States), with the proportion of patients prescribed active vitamin D ranging from 45% to 55% at HD start to 55% to 75% after 1 year of HD therapy. In contrast, cinacalcet was prescribed to only 2% to 4% of patients at HD start, increasing to 5% to 11% after 1 year. However, despite these apparently similar approaches to the use of PTH-controlling medications, our study reveals substantial international differences in the level of PTH control that is achieved. At HD initiation, mean PTH levels ranged from ~240 pg/mL in Japan to 300 to 350 pg/mL in Europe and among non–black/African American US patients and 500 pg/mL among US black/African American patients (Fig 1A). In the first 4 to 6 months of HD, large decreases in mean PTH levels were observed in each region, concurrent with increases in active vitamin D prescriptions. However, despite this initial PTH suppression, in Europe and the United States, mean PTH levels subsequently began increasing at approximately

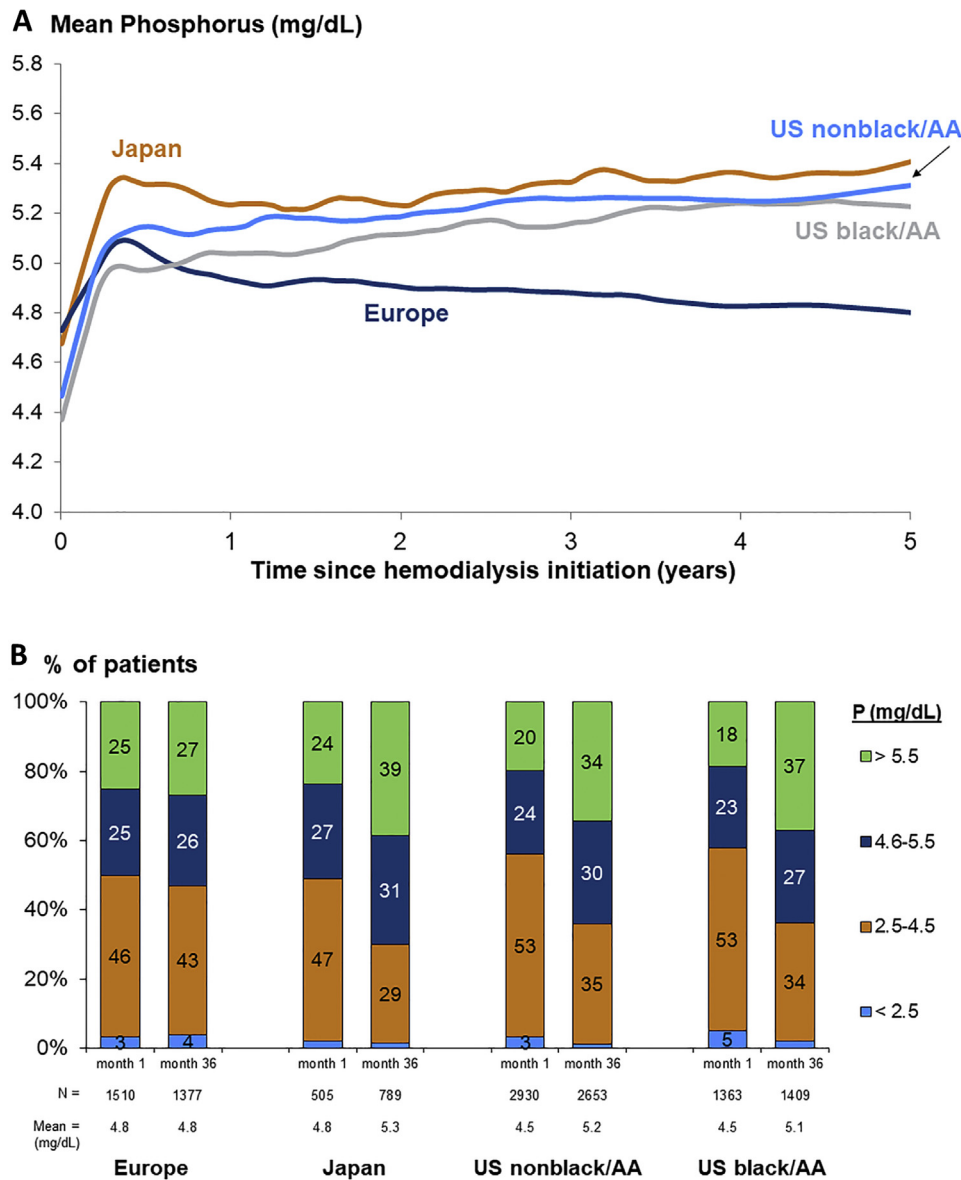


**Figure 3.** (A) Mean serum calcium (Ca) levels in US black/African American (AA), US non-black/African American, European, and Japanese hemodialysis (HD) populations during the first 5 years of HD. Locally weighted regression (LOESS) model includes 443,701 calcium measurements from 32,237 patients. (B) Distribution of serum calcium levels at months 1 and 36 after initiating HD in US black/African American, US non-black/African American, European, and Japanese HD populations.

6 months post-HD start and continued to increase during the next 4.5 years of HD therapy to approximately 335, 410, and 520 pg/mL for European, US non-black/African American, and US black/African American HD patients, respectively. In striking contrast, mean PTH levels in Japan continued to decline after 6 months of HD until reaching a mean of ~140 pg/mL by 1 to 2 years on HD and were maintained in this range throughout the 5-year observation period.

PTH level decline during the first 4 to 6 months of HD could be explained by resolving uremia when dialysis commences combined with the initial surge in active vitamin D use that inhibits PTH production<sup>14</sup> and increases

gut absorption of calcium and phosphorus. These findings were consistent after excluding patients who died in the first 4 months of HD, demonstrating robustness to the high competing incident mortality risk.<sup>12,13</sup> Overall, our findings are consistent with the earlier work of Levin et al<sup>15</sup> that many patients are undertreated for MBD prior to starting dialysis, with greater efforts on managing secondary hyperparathyroidism and avoiding hyperphosphatemia being needed during predialysis chronic kidney disease (CKD), consistent with current Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations.<sup>16</sup> Our results suggest that PTH management before end-stage kidney disease may be best among

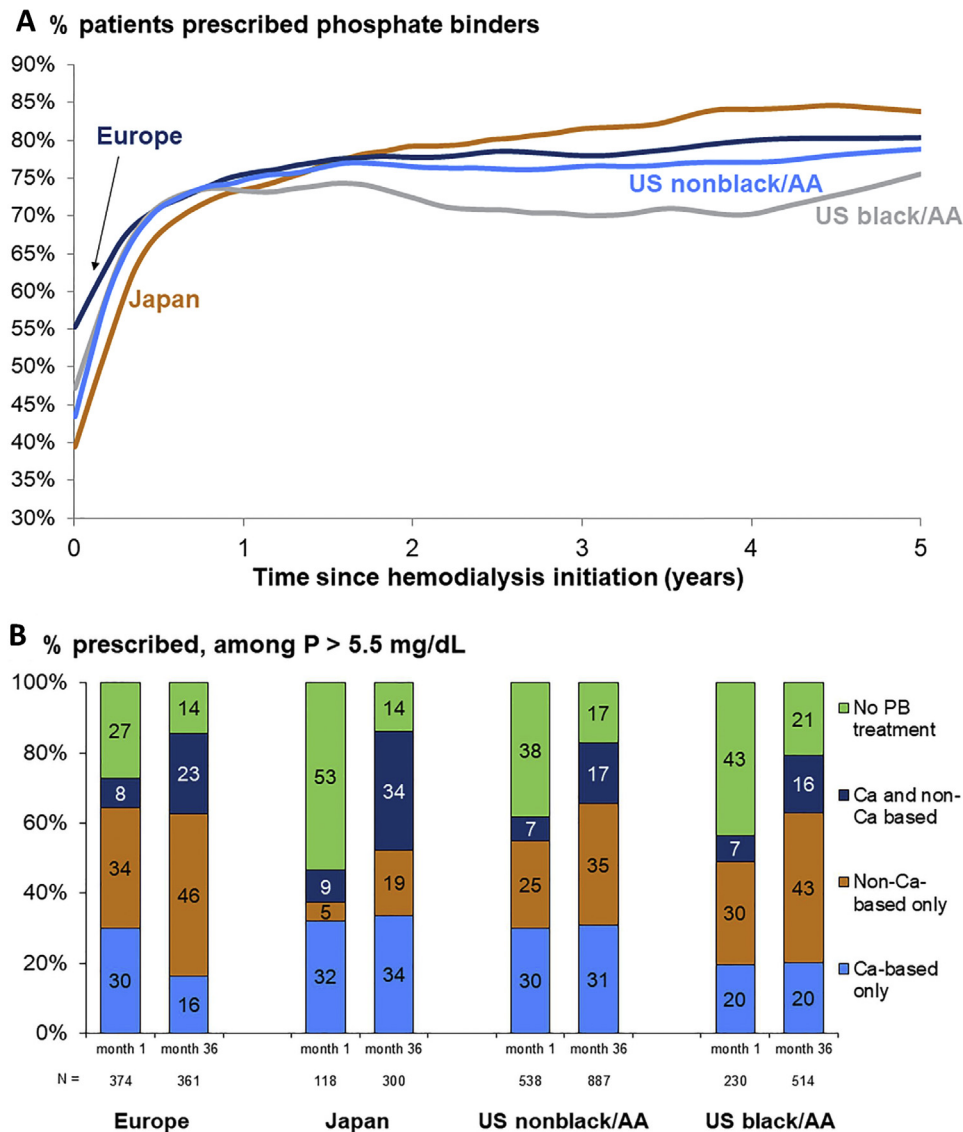


**Figure 4.** (A) Mean serum phosphorus (P) levels in US black/African American (AA), US non-black/African American, European, and Japanese hemodialysis (HD) populations during the first 5 years of HD. Locally weighted regression (LOESS) model includes 458,102 phosphorus measurements from 33,188 patients. (B) Distribution of serum phosphorus levels at months 1 and 36 after initiating HD in US black/African American, US non-black/African American, European, and Japanese HD populations.

Japanese patients with CKD and poorest for US black/African American patients based on mean PTH levels at HD start of 245 pg/mL versus 507 pg/mL, respectively. This lower PTH level is seen for Japanese patients even though prior DOPPS analyses have indicated that Japanese patients initiate HD at a lower mean estimated glomerular filtration rate than US patients.<sup>17</sup> Suppressing PTH early during the predialysis period and immediately when patients initiate HD therapy may limit the progression of secondary hyperparathyroidism to its tertiary form, thereby providing for better, more effective subsequent management of PTH levels. However, it is possible that the very low PTH levels

observed in Japan (22% with PTH < 70 pg/mL after 3 years on HD) may also increase the risks for poor bone turnover and related adverse outcomes.

An understanding of the observed differences in PTH control by international region and race is aided when viewed through the lens of guideline differences and treatment approaches that minimize subsequent parathyroid gland hypertrophy. Low observed PTH levels in Japan are likely driven in part by low target levels established by the Japanese Society for Dialysis Therapy, which had recommended keeping PTH levels between 60 and 180 pg/mL before 2012 and between 60 and 240 pg/mL



**Figure 5.** (A) Prevalence of phosphate binder (PB) prescription in US black/African American (AA), US non–black/African American, European, and Japanese hemodialysis (HD) populations during the first 5 years of HD. Locally weighted regression (LOESS) model includes 481,443 months of data from 32,619 patients. (B) Prevalence of calcium (Ca)-based and non–calcium-based phosphate binder prescription at months 1 and 36 after initiating HD in US black/African American, US non–black/African American, European, and Japanese HD populations, among patients with serum phosphorus (P) levels > 5.5 mg/dL in the prior month.

since 2012.<sup>18</sup> In contrast, US and European nephrologists appear to follow the 2009 KDIGO (Kidney Disease: Improving Global Outcomes) CKD-MBD guidelines that recommend PTH level be maintained between 2 to 9 times the normal range of PTH,<sup>19</sup> with many US and European DOPPS Study site medical directors indicating their upper PTH target to be 600 pg/mL.<sup>4</sup> Regional variation in PTH levels observed in our study was consistent with these guideline differences.

Although most dialysis patients have secondary hyperparathyroidism, some will progress to tertiary hyperparathyroidism, which is characterized by extremely high PTH levels that are refractory to medical treatment.<sup>20</sup> A striking finding in the present study is that

despite substantially greater prescription of cinacalcet and active vitamin D in the United States, PTH levels were higher in the United States, especially among black/African American patients, than in Japan or Europe. One possible explanation is an increased prevalence of tertiary hyperparathyroidism in the United States, resulting in parathyroid glands requiring much greater drug use to control PTH levels. A difference in parathyroidectomy rates is an unlikely explanation for the observed international differences in PTH control, as an earlier DOPPS showed relatively low parathyroidectomy rates in Japan.<sup>21</sup>

Another possibility is that genetic differences could influence the ability to control PTH levels in different racial



groups. Recent work by Fuller et al<sup>22</sup> has shown higher PTH levels despite greater cinacalcet use among black/African American versus non-black/African American US HD patients. Further studies are needed to determine whether inherited or other factors explain higher PTH levels among US black/African American patients and how such factors may affect therapeutic approaches to improve PTH management and ultimately minimize consequent bone and cardiovascular complications. This is important because high PTH levels are known to activate bone resorption, thereby precipitating renal osteodystrophy and elevating calcium and phosphorus levels through gut absorption and bone resorption.<sup>23</sup> Elevated calcium and phosphorus levels are associated with greater coronary artery calcification, which is strongly related to increased mortality and excess cardiovascular events.<sup>24–28</sup> Additionally, although Tentori et al<sup>21</sup> observed no effect modification of the PTH-mortality association by black/African American race, we show that a greater proportion of US black/African American (vs non-black/African American) patients are included in the highest risk category (PTH > 600 pg/mL) despite greater cinacalcet and active vitamin D use.

Compared with US and European patients, Japanese HD patients had the lowest serum calcium levels despite greater use of calcium-based binders, higher dialysate calcium concentrations (than the United States), and less use of cinacalcet, which can cause hypocalcemia. Lower calcium levels in Japanese patients may be partially explained by lower PTH levels.

Mean phosphorus levels increased by 0.35 to 0.65 mg/dL in the first 4 months in all regions, with a small gradual increase thereafter in the United States, while decreasing in Europe during the next 4.5 years of HD to 4.8 mg/dL, much lower than in the United States and Japan. Phosphorus levels were highest in Japan throughout the 5-year study period even though Japanese patients had the lowest PTH levels, which can lead to lower gut phosphorus absorption and lower release of calcium/phosphorus from bones.<sup>29</sup>

The initial phosphorus level increase could be explained by resolving uremic anorexia following dialysis initiation, gradual loss of residual kidney function, and the initial surge in active vitamin D use that increases gut absorption of calcium and phosphorus. Although phosphate binder use was comparable across countries, active vitamin D use was considerably lower in European versus US and Japanese patients, which could contribute to the lower serum phosphorus levels observed. However, it is also conceivable that dietary phosphorus intake may be lower in Europe.

Strengths of our study include the nationally representative sampling design and large DOPPS database with information for hundreds of thousands of monthly data points. However, the descriptive nature of this study limits our ability to explain international and racial differences and trends in MBD indicator levels during the first 5 years

of HD. Not all patients were followed from their first day of dialysis and so we used repeated cross-sections to fully utilize our longitudinal data to obtain trajectories during the first 5 years of HD. Although prescription of medications was captured, medication dosages were not widely available and we lacked data for over-the-counter medications and patient adherence to prescriptions that may have further informed the observed findings. It is also possible that practice changes occurring during the study period may have altered trajectories; however, between DOPPS phase 4 (2009–2011) and phase 5 (2012–2015), only small changes were observed for most of the depicted MBD-related measures.<sup>21,30,31</sup> Two exceptions are that cinacalcet use increased dramatically in Japan<sup>21</sup> and mean PTH levels increased in the United States.<sup>30</sup> PTH trajectories in DOPPS phase 4 and phase 5 are illustrated in Fig S2; differences were minimal in Japan, Europe, and US non-black/African American patients. In US black/African American patients, PTH levels had the same J-shaped trajectory, but at a slightly higher mean PTH level. Despite temporal trends in some measures, the basic patterns illustrated in our study smooth out these differences, reflecting time-averaged results.

In conclusion, large international differences exist in the levels and trajectories of MBD markers and medications during the first 5 years of HD therapy. In particular, mean PTH levels were much higher in the United States, especially among black/African American patients, than in Japan and Europe despite substantially greater prescription of cinacalcet and active vitamin D in the United States. Future study is warranted to explore other potential contributors to international and racial differences in PTH levels and how they may affect therapeutic approaches to improve PTH management and ultimately minimize consequent bone and cardiovascular complications.

## SUPPLEMENTARY MATERIAL

### Supplementary File (PDF)

**Figure S1:** Prevalence of (a) calcium (Ca)-based and (b) non-Ca-based phosphate binder (PB) prescription in US black/African Americans, US non-black/African Americans, European, and Japanese hemodialysis populations over the first 5 years of hemodialysis. LOESS model includes 480,633 months of data from 32,611 patients.

**Figure S2:** Mean parathyroid hormone (PTH) levels in US black/African Americans, US non-black/African Americans, European, and Japanese hemodialysis populations over the first 5 years of hemodialysis, by DOPPS phase. LOESS models include 80,336 PTH measurements from 11,007 patients in DOPPS phase 4 (2009–2011) and 173,573 PTH measurements from 20,979 patients in DOPPS phase 5 (2012–2015).

## ARTICLE INFORMATION

**Authors' Full Names and Academic Degrees:** Kevin Chan, MD, Angelo Karaboyas, MS, Hal Morgenstern, PhD, Bruce M. Robinson, MD, Friedrich K. Port, MD, Stefan H. Jacobson, MD,

Masafumi Fukagawa, MD, Yvonne Meier, PhD, Philipp A. Csomor, PhD, and Ronald L. Pisoni, PhD.

**Authors' Affiliations:** Division of Nephrology, Massachusetts General Hospital, Boston, MA (KC); Arbor Research Collaborative for Health (AK, BMR, RLP); Departments of Epidemiology (AK, HM, FKP) and Environmental Health Sciences (HM), School of Public Health, and Departments of Urology (HM) and Internal Medicine-Nephrology (BMR, FKP), University of Michigan Medical School, Ann Arbor, MI; Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden (SHJ); Tokai University School of Medicine, Isehara, Japan (MF); and Vifor Pharma Ltd, Glattbrugg, Switzerland (YM, PAC).

**Address for Correspondence:** Ronald L. Pisoni, PhD, Arbor Research Collaborative for Health, 340 E Huron St, Ste 300, Ann Arbor, MI 48104. E-mail: [ronald.pisoni@arborresearch.org](mailto:ronald.pisoni@arborresearch.org)

**Authors' Contributions:** Research idea and study design: KC, AK, RLP, FKP, YM, PAC, MF, BMR; data acquisition: SJ, AK, RLP, BMR; data analysis/interpretation: KC, SJ, AK, RP, FKP, HM, YM, PAC, MF, BMR; statistical analysis: AK; supervision or mentorship: RLP, FKP, HM, BMR. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

**Support:** This manuscript was directly supported by Vifor-Fresenius Medical Care Renal Pharma Ltd. Global support for the ongoing DOPPS Programs is provided without restriction on publications. See <https://www.dopps.org/AboutUs/Support.aspx> for more information. Vifor-Fresenius Medical Care Renal Pharma Ltd had a role in study design.

**Financial Disclosure:** Mr Karaboyas and Drs Pisoni, Robinson, and Port are employees of Arbor Research Collaborative for Health, which administers the DOPPS. Dr Meier was an employee of Vifor Fresenius. Dr Csomor is an employee of Vifor Pharma. Dr Fukagawa has received consulting fees from Kyowa-Hakko Kirin (KHK) and Ono Pharmaceutical; lecture fees from KHK, Bayer, Torii Pharmaceutical, and Ono Pharmaceutical; and grants from KHK and Bayer. Dr Chan has acted as a consultant to Relypsa. Drs Jacobson and Morgenstern have no conflicts of interest to declare.

**Acknowledgements:** Jennifer McCready-Maynes, an employee of Arbor Research Collaborative for Health, provided editing support for this article.

**Peer Review:** Received November 27, 2018. Evaluated by 2 external peer reviewers, with direct editorial input from the Statistical Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form Apr 29, 2019.

## REFERENCES

- Kakuta T, Tanaka R, Hyodo T, et al. Effect of sevelamer and calcium-based phosphate binders on coronary artery calcification and accumulation of circulating advanced glycation end products in hemodialysis patients. *Am J Kidney Dis.* 2011;57(3):422-431.
- Russo D, Corrao S, Battaglia Y, et al. Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. *Kidney Int.* 2011;80(1):112-118.
- Cozzolino M, Messa P, Brancaccio D, et al. Achievement of NKF/K-DOQI recommended target values for bone and mineral metabolism in incident hemodialysis patients: results of the FARO-2 cohort. *Blood Purif.* 2014;38(1):37-45.
- Tentori F, Zepel L, Fuller DS, et al. The DOPPS Practice Monitor for US dialysis care: PTH levels and management of mineral and bone disorder in US hemodialysis patients. *Am J Kidney Dis.* 2015;66(3):536-539.
- Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int.* 2005;67(3):1179-1187.
- Kalantar-Zadeh K, Miller JE, Kovesdy CP, et al. Impact of race on hyperparathyroidism, mineral disarrays, administered vitamin D mimetic, and survival in hemodialysis patients. *J Bone Miner Res.* 2010;25(12):2448-2458.
- Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2016;67(3)(suppl 1):S1-S434.
- Natoli JL, Boer R, Nathanson BH, et al. Is there an association between elevated or low serum levels of phosphorus, parathyroid hormone, and calcium and mortality in patients with end stage renal disease? A meta-analysis. *BMC Nephrol.* 2013;14:88.
- Young EW, Goodkin DA, Mapes DL, et al. The Dialysis Outcomes and Practice Patterns Study (DOPPS): an international hemodialysis study. *Kidney Int.* 2000;57(suppl):S74-S81.
- Pisoni RL, Gillespie BW, Dickinson DM, et al. The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. *Am J Kidney Dis.* 2004;44(5)(suppl 2):7-15.
- Cleveland WS, Devlin SJ. Locally weighted regression: an approach to regression analysis by local fitting. *J Am Stat Assoc.* 1988;83(403):596-610.
- Bradbury BD, Fissell RB, Albert JM, et al. Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol.* 2007;2(1):89-99.
- Chan KE, Maddux FW, Tolkoff-Rubin N, et al. Early outcomes among those initiating chronic dialysis in the United States. *Clin J Am Soc Nephrol.* 2011;6(11):2642-2649.
- Ritter CS, Armbrecht HJ, Slatopolsky E, Brown AJ. 25-Hydroxyvitamin D(3) suppresses PTH synthesis and secretion by bovine parathyroid cells. *Kidney Int.* 2006;70(4):654-659.
- Levin A, Bakris GL, Molitch M, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int.* 2007;71(1):31-38.
- Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO chronic kidney disease—mineral and bone disorder (CKD-MBD) guideline update: what's changed and why it matters. *Kidney Int.* 2017;92(6):26-36.
- Robinson BM, Akizawa T, Jager KJ, et al. Factors affecting outcomes in patients reaching end-stage kidney disease worldwide: differences in access to renal replacement therapy, modality use, and haemodialysis practices. *Lancet.* 2016;388(10041):294-306.
- Fukagawa M, Yokoyama K, Koiwa F, et al. Clinical practice guideline for the management of chronic kidney disease—mineral and bone disorder. *Ther Apher Dial.* 2013;17(3):247-288.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease—mineral and bone disorder (CKD-MBD). *Kidney Int Suppl.* 2009;113:S1-S130.
- Jamal SA, Miller PD. Secondary and tertiary hyperparathyroidism. *J Clin Densitom.* 2013;16(1):64-68.
- Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among

- patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. *Clin J Am Soc Nephrol*. 2015;10(1):98-109.
22. Fuller DS, Xing S, Belozeroff V, et al. Variability in cinacalcet prescription across US hemodialysis facilities. *Clin J Am Soc Nephrol*. 2019 Feb 7;14(2):241-249. <https://doi.org/10.2215/CJN.09550818>.
  23. Daugirdas J, Ing T, Blake P. Handbook of dialysis. <http://www.lavoisier.fr/livre/notice.asp?ouvrage=1245698>. Accessed May 4, 2018.
  24. Goodman WG, London G, Amann K, et al. Vascular calcification in chronic kidney disease. *Am J Kidney Dis*. 2004;43(3):572-579.
  25. Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J*. 2001;141(3):375-382.
  26. Anaya P, Blomquist G, Davenport D, et al. Coronary artery calcification in CKD-5D patients is tied to adverse cardiac function and increased mortality. *Clin Nephrol*. 2016;86(12):291-302.
  27. Park KS, Park J, Choi SH, et al. Serum phosphorus concentration and coronary artery calcification in subjects without renal dysfunction. *PLoS One*. 2016;11(3):e0151007.
  28. Gao Z, Li X, Miao J, et al. Impacts of parathyroidectomy on calcium and phosphorus metabolism disorder, arterial calcification and arterial stiffness in haemodialysis patients. *Asian J Surg*. 2019;42(1):6-10.
  29. Guyton AC, Hall JE. *Textbook of Medical Physiology*. 9th ed. Philadelphia, PA: W.B. Saunders Company; 1996.
  30. Tentori F, Fuller DS, Port FK, Bieber BA, Robinson BM, Pisoni RL. The DOPPS practice monitor for US dialysis care: potential impact of recent guidelines and regulatory changes on management of mineral and bone disorder among US hemodialysis patients. *Am J Kidney Dis*. 2014;63(5):851-854.
  31. DOPPS Practice Monitor. <https://www.dopps.org/OurStudies/DOPPSPracticeMonitor.aspx>. Accessed April 11, 2019.