ORIGINAL ARTICLE

Associations of time-dependent changes in phosphorus levels with cardiovascular diseases in patients undergoing hemodialysis: results from the Japan Dialysis Active Vitamin D (J-DAVID) randomized clinical trial

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ABSTRACT

Background. While the risk of exceeding the standard range of phosphorus levels has been investigated, the impact of the degree of fluctuations has not been investigated.

Methods. Data were derived from the Japan Dialysis Active Vitamin D trial, a 4-year prospective, randomized study involving 976 patients without secondary hyperparathyroidism undergoing hemodialysis in Japan. Laboratory data were collected every 6 months and the primary outcome was the time to the occurrence of cardiovascular events. The effect of time-dependent changes in phosphorus levels was assessed using a time-varying Cox proportional hazards regression model.

Results. The median serum phosphorus levels at baseline and at the final observation were 4.70 mg/dl (interquartile range [IQR] 3.90–5.30) and 5.00 mg/dl (IQR 4.20–5.80), respectively. Over each 6-month period, phosphorus changes ranged from −7.1 to +6.7 mg/dl, with a median value of −0.1 to +0.3 mg/dl. During follow-up, composite cardiovascular events occurred in 103 of 964 patients. Although the P-value for the interaction between serum phosphorus level fluctuations and baseline phosphorus levels was insignificant, the following trends were observed. First, patients with
relatively high initial phosphorus levels over a 6-month period showed a trend towards a higher hazard, with greater changes in the phosphorus level over the 6-month period. Second, it was suggested that oral vitamin D receptor activators could contribute to the relationship between fluctuating phosphorus levels and cardiovascular events.

**Conclusions.** Our results suggest the importance of maintaining stable phosphorus levels, not only in the normal range, but also without fluctuations, in the risk of cardiovascular events among patients without secondary hyperparathyroidism undergoing maintenance hemodialysis.

**GRAPHICAL ABSTRACT**

**Introduction**

Chronic kidney disease–mineral and bone disease (CKD-MBD) is one of the most important complications in patients undergoing dialysis because it is strongly associated with mortality [1]. Phosphorus level is an important factor in CKD-MBD. The 2006 [2] and 2012 [3] versions of the Clinical Practice Guidelines of the Japanese Society for Dialysis Therapy indicate that the target range for serum phosphate levels should be between 3.5 and 6.0 mg/dl; this criterion is used the standard for medical care in Japan. Meanwhile, the Kidney Disease: Improving Global Outcomes 2017 clinical practice guideline suggests lowering the phosphate level to the normal range for adults (2.5–4.5 mg/dl) [4].

Although previous studies have demonstrated an association between high phosphorus levels and worse clinical outcomes, many have used a single baseline phosphorus level as a predictor or assumed that the time course changes in each patient were equal. However, in clinical settings, phosphorus levels can easily fluctuate, depending on variations in food intake [5], drug adherence and the time interval between dialysis sessions [6]. Transient elevations in phosphorus levels have been suggested to impair vascular endothelial function in healthy men [7]. Furthermore, repetitive diet-induced fluctuations in plasma phosphorus levels increase inflammatory factors and oxidative stress levels, causing inflammation and vascular calcification in both normal [8] and early-stage CKD rats [9]. To investigate the potential burden of excess serum phosphate, several researchers have used different approaches focusing on the mean serial monthly phosphorus measurement [10], the number of months with the phosphorus level on the target [11] and the area under the curve for phosphorus level control [12].

The Japan Dialysis Active Vitamin D (J-DAVID) [13] trial aimed to determine whether vitamin D receptor activators (VDRAs) reduce cardiovascular events and mortality in patients without secondary hyperparathyroidism undergoing hemodialysis. Therein, oral alfacalcidol did not reduce the risk of cardiovascular events among the patients, despite the investigators’ expectations; laboratory data, including phosphorus levels, were collected every 6 months.
Observational studies have revealed that excessively high or low phosphorus levels may lead to worse clinical outcomes in patients undergoing hemodialysis (HD) [14]. However, the associations between fluctuations in phosphorus levels and patients’ morbidity and mortality have been controversial. In this study, phosphorus level fluctuations were indirectly assessed based on the initial level and changes in phosphorus during each 6-month period. Herein we aimed to explore the association between time-dependent changes in phosphorus levels and cardiovascular diseases (CVDs) in patients undergoing HD as a secondary analysis of data from the J-DAVID randomized clinical trial.

MATERIALS AND METHODS

Participants

This study was performed as a post hoc analysis of data from the J-DAVID trial, a randomized, open-label, blinded-endpoint study that compared the effects of alfacalcidol and standard medical care on cardiovascular events in patients in hospital in Japan. The inclusion criteria were as follows: age 20–80 years, maintenance HD without any VDRAs at randomization, serum calcium ≤10.0 mg/dl, phosphorus ≤6.0 mg/dl and intact parathyroid hormone (iPTH) ≤180 pg/ml. The study included 964 patients divided into two groups: the intervention group, treated with oral alfacalcidol (0.5 μg/day; n = 495), and the control group, treated without VDRAs (n = 481). After excluding 12 patients (7 in the oral alfacalcidol group and 5 in the control group) who had been using VDRAs at the time of randomization, 960 patients were analyzed. The details of the study protocol and primary study results have been previously published [13, 15].

Outcome measure

The primary outcome measure was the time of the composite measure of fatal and nonfatal cardiovascular events, including acute myocardial infarction, congestive heart failure requiring hospitalization, stroke, aortic dissection/torsion, amputation of the ischemic limb, sudden cardiac death, coronary intervention or bypass grafting and lower-limb artery intervention or bypass grafting. Laboratory data were collected every 6 months.

Statistical analysis

A time-varying Cox proportional hazards regression model was used to estimate the impact of the time-dependent changes in the phosphorus level over 6 months and the phosphorus level changes, we performed a similar regression analysis considering three- and two-way cross-product terms between the phosphorus level changes during the 6-month period and 6 months and VDRA prescription, measured at each time point.

All statistical hypothesis tests were performed with a two-sided significance level of 5% using R software (https://cran.r-project.org/). Figure 1 shows the outline of the analysis.

Ethics

This study was performed per the Ethical Guidelines for Clinical Research of the Japanese Ministry of Health, Labour, and Welfare (created 30 July 2003; full revision 28 December 2004; full revision 31 July 2008) and the Declaration of Helsinki (revision 2013). This study was approved by the ethics committee of the Osaka City University Graduate School of Medicine in Japan (approval numbers 1227, 1297, 1385 and 1525) and the relevant ethics committees or institutional review boards at the study sites. All participants provided written informed consent prior to participating in the study.

RESULTS

Data at baseline

A total of 964 patients were analyzed (control group, n = 476; oral alfacalcidol group, n = 488). Table 1 shows the baseline characteristics of the participants: median age 65.00 years [interquartile range (IQR) 58.00–71.00], male 60.0%, median dialysis duration 5.0 years (IQR 2.0–11.0), diabetes mellitus 46%, CVD history 25.3%, median phosphorus level 4.70 mg/dl (IQR 3.90–5.30), median corrected calcium level 9.10 mg/dl (IQR 8.80–9.50) and median iPTH level 85.35 pg/ml (IQR 46.08–129.20). More than 80% of patients used calcium carbonate. The patients were divided into four groups according to the change in phosphorus levels during the first 6 months. Their baseline characteristics are shown in Table 2. The median phosphorus level change during the first 6 months of follow-up was 0.3 mg/dl (IQR −0.5–1.0). The group with negative phosphorus level changes between 0 and 6 months of follow-up had a high phosphorus level at 0 months, whereas the group with positive phosphorus level changes had a low phosphorus level at 0 months.

Data changes during follow-up

The median follow-up period was 4 years. The median phosphorus, corrected calcium and iPTH levels for every 6 months are shown in Fig. 2. Although the serum phosphorus and corrected calcium levels remained almost stable within the target range, the iPTH levels gradually increased over time. The values at the last observation (48 months) were as follows: median phosphorus level 5.00 mg/dl (IQR 4.20–5.80), median corrected calcium level 9.20 mg/dl (IQR 8.80–9.60) and median iPTH level 113.00 pg/ml (IQR 62.25–190.70). The results for the oral alfacalcidol and control groups have been previously described [13]. Twenty participants who were lost to follow-up were censored on the last day of follow-up and the outcomes of these participants were unknown. The assigned treatment was discontinued in 158 of the 488 patients in the oral alfacalcidol group and 169
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Initial phosphorus level of the 6-month period 

Calculated impact of the above two factors on cardiovascular events 

Change of phosphorus
- 0–6 months: $x(1)$
- 6–12 months: $x(2)$
- 12–18 months: $x(3)$
- 18–24 months: $x(4)$
- 24–30 months: $x(5)$
- 30–36 months: $x(6)$
- 36–42 months: $x(7)$
- 42–48 months: $x(8)$

This calculation was performed for all the patients and the results were combined to draw a graph with the phosphorus level change on the x-axis and log hazard on the y-axis. Initial phosphorus values over a 6-month period are expressed by color coding.

Association of phosphorus level fluctuations with the CVD risk

During follow-up, composite cardiovascular events occurred in 103 (19.5%) of 964 patients, including acute myocardial infarction ($n = 21$), congestive heart failure requiring hospitalization...
Table 1. Baseline characteristics of the patients

| Characteristics                  | Overall (N = 964) | Control (n = 476) | Oral alfalcaldol (n = 488) |
|----------------------------------|-------------------|------------------|---------------------------|
| Age (years)                      | 65.00 (58.00–71.00) | 65.00 (58.00–71.00) | 65.00 (58.00 – 70.25)     |
| Male, n (%)                      | 578 (60.0)        | 277 (58.2)       | 201 (61.7)                |
| Dialysis duration (years)        | 5.0 (2.0–11.0)    | 5.0 (2.0–11.0)   | 6.0 (2.0–10.0)            |
| CVD history, n (%)               | 244 (25.3)        | 117 (24.6)       | 127 (26.0)                |
| Diabetes mellitus, n (%)         | 443 (46.0)        | 226 (47.5)       | 217 (44.5)                |
| SBP (mmHg)                       | 146 (133–160)     | 148 (134–160)    | 145 (130–160)             |
| BMI (kg/m²)                      | 21.07 (19.05–23.31) | 21.07 (19.08–23.27) | 21.08 (19.05–23.34)     |
| CRP (mg/dl)                      | 0.10 (0.05–0.29)  | 0.10 (0.05–0.26) | 0.10 (0.05–0.30)          |
| ALP (IU/l)                       | 234.00 (183.00–296.25) | 235.00 (184.00–299.00) | 233.00 (182.00–295.00)   |
| Albumin (mg/dl)                  | 3.80 (3.50–4.00)  | 3.75 (3.50–4.00) | 3.80 (3.50–3.90)          |
| Phosphorus (mg/dl)               | 4.70 (3.90–5.30)  | 4.70 (4.00–5.40) | 4.60 (3.90–5.20)          |
| Corrected calcium (mg/dl)        | 9.10 (8.80–9.50)  | 9.10 (8.70–9.50) | 9.10 (8.80–9.50)          |
| iPTH (pg/ml)                     | 85.35 (46.08–129.20) | 86.10 (47.00–127.28) | 85.05 (45.67–130.00)     |
| Hemoglobin (g/dl)                | 10.60 (10.10–11.30) | 10.70 (10.10–11.30) | 10.60 (10.00–11.30)     |

Medication, n (%)
- Calcium carbonate: 804 (83.4) 392 (82.4) 412 (84.4)
- Sevelamer hydrochloride: 308 (32.0) 155 (32.6) 153 (31.4)
- Lanthanum carbonate: 118 (12.2) 49 (10.3) 69 (14.1)
- Cinacalcet hydrochloride: 56 (5.8) 29 (6.1) 27 (5.5)
- Active vitamin D sterol: 0 (0.0) 0 (0.0) 0 (0.0)

Values are presented as median (IQR) unless stated otherwise.
SBP, systolic blood pressure; BMI, body mass index; CRP, C-reactive protein; ALP, alkaline phosphatase.

Table 2. Baseline characteristics of four groups of patients classified according to the degree of phosphorus variability during the first 6 months

| Change in phosphorus over 0–6 months | 1st quartile (<25%) (n = 214) | 2nd quartile (≥25%–<50%) (n = 234) | 3rd quartile (≥50%–<75%) (n = 229) | 4th quartile (≥75%–<100%) (n = 247) |
|-------------------------------------|---------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| Range of phosphorus variability     | −4.2 to −0.5                    | −0.5 to +0.3                         | +0.3 to +1.0                        | +1.0 to +6.5                        |
| Age (years)                         | 65.00 (57.25–71.00)             | 65.00 (59.00–70.00)                 | 64.00 (58.00–71.00)                 | 65.00 (58.50–70.00)                 |
| Male, n (%)                         | 139 (65.0)                      | 143 (61.1)                          | 128 (55.9)                         | 149 (60.3)                          |
| Dialysis duration (years)           | 6.00 (2.00–11.00)               | 6.00 (2.00–12.00)                   | 5.00 (2.00–10.00)                  | 5.00 (2.00–10.00)                   |
| CVD history, n (%)                  | 52 (24.3)                       | 54 (23.1)                           | 62 (27.1)                          | 62 (25.1)                           |
| Diabetes mellitus, n (%)            | 95 (44.4)                       | 114 (48.7)                          | 106 (46.3)                         | 113 (45.7)                          |
| SBP (mmHg)                          | 147.00                          | 144.50                              | 146.00                              | 149.00                              |
| BMI (kg/m²)                         | (133.00–163.00)                 | (132.00–159.75)                     | (134.00–160.00)                    | (134.50–161.50)                     |
| CRP (mg/dl)                         | 20.81 (18.82–23.07)             | 21.47 (19.27–23.37)                 | 20.95 (19.00–23.08)                | 21.44 (19.36–23.85)                 |
| ALP (IU/l)                          | 0.10 (0.05–0.30)                | 0.10 (0.05–0.25)                    | 0.10 (0.05–0.23)                   | 0.11 (0.05–0.32)                    |

Medication, n (%)
- Calcium carbonate: 804 (83.4) 392 (82.4) 412 (84.4)
- Sevelamer hydrochloride: 308 (32.0) 155 (32.6) 153 (31.4)
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- Active vitamin D sterol: 0 (0.0) 0 (0.0) 0 (0.0)

Values are presented as median (IQR) unless stated otherwise.
SBP, systolic blood pressure; BMI, body mass index; CRP, C-reactive protein; ALP, alkaline phosphatase.
FIGURE 2: Changes in phosphorus, corrected calcium and iPTH levels. Phosphorus, corrected calcium and iPTH levels in all participants every 6 months. Data are expressed as median (IQR).
Fluctuations of phosphorus in HD patients

FIGURE 3: Changes in phosphorus levels of the four groups of patients classified according to the degree of phosphorus level variability during the first 6 months. The changes in the phosphorus level over time from 6 months onwards for the four groups in Table 2 (i.e. quartile groups of phosphorus level change in the first 6 months) are shown. 1Q (n = 214): 1st quartile (−4.2 to −0.5 mg/dl), 2Q (n = 234): 2nd quartile (−0.5–0.3 mg/dl), 3Q (n = 229): 3rd quartile (0.3–1.0 mg/dl) and 4Q (n = 247): 4th quartile (1.0–6.5 mg/dl). They eventually converged to similar values.

Table 3. Range of phosphorus fluctuations (mg/dl) in each of the 6-month periods

| Values       | 0–6 months | 6–12 months | 12–18 months | 18–24 months | 24–30 months | 30–36 months | 36–42 months | 42–48 months |
|--------------|------------|-------------|--------------|--------------|--------------|--------------|--------------|--------------|
| Minimum      | −4.2       | −7.1        | −5.6         | −4.9         | −5.6         | −4.6         | −6.2         | −6.1         |
| Median       | 0.3        | 0           | −0.1         | 0            | 0.1          | −0.1         | 0            | 0.1          |
| IQR          | −0.50–1.00 | −0.70–0.80  | −0.90–0.80   | −0.80–0.80   | −0.90–0.90   | −1.00–0.80   | −0.90–0.70   | −0.70–0.90   |
| Maximum      | 6.5        | 6.3         | 6.2          | 4.7          | 6.0          | 6.7          | 5.3          | 5.2          |

for the quartiles of phosphorus levels at the start of the trial: 1.1 (minimum), 3.9 (first quartile), 4.7 (second quartile), 5.3 (third quartile) and 6.0 (maximum).

The relationship between fluctuating phosphorus levels and cardiovascular events varied depending on the phosphorus level at the start of the 6-month period of interest. Positive changes of extremely low phosphorus over the 6-month period were associated with a relatively low hazard of cardiovascular events. In contrast, the logarithmic hazard graph for the remaining patients exhibited a U-shape. More specifically, fluctuations in phosphorus levels (both increases and decreases) were associated with an increased log hazard. The P-value for the interaction between the amount of change in the phosphorus level and the level 6 months earlier was .826 (Fig. 4).

Furthermore, the prescription of oral VDRA may contribute to the relationship between fluctuating phosphorus levels and cardiovascular events (Fig. 5). In the patients prescribed oral VDRA, fluctuations in the phosphorus level (both increases and decreases) were associated with an increased log hazard. On the other hand, in patients not prescribed VDRA, positive changes in phosphorus levels appeared to be less associated with an increased log hazard of CVD events. The P-value for the interaction between the amount of change in the phosphorus level, phosphorus level 6 months prior and prescription of oral VDRA was .648. Supplementary Figures 1 and 2 extend the y-axis graphical range of Figs. 4 and 5, respectively.

**DISCUSSION**

The impact of cross-sectional values, such as high and low phosphorus levels, on the risk of CVDs has been investigated previously. The point of this study focuses not only on whether the values are high or low, but also on how much they fluctuate. CKD patients are known to have a higher risk of developing CVD. Previous studies have suggested that CKD-MBD progression is related to mortality and morbidity in patients with end-stage kidney disease. Several hormones are involved in CKD-MBD pathogenesis. For example, transient elevations in phosphorus levels have been suggested to impair vascular endothelial function and increase inflammatory factor and oxidative stress levels, causing inflammation and vascular calcification.

Based on previous cohort studies reporting that VDRAs were associated with a lower risk for CVD-related mortality and CVD events in patients undergoing HD, the J-DAVID randomized clinical trial focused on the effect of oral VDRAs...
on the risk of cardiovascular events by comparing treatment with 0.5 μg/day of oral alfacalcidol with standard care without VDRAs. Using data from the J-DAVID trial, we conducted a secondary analysis to examine the association between the fluctuations in phosphorus levels and the risk of cardiovascular events.

The fact that elevation of the phosphorus level over the 6-month period from an excessively low level was associated with a relatively low hazard of cardiovascular events than the same extent of elevation from a higher baseline may reflect an improvement in nutritional status. In contrast, it has been suggested that both an increase and decrease over a 6-month period may have associations with increased cardiovascular events if the baseline phosphorus level is within the normal range. This means that it is important to maintain the phosphorus level not only in the normal range, but also without fluctuations in patients undergoing maintenance HD. Although it has been reported that excessively high or low phosphorus levels are related to an unfavorable prognosis [14], to the best of our knowledge, no previous studies have demonstrated the clinical significance of fluctuations in phosphorus levels in the prognosis of patients with end-stage renal disease.

In addition, CVD risk related to fluctuating phosphorus levels tended to be more prominent when oral VDRAs were prescribed. Excessive use of VDRAs has been suggested to lead to vascular calcification and an increase in serum fibroblast growth factor 23 (FGF23) [21]. A previous study reported that increased serum FGF23 levels could cause left ventricular hypertrophy and inflammation in patients with CKD [22–24]. Therefore it is suggested that the serum phosphorus level should be strictly controlled in patients prescribed VDRA [25], and fluctuations could also be associated with poorly controlled phosphaturic hormones, such as FGF23.

In our analysis, the $P$-value for the interaction between serum phosphorus level fluctuations and baseline phosphorus levels or VDRA prescription was insignificant. There are two reasons that could explain this finding. First, the final number of participants was 976, which was smaller than the expected sample size ($n = 1600$), and fewer cardiovascular events occurred than were expected. While the investigators estimated the proportion of patients who experienced a composite of CVD to be 7–9% in 1 year or 28–36% in 4 years, the actual occurrence was 19.5% during the 4-year follow-up. Second, it is possible that patients with relatively low phosphorus level variability were originally selected as participants for the J-DAVID trial. To assemble a control group not prescribed VDRAs, the investigators included specific patients without secondary hyperparathyroidism receiving maintenance HD whose serum calcium levels were $<10.0$ mg/dL, phosphate levels were $<6.0$ mg/dL and iPTH levels were $<180$ pg/ml and who were not taking any VDRAs at randomization. In addition, participants were encouraged to restrict dietary phosphate intake to $<800$ mg/day and their serum phosphorus levels were strictly controlled using medications, such as phosphate binders and cinacalcet, during the trial. In fact, the maximum quartile of the baseline phosphorus level in the analysis was 6.0 mg/dL. Adjusting the serum calcium level and subanalysis of alfacalcidol to exclude the effect of vitamin D–induced hypercalcemia did not result in significant $P$-values. However, as this study was originally designed to examine the general tendencies related to phosphorus level changes and

FIGURE 4: Logarithmic hazard for cardiovascular events according to the impact of the time-dependent changes in initial level and changes of phosphorus during each 6-month period. A time-varying Cox proportional hazards regression model was used for the estimation. Each curve represents the initial phosphorus level within the 6-month period of interest: 1.1 (minimum, red), 3.9 (1st quartile, brown), 4.7 (2nd quartile, green), 5.3 (3rd quartile, blue) and 6.0 (maximum, purple). The confidence interval is expressed as a part highlighted in each corresponding color. The x-axis represents the change in the phosphorus level over months.
Fluctuations of phosphorus in HD patients

FIGURE 5: Logarithmic hazard for cardiovascular events according to the impact of the time-dependent changes in initial level and changes in phosphorus during each 6-month period and prescription of VDRA. (A) Patients with prescription of VDRA and (B) patients without prescription of VDRA 6 months earlier. A time-varying Cox proportional hazards regression model was used for the estimation. Each curve represents the initial phosphorus level within the 6-month period of interest: 1.1 (minimum, red), 3.9 (first quartile, brown), 4.7 (second quartile, green), 5.3 (third quartile, blue) and 6.0 (maximum, purple). The confidence interval is expressed as a part highlighted in each corresponding color. The x-axis represents the change in the phosphorus level over 6 months.

cardiovascular risk, it is not crucial to interpret the P-value as <.05 in this post hoc analysis.

This study’s novelty and clinical importance are as follows. First, although the effect of hyperphosphatemia has been relatively well documented, few studies have directly assessed fluctuations in phosphorus levels, particularly in patients with end-stage kidney disease. Therefore this study partly addressed whether more or less phosphorus variability is associated with a better prognosis. Second, this study demonstrated the clinical implications of both excess and insufficient phosphorus. Third, in clinical practice, clinicians tend to decide the treatment approach depending on the patient’s condition, which introduces bias into the estimated treatment effect by considering the treatment and covariate information at a single time point. However, this problem has been ignored in several clinical studies. Therefore, as one of the novelties of this study, we considered time-varying treatment and covariates in our regression model, which was thought to be more appropriate for this study. This analysis answers the clinical question of which patient has a favorable prognosis, a patient whose phosphorus levels are generally within the normal range but are unsettled or a patient whose phosphorus levels are stable at high or low levels. We believe that our results provide clues to answer this question.

Our study has some limitations. First, this study focused on the overall general trend by integrating the clinical risk by period rather than individual phosphorus level fluctuations. Other analysis methods are needed to assess the impact of individual phosphorus level trajectories. Second, the definition of ‘fluctuations in phosphorus level’, especially for the period and threshold, is unclear. Although this study used data collected every 6 months in many facilities in Japan, laboratory data from patients undergoing maintenance HD were checked every 2 weeks, therefore it may be inappropriate to extrapolate our findings to this clinical situation. Third, this study was a post hoc analysis of data from a randomized clinical trial. The J-DAVID trial included specific inclusion criteria for CKD-MBD status. Another analysis that includes patients with secondary hyperparathyroidism may be desirable if possible. Furthermore, our study included a few patients with high phosphate levels, leading to variance inflation of the effect estimator in the patient population with higher phosphate levels.

In conclusion, our results suggest the importance of maintaining stable phosphorus levels, not only in the normal range, but also without fluctuations, against the risk of cardiovascular events among patients without secondary hyperparathyroidism undergoing maintenance HD. In particular, the risk of cardiovascular events in patients prescribed oral VDRAs or with high baseline serum phosphorus levels may be susceptible to fluctuations in phosphorus levels; however, further studies are required to confirm this finding.

SUPPLEMENTARY DATA
Supplementary data are available at ckj online.

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AUTHORS’ CONTRIBUTIONS

E.K.I., D.I. and Y.Y. participated in the design of this study and writing the manuscript. T.S., M.I., M.E., K.M., T.M., S.N. and D.I. participated in the conduct of the J-DAVID trial. H.I., D.K. and A.S. participated in the analysis of data. All authors were involved in drafting and reviewing and have approved the final manuscript for submission.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the performance of other subanalyses. The data will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

D.I. has received lecture fees from Ono Pharmaceutical and Kyowa Hakko Kirin. Y.Y. has received research support grants from Otsuka Pharmaceutical, Kyowa Hakko Kirin and Chugai Pharmaceutical. D.K. has received personal fees from Chugai Pharmaceutical, research grant and consultation fees for statistical analysis from Kyowa Kirin and personal fees and research grants from Bayer Yakuhin outside the submitted work. A.S. has received personal fees from Chugai Pharmaceutical, Bayer Yakuhin and Ono Pharmaceutical and personal fees and research grants from Kyowa Kirin, Takeda Pharmaceutical and Daiichi Sankyo outside the submitted work. S.N. has received personal fees from Chugai Pharmaceutical, Kyowa Kirin, Bayer Yakuhin, Ono Pharmaceutical, Kissei Pharmaceutical and Torii Pharmaceutical. T.M. has received personal fees from Ono Pharmaceutical. K.M. has received personal fees from Ono Pharmaceutical, served as the principal investigator of a clinical trial for Kyowa Kirin and received personal fees and research grants from Mitsubishi Tanabe outside the submitted work. M.I. has received personal fees from Chugai Pharmaceutical, Kyowa Kirin, Bayer Yakuhin, Ono Pharmaceutical, Kissei Pharmaceutical and Torii Pharmaceutical outside the submitted work. M.E. has received personal fees from Kissei Pharmaceutical, AstraZeneca and Torii Pharmaceutical and personal fees and research grants from Chugai Pharmaceutical, Kyowa Kirin, Ono Pharmaceutical, Nippon Boehringer Ingelheim and Mitsubishi Tanabe outside the submitted work. T.S. has received personal fees from Chugai Pharmaceutical, Kyowa Kirin and Kissei Pharmaceutical and personal fees and research grants from Bayer Yakuhin and Ono Pharmaceutical outside the submitted work. The remaining authors declare no competing financial interests or personal relationships that could have influenced the work reported in this study.

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