

# Clinical Implication of Consistently Strict Phosphate Control for Coronary and Valvular Calcification in Incident Patients Undergoing Hemodialysis

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**Aims:** Serum phosphate control is crucial for the progression of vascular and valvular calcifications. Strict phosphate control is recently suggested; however, there is a lack of convincing evidence. Therefore, we explored the effects of strict phosphate control on vascular and valvular calcifications in incident patients undergoing hemodialysis.

**Methods:** A total of 64 patients undergoing hemodialysis from our previous randomized controlled trial were included in this study. Coronary artery calcification score (CACS) and cardiac valvular calcification score (CVCS) were evaluated using computed tomography and ultrasound cardiography at baseline and 18 months after the initiation of hemodialysis. The absolute changes in CACS ( $\Delta$ CACS) and CVCS ( $\Delta$ CVCS) and the percent change in CACS ( $\% \Delta$ CACS) and CVCS ( $\% \Delta$ CVCS) were calculated. Serum phosphate level was measured at 6, 12, and 18 months after the initiation of hemodialysis. Moreover, phosphate control status was evaluated using the area under the curve (AUC) by the amount of time spent with a serum phosphate level of  $\geq 4.5$  mg/dL and the extent to which this threshold exceeded over the observation period.

**Results:**  $\Delta$ CACS,  $\% \Delta$ CACS,  $\Delta$ CVCS, and  $\% \Delta$ CVCS were significantly lower in the low AUC group than in the high AUC group.  $\Delta$ CACS and  $\% \Delta$ CACS were also significantly lower.  $\Delta$ CVCS and  $\% \Delta$ CVCS tended to be lower in patients whose serum phosphate level never exceeded 4.5 mg/dL than in those whose serum phosphate level continuously exceeded 4.5 mg/dL. AUC significantly correlated with  $\Delta$ CACS and  $\Delta$ CVCS.

**Conclusion:** Consistently strict phosphate control may slow the progression of coronary and valvular calcifications in incident patients undergoing hemodialysis.

*See editorial vol. 30: 1549-1551*

**Key words:** Cardiac valvular calcification, Coronary artery calcification, Hemodialysis, Strict phosphate control

## Introduction

Cardiovascular disease (CVD) is a leading cause of death in patients undergoing hemodialysis. It is well known that cardiac calcification is an important risk factor for CVD events and mortality<sup>1, 2</sup>. Cardiac calcification primarily consists of coronary artery calcification (CAC) and cardiac valvular calcification (CVC). Several patients with advanced-stage chronic kidney disease (CKD) already have CAC and CVC at the initiation of hemodialysis<sup>3</sup>. Moreover, these

abnormalities gradually or sometimes rapidly progress as the patients undergo hemodialysis for a long time. The most important problem is that cardiac calcification is closely related to the pathophysiology that results in the occurrence of various CVDs such as coronary artery disease, aortic disease, and stroke<sup>4, 5</sup>. Therefore, it is believed that halting the progression of cardiac calcification after the initiation of hemodialysis is crucial.

There are several risk factors for cardiac calcification. The classic risk factors commonly

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Received: January 5, 2023 Accepted for publication: March 15, 2023

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observed in patients undergoing hemodialysis are aging, diabetes mellitus, smoking, dyslipidemia, and hypertension<sup>6</sup>). The non-classic risk factors are anemia, uremic toxins, mineral disorders, oxidative stress, inflammation, activation of the renin-angiotensin-aldosterone and sympathetic nervous system, and volume overload. They are associated with the progression of cardiac calcification in this population<sup>7-9</sup>). Hyperphosphatemia is the most important risk factor for cardiac calcification<sup>10, 11</sup>) and most closely related to worse clinical outcomes<sup>12-14</sup>). The KDIGO guideline recommends lowering serum phosphate levels to the normal range in patients with CKD stage 3a-5D<sup>15</sup>). However, as this recommendation is primarily based on the results of observational studies, there is a lack of firm evidence regarding the target level of serum phosphorus control in patients with CKD, including patients undergoing hemodialysis.

This study aimed to investigate the relationship between consistently strict phosphate control status and CAC and CVC progression after the initiation of hemodialysis.

## Methods

### Study Design and Population

This study was a post hoc analysis of our previous randomized controlled trial (RCT) wherein we compared the effect of lanthanum carbonate (LC) with that of calcium carbonate (CC) on CAC and cardiac abnormalities after the initiation of hemodialysis<sup>16</sup>). Patients with contraindications to LC and CC and those with a history of parathyroidectomy were excluded from the previous study. Furthermore, those with insufficient data were excluded from this study. Among participants of the previous study, 64 patients whose CAC score (CACS) was  $\geq 30$  at baseline were included in this study. Moreover, we evaluated the CVC score (CVCS) for 34 patients who had available data. Serum phosphate levels were controlled between 3.5 and 6.0 mg/dL using appropriate phosphate binders according to the Japanese Society of Dialysis Therapy guidelines for managing chronic kidney disease-mineral and bone disorder (CKD-MBD)<sup>17</sup>). Our previous study was conducted according to the principles of the Declaration of Helsinki. The study protocols were approved by the Institutional Review Board of Kobe University Graduate School of Medicine (approval No. 230019). Written informed consent was obtained from all individual participants included in the study.

### Evaluation of Serum Phosphate Control Status

Serum phosphate levels were evaluated at 6, 12, and 18 months after the initiation of hemodialysis. Blood samples were collected from patients before dialysis on the first day of a weekly dialysis session. To evaluate the burden of serum phosphate excursions during the observation periods, we calculated the total area under the curve (AUC) for serum phosphate levels according to the previous study<sup>18</sup>): total AUC = sum of the surface areas of two trapezoids created by the amount of time spent with a serum phosphate level of  $\geq 4.5$  mg/dL and the extent to which this threshold exceeded over the 6-month period. Subsequently, the mean monthly AUC was calculated by dividing the total AUC by 12 (**Fig. 1A**). The median AUC for all patients was 0.443. The patients were classified into two groups based on the value. Moreover, to evaluate the excursions in serum phosphate control, we counted the number of times wherein the serum phosphate level exceeded 4.5 mg/dL among three observational time points (6, 12, and 18 months) in each patient (**Fig. 1B**).

### Evaluation of Changes in CAC and CVC

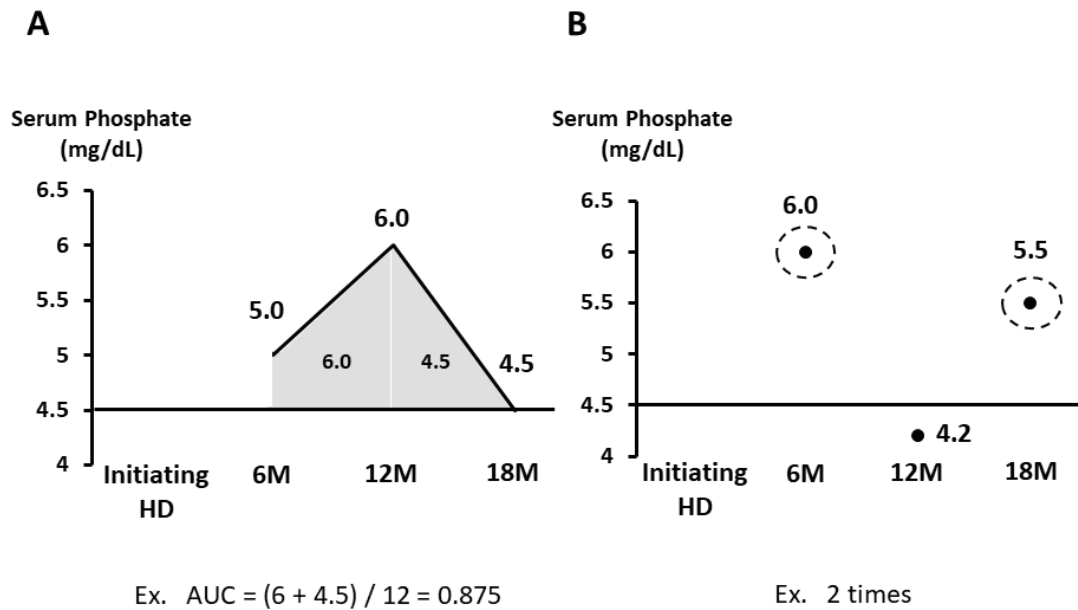
CAC was evaluated using a multidetector-row computed tomography scanner (Optima CT660; GE Healthcare, Aquilion ONE; TOSHIBA), and CACS was calculated at baseline and 18 months after the initiation of hemodialysis as the Agatston score according to a previous study<sup>19</sup>).

CVC was evaluated by determining the calcification of the aortic valve, mitral valve, and mitral annulus by transthoracic echocardiography at baseline and 18 months after the initiation of hemodialysis, and CVCS was calculated according to the evaluation method described in a previous study<sup>20</sup>).

Based on the calculated CACS and CVCS, we evaluated the absolute change in CACS ( $\Delta$ CACS) and CVCS ( $\Delta$ CVCS) and the percentage change in CACS ( $\% \Delta$ CACS) and CVCS ( $\% \Delta$ CVCS).

### Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 27.0 (SPSS Inc., Illinois, USA). Continuous variables were expressed as mean  $\pm$  standard deviation or median (interquartile range). Student's *t*-tests,  $\chi^2$  test, and Wilcoxon signed-rank test were used to compare patient characteristics at baseline and changes in CACS and CVCS. Spearman's correlation analysis was performed to investigate the correlation of AUC with  $\Delta$ CACS,  $\Delta$ CVCS,  $\% \Delta$ CACS, and  $\% \Delta$ CVCS. A multiple regression analysis was conducted to determine the independent factors



**Fig. 1.** Evaluation of serum phosphate control

A. AUC for serum phosphate levels

B. Number of times wherein the serum phosphate level exceeded 4.5 mg/dL

AUC, area under the curve

that correlated with CACS and CVCS. *P*-values of < 0.05 were considered statistically significant.

## Results

### Patient Characteristics

**Table 1** shows the characteristics of study patients at baseline. A total of 64 patients were divided into two groups according to the median of AUC: low AUC group ( $n=32$ ) and high AUC group ( $n=32$ ). The conventional risk factors for CVD were comparable between the two groups. Regarding the CKD-MBD parameters, serum phosphate levels were significantly lower in the low AUC group than in the high AUC group ( $4.4 \pm 1.1$  vs.  $5.6 \pm 1.0$  mg/dL,  $p < 0.001$ ). Serum calcium levels, serum intact PTH levels, and the use of phosphate binders and vitamin D agents were similar between the two groups. Moreover, baseline CACS showed no difference between the two groups. When they were divided into two groups based on the number of times wherein the serum phosphate level exceeded 4.5 mg/dL among three observational time points (0-time group or 3-times group), there were no significant differences in the clinical characteristics except for age and serum phosphate levels (**Supplementary Table 1**).

### Effects of Serum Phosphate Control on CAC Progression

We evaluated the serum phosphate control status in two aspects: the burden and times of deviations from the strict target for phosphate control (target range of serum phosphate levels < 4.5 mg/dL). To evaluate the effects of strict control of serum phosphate on CAC progression, we compared the  $\Delta$ CACS and % $\Delta$ CACS between the low and high AUC groups.  $\Delta$ CACS and % $\Delta$ CACS were significantly lower in the low AUC group than in the high AUC group (**Fig. 2A and B**). Furthermore,  $\Delta$ CACS and % $\Delta$ CACS significantly and positively correlated with AUC (**Fig. 3**). After adjustment by classic risk factors such as age, smoking, hyperlipidemia, and diabetes mellitus, AUC significantly correlated with  $\Delta$ CACS ( $r=0.269$ ,  $p < 0.05$ ). Even adjusted by age, sex, and baseline CACS, AUC significantly correlated with  $\Delta$ CACS (**Supplementary Table 2**). Regarding the number of times wherein the serum phosphate level exceeded 4.5 mg/dL among the three observational time points,  $\Delta$ CACS and % $\Delta$ CACS were significantly lower in patients with zero excursions than in those with three excursions (**Fig. 2C and D**).

### Effects of Serum Phosphate Control on CVC Progression

The low and high AUC groups showed no

**Table 1.** Clinical characteristics between the low and high AUC groups at baseline

	All (n=64)	Low AUC (n=32)	High AUC (n=32)	P
Age (year)	67 ± 10	69 ± 10	65 ± 11	0.088
Male (%)	50 (78.1)	26 (81.3)	24 (75.0)	0.545
Smoking (%)	28 (43.8)	13 (40.6)	15 (46.9)	0.614
HT (%)	63 (98.4)	31 (96.9)	32 (100)	0.500
DM (%)	33 (51.6)	14 (43.8)	19 (59.4)	0.211
DLp (%)	21 (32.8)	9 (28.1)	12 (37.5)	0.424
SBP (mmHg)	146.2 ± 20.8	145.8 ± 17.3	146.4 ± 23.8	0.910
DBP (mmHg)	72.7 ± 13.5	73.1 ± 11.3	72.3 ± 15.3	0.807
ACE-I/ARB (%)	29 (45.3)	15 (46.9)	14 (43.8)	0.896
Statin (%)	23 (35.9)	12 (37.5)	11 (34.4)	0.872
LC (%)	29 (45.3)	12 (37.5)	17 (53.1)	0.209
CC (%)	35 (54.7)	20 (62.5)	15 (46.9)	0.209
Sevelamer (%)	4 (6.3)	2 (6.3)	2 (6.3)	0.650
Bixalomer (%)	5 (7.8)	2 (6.3)	3 (9.4)	0.555
Vitamin D (%)	31 (48.4)	15 (46.9)	16 (50.0)	0.487
Warfarin (%)	3 (4.7)	2 (6.3)	1 (3.1)	0.500
Hb (g/dL)	10.8 ± 0.9	10.8 ± 0.9	10.7 ± 0.8	0.785
cCa (mg/dL)	8.9 ± 0.6	8.9 ± 0.6	8.8 ± 0.6	0.553
P (mg/dL)	5.0 ± 1.2	4.4 ± 1.1	5.6 ± 1.0	<0.001
Albumin (g/dL)	3.8 ± 0.3	3.8 ± 0.3	3.8 ± 0.3	0.900
Intact PTH (pg/mL)	152.8 (63.4–265.5)	138.8 (57.6–226.1)	173.0 (79.2–436.9)	0.398
CACS	540.3 (149.7–1119.1)	441.0 (109.3–1234.7)	625.6 (185.1–1077.9)	0.909
CVCS	2.0 (0.0–3.0)	2.0 (0.5–4.0)	2.0 (0.0–2.5)	0.231

AUC, area under the curve; HT, hypertension; DM, diabetes mellitus; DLp, dyslipidemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; Hb, hemoglobin; cCa, corrected calcium; P, phosphate; PTH, parathyroid hormone; CACS, coronary artery calcium score; CVCS, cardiac valvular calcification score; CC, calcium carbonate; LC, lanthanum carbonate

Values are presented as mean ± SD or median (interquartile range).

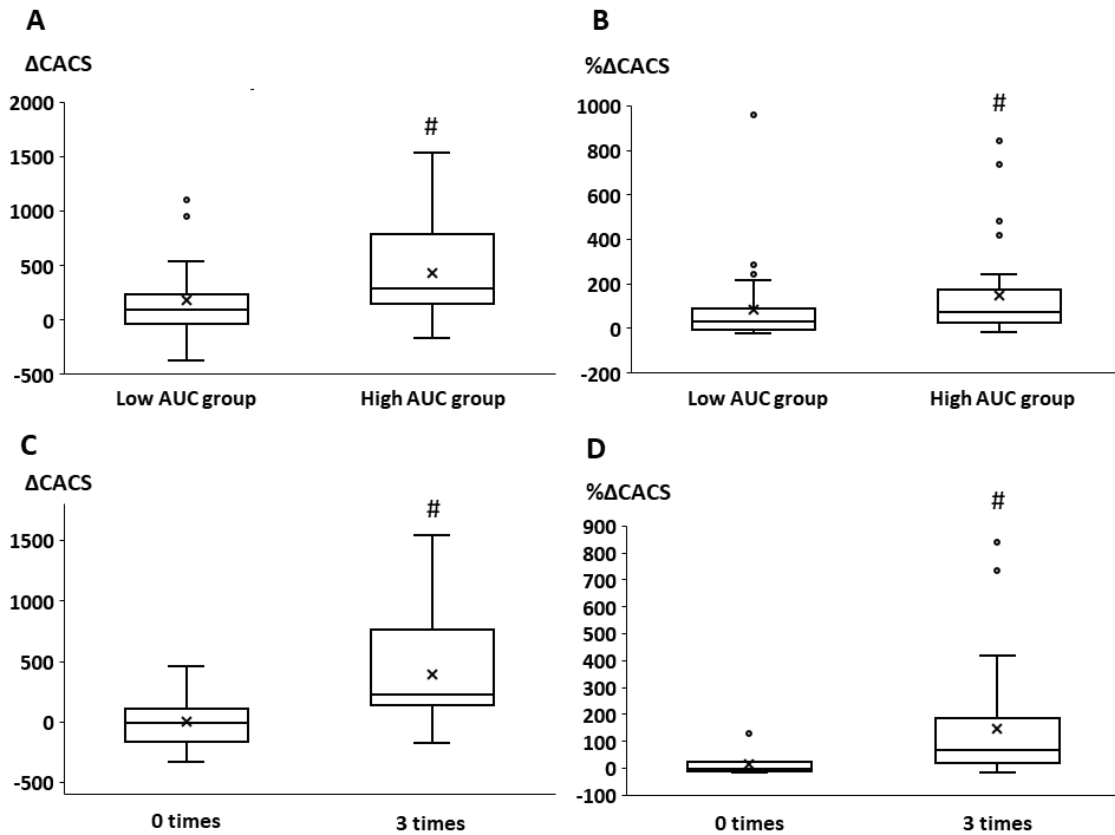
differences in CVCS at baseline. Other clinical characteristics except for serum phosphate levels were similar between the two groups (**Supplementary Tables 3 and 4**).  $\Delta$ CVCS and % $\Delta$ CVCS were significantly higher in the high AUC group than in the low AUC group (**Fig. 4A and B**).  $\Delta$ CVCS and % $\Delta$ CVCS were also significantly correlated with AUC (**Fig. 5**). Even after adjustment by classic risk factors such as age, smoking, hyperlipidemia, and diabetes mellitus, AUC significantly correlated with  $\Delta$ CVCS and % $\Delta$ CVCS ( $\Delta$ CVCS:  $r=0.456$ ,  $p<0.05$ ; % $\Delta$ CVCS:  $r=0.492$ ,  $p<0.05$ ). Even adjusted by age, sex, and baseline CACS, AUC significantly correlated with  $\Delta$ CVCS (**Supplementary Table 2**). Regarding the number of serum phosphate excursions,  $\Delta$ CVCS and % $\Delta$ CVCS were lower in patients with zero excursions than in those with three excursions (**Fig. 4C and D**).

## Discussion

Our study demonstrated the following: (1) the

progression of coronary and valvular calcifications was significantly slower in the low AUC group than in the high AUC group, (2) the changes in CACS were significantly lower and the changes in CVCS tended to be lower in patients whose serum phosphate level never exceeded 4.5 mg/dL than in those whose serum phosphate level continuously exceeded 4.5 mg/dL, and (3) AUC significantly correlated with the changes in CACS and CVCS.

In the clinical setting, we must focus on the serum phosphate level because it significantly contributes to CVD progression, such as vascular and valvular calcifications<sup>11</sup>. Phosphate is taken up into vascular smooth muscle cells (VSMCs) through the sodium-dependent phosphate cotransporter, PiT-1, on the surface of VSMCs and induces cellular apoptosis and the transformation of VSMCs into osteoblast-like cells<sup>21, 22</sup>. These changes may be dependent on phosphate concentrations. These pathophysiological alterations in VSMCs lead to the progression of vascular calcification. Similar to that in VSMCs, phosphate also induces the transformation of



**Fig. 2.** Changes in CAC

A. Changes in CACS between the low and high AUC groups

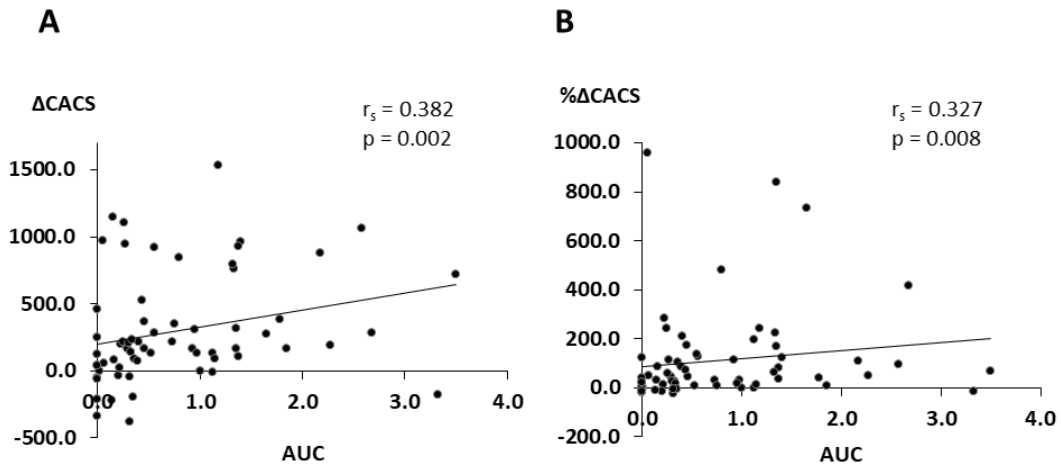
B. Percentage changes in CACS between the low and high AUC groups

C. Changes in CACS between patients with zero excursions from the target serum phosphate range and those with three excursions

D. Percentage changes in CACS between patients with zero excursions from the target serum phosphate range and those with three excursions

CAC, coronary artery calcification; CACS, coronary artery calcification score; AUC, area under the curve

#;  $p < 0.05$

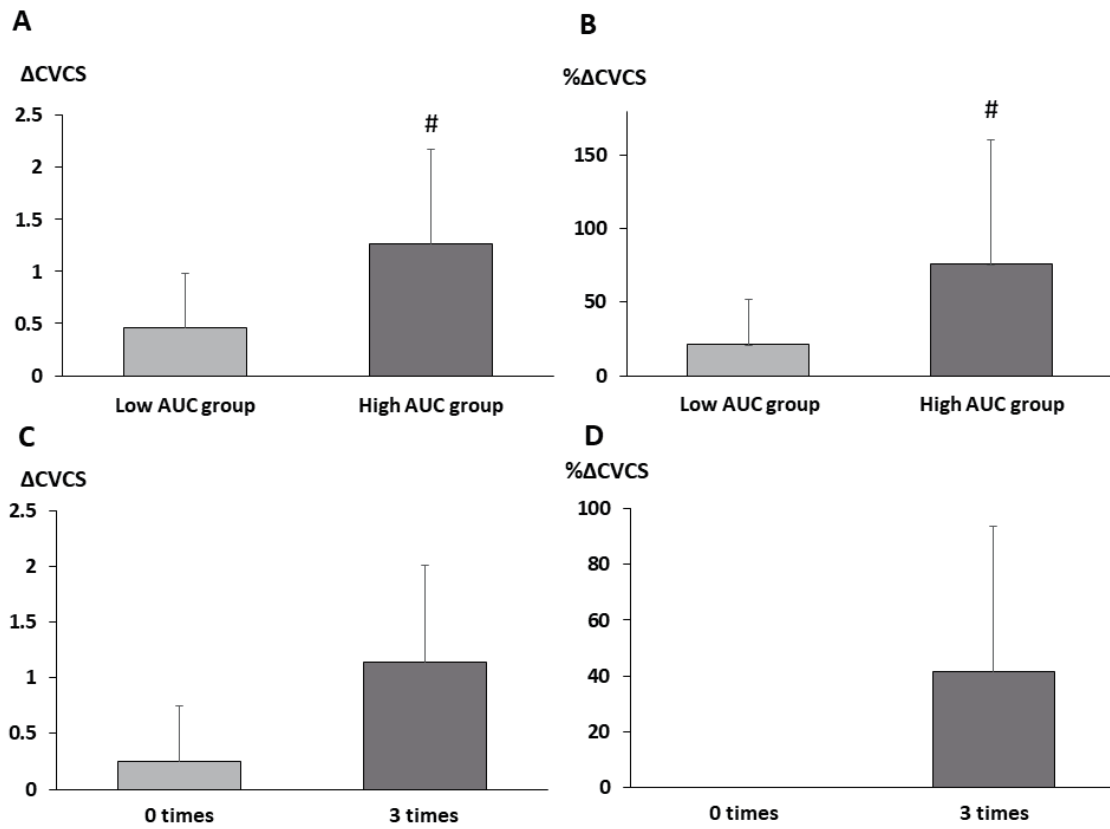


**Fig. 3.** Correlation between changes in CAC and AUC for serum phosphate levels

A. Relationship between changes in CACS and AUC

B. Relationship between percentage changes in CACS and AUC

CAC, coronary artery calcification; CACS, coronary artery calcification score; AUC, area under the curve



**Fig. 4.** Changes in CVC

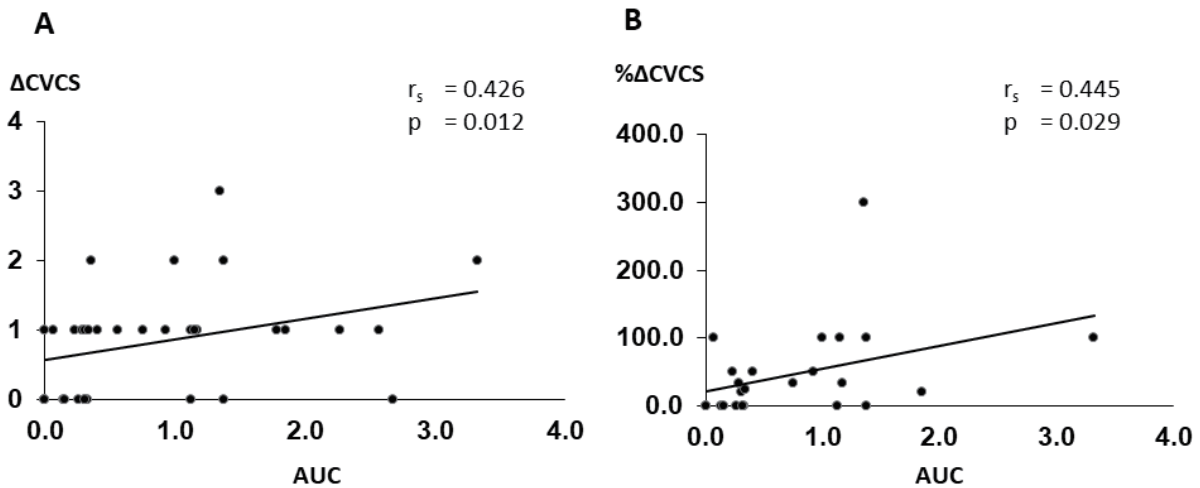
A. Changes in CVCS between the low and high AUC groups

B. Percentage changes in CVCS between the low and high AUC groups

C. Changes in CVCS between patients with zero excursions from the target serum phosphate range and those with three excursions

D. Percentage changes in CVCS between patients with zero excursions from the target serum phosphate range and those with three excursions

CVC, cardiac valvular calcification; CVCS, cardiac valvular calcification score; AUC, area under the curve  
 #;  $p < 0.05$



**Fig. 5.** Correlation between changes in CVC and AUC for serum phosphate levels

A. Relationship between changes in CVCS and AUC

B. Relationship between percentage changes in CVCS and AUC

CVC, cardiac valvular calcification; CVCS, cardiac valvular calcification score; AUC, area under the curve



interstitial valvular cells into osteoblast-like cells<sup>23, 24</sup>). In addition to these changes, a decrease in the levels of inhibitors against vascular calcification also causes the progression of vascular and valvular calcifications<sup>25</sup>). Phosphate is also known to be related to both vascular intimal and medial calcifications<sup>26, 27</sup>). Mild-to-moderate coronary intimal calcification is associated with coronary events, such as acute myocardial infarction and unstable angina, and severe intimal and medial calcifications are related to impaired coronary microvascular circulation<sup>28</sup>). Therefore, an appropriate control of serum phosphate levels may be essential in patients with CKD.

There is extensive research on the association between phosphate and vascular calcifications; however, several studies have reported that serum phosphate is an essential risk factor for valvular calcification. For instance, a large study on 6814 people without CVD demonstrated that higher serum phosphate levels were associated with a significantly greater prevalence of aortic valve calcification<sup>29</sup>). Moreover, another study reported that higher serum phosphate levels that were within the normal range were associated with valvular and annular calcifications in a community-based cohort of older adults<sup>30</sup>). Our recent study, which used the same original data as the present study, also indicated that changes in CVCS significantly correlated with average phosphate levels and were significantly higher in the high serum phosphate group than in the low serum phosphate group<sup>20</sup>). Altogether, phosphate control might be a crucial strategy to prevent vascular and valvular calcifications. The results of this study may support these findings.

There are several investigations regarding the target range of serum phosphate levels in patients undergoing hemodialysis. For example, data from the United States indicated that serum phosphorus concentrations of  $>5.0$  mg/dL were associated with an increased relative risk of death<sup>31</sup>) and those of  $>4.5$  mg/dL with an increased relative risk of developing CVD<sup>32</sup>). A recent study based on data from European countries also reported that serum phosphate levels of 4.4 mg/dL were associated with the minimum relative risk of mortality<sup>33</sup>). Similarly, a Japanese study demonstrated that hazard ratios for mortality were significantly higher in patients with serum phosphate levels of  $>5.0$  mg/dL than in those with serum phosphate levels of 4.0–4.9 mg/dL<sup>34</sup>). Furthermore, a recent RCT on patients undergoing hemodialysis demonstrated that the changes in CAC were significantly smaller in the strict phosphate control group (3.5–4.5 mg/dL) than in the standard phosphate control group (5.0–6.0 mg/dL)<sup>35</sup>). Based

on these findings, we considered  $<4.5$  mg/dL as the target serum phosphate level.

As mentioned earlier, although the control of serum phosphate levels is necessary to improve clinical outcomes in patients undergoing hemodialysis, they show frequent fluctuations in a time-dependent manner. Consequently, the evaluation of serum phosphate levels is a difficult and particularly important issue. There are several methods for evaluating the serum phosphate control status, but it is important to consider those that are more accurate and related to clinical outcomes<sup>36</sup>). A recent study reported the association between the calculated AUC by multiplying the time spent with serum phosphate levels of  $>4.5$  mg/dL over a 6-month run-in period by the extent to which this threshold exceeded and CVD mortality<sup>18</sup>). The result of that study demonstrated that the adjusted hazard ratio of CVD mortality was significantly higher in patients whose monthly average AUC was  $>1$  than in those whose monthly average AUC was 0. Similarly, we also evaluated the association between monthly average AUC and CAC and CVC progression. Consistent with the results of that study, our findings also indicated significant associations between these parameters. In addition, a recent review advocated that clinicians should take necessary action when a patient's phosphate level exceeds the target range multiple times in a certain time period<sup>36</sup>). Therefore, it is also important to evaluate the amount of time spent within target serum phosphate levels in a certain time period. In fact, one study demonstrated a significant association between the time of achieving the guideline-recommended target phosphate range and all-cause death<sup>12</sup>). Even in this study, the progression of CAC and CVC was slower in patients whose serum phosphate level never exceeded 4.5 mg/dL than in those whose serum phosphate level continuously exceeded 4.5 mg/dL. These findings have drawn further attention to the importance of strict phosphate control in patients undergoing hemodialysis.

This study has some limitations. First, because the number of enrolled patients was relatively small, we could not perform statistically sufficient adjustments. However, as this study is a part of a previous RCT, the study patients were closely followed up and the quality of data was reliable. Second, this is not a prospective study but a post hoc analysis of our previous study. Therefore, to ascertain the clinical implication of consistently strict phosphate control for coronary and valvular calcifications, it is necessary to conduct a further prospective study in the near future. Third, we could not distinguish coronary intimal

lesions from medial lesions. In this study, CACS was supposed to consist both intimal and medial calcifications because it is impossible to distinguish coronary intimal lesions from medial lesions using the currently available clinical imaging modalities. This remains a crucial issue in the clinical setting because both are important for the occurrence of CVD. Finally, since this study compared only baseline data and does not include all confounding factors, we cannot rule out the possibility that the serial changes in confounding factors and unknown confounding factors might influence the results.

### Conclusion

The findings of our study suggested that consistently strict phosphate control slows the progression of coronary and valvular calcifications in incident patients undergoing hemodialysis.

### Competing Interests

H. F. received speaker fees as honoraria from Kyowa Kirin, Bayer, Kissei, and Astellas and we received scholarship grants from Kyowa Kirin, Bayer and Chugai.

### Funding

This research was partly supported by Bayer.

### Author Contributions

M.S. wrote the text. H.F. revised it critically for important intellectual content. S.G. and K.K. analyzed the data. K.W. and K.S. interpreted the data. S.N. drafted this study. All co-authors reviewed and approved this paper.

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**Supplementary Table 1.** Clinical characteristics depending on the serum phosphate excursions

	All (n=33)	0 times (n=8)	3 times (n=25)	<i>p</i>
Age (year)	67.9 ± 9.9	74.1 ± 10.2	65.9 ± 9.1	0.038
Male (%)	27 (81.8)	8 (100)	19 (76.0)	0.160
Smoking (%)	14 (42.4)	3 (37.5)	11 (44.0)	0.539
HT (%)	33 (100)	8 (100)	25 (100)	-
DM (%)	17 (51.5)	3 (37.5)	14 (56.0)	0.307
DLp (%)	9 (27.3)	0 (0.0)	9 (36.0)	0.053
SBP (mmHg)	150.1 ± 23.1	149.7 ± 20.2	150.2 ± 24.3	0.959
DBP (mmHg)	74.9 ± 14.9	76.9 ± 14.4	74.4 ± 15.2	0.706
ACE-I/ARB (%)	19 (57.6)	4 (50.0)	15 (60.0)	0.461
Statin (%)	12 (36.4)	2 (25.0)	10 (40.0)	0.373
Lanthanum carbonate (%)	18 (54.5)	4 (50.0)	14 (56.0)	0.541
Calcium carbonate (%)	15 (45.5)	4 (50.0)	11 (44.0)	0.541
Sevelamer (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Bicalomer (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Vitamin D (%)	10 (30.3)	2 (25.0)	8 (32.0)	0.539
Warfarin (%)	2 (6.1)	1 (12.5)	1 (4.0)	0.432
Hb (g/dL)	8.8 ± 1.3	9.2 ± 0.8	8.7 ± 1.4	0.074
cCa (mg/dL)	8.7 ± 0.6	8.5 ± 0.4	8.8 ± 0.6	0.279
P (mg/dL)	5.5 ± 1.3	4.7 ± 1.6	5.8 ± 1.0	0.018
Albumin (g/dL)	3.4 ± 0.5	3.5 ± 0.6	3.3 ± 0.4	0.444
Intact PTH (pg/mL)	239.0 (134.7 – 397.2)	252.6 (95.9 – 500.5)	239.0 (140.2 – 397.2)	0.848
CACS	632.4 (131.8 – 1144.5)	864.8 (219.1 – 1927.3)	632.4 (108.4 – 1098.5)	0.352
CVCS	2.0 (0.0 – 2.25)	1.0 (0.0 – 2.75)	2.0 (0.0 – 2.25)	0.721

AUC, area under the curve; HT, hypertension; DM, diabetes mellitus; DLp, dyslipidemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; Hb, hemoglobin; cCa, corrected calcium; P, phosphate; PTH, parathyroid hormone; CACS, coronary artery calcium score; CVCS, cardiac valvular calcification score.

Values are presented as mean ± SD or median (interquartile range).

**Supplementary Table 2.** Correlation of vascular and valvular calcifications with clinical factors

	ΔCACS				ΔCVCS			
	Univariate		Multivariate		Univariate		Multivariate	
	<i>r</i>	<i>p</i>	$\beta$	<i>p</i>	<i>r</i>	<i>p</i>	$\beta$	<i>p</i>
Age	-0.189	0.135	-0.159	0.263	0.156	0.377	0.237	0.217
Gender	0.013	0.922	0.087	0.510	0.148	0.405	-0.005	0.979
AUC	0.299	0.016	0.271	0.035	0.394	0.021	0.401	0.025
baseline CACS	-0.081	0.525	-0.003	0.983	-0.216	0.219	-0.145	0.447

**Supplementary Table 3.** Clinical characteristics between the low AUC and high AUC groups among patients with CVCS

	All ( <i>n</i> =34)	Low AUC ( <i>n</i> =17)	High AUC ( <i>n</i> =17)	<i>p</i>
Age (year)	69.4 ± 9.2	70.9 ± 10.0	67.8 ± 8.4	0.342
Male (%)	26 (78.1)	13 (76.5)	13 (76.5)	0.656
Smoking (%)	22 (64.7)	12 (70.6)	10 (58.8)	0.473
HT (%)	34 (100.0)	17 (100.0)	17 (100.0)	-
DM (%)	16 (47.1)	7 (41.2)	9 (52.9)	0.492
DLp (%)	16 (47.1)	6 (35.3)	10 (58.8)	0.169
SBP (mmHg)	145.2 ± 19.3	144.5 ± 16.9	145.9 ± 22.0	0.828
DBP (mmHg)	68.4 ± 11.1	69.7 ± 10.8	67.1 ± 11.5	0.503
ACE-I/ARB (%)	23 (45.3)	11 (64.7)	12 (70.6)	0.714
Statin (%)	23 (67.6)	10 (58.8)	13 (76.5)	0.271
Lanthanum carbonate (%)	16 (47.1)	7 (41.2)	9 (52.9)	0.492
Calcium carbonate (%)	18 (52.9)	10 (58.8)	8 (47.1)	0.492
Sevelamer (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Bicalomer (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Vitamin D (%)	11 (32.4)	4 (23.5)	7 (41.2)	0.271
Warfarin (%)	3 (8.8)	2 (11.8)	1 (5.9)	0.500
Hb (g/dL)	8.7 ± 1.2	8.7 ± 1.3	8.9 ± 1.2	0.568
cCa (mg/dL)	8.8 ± 0.5	8.8 ± 0.7	8.7 ± 0.4	0.469
P (mg/dL)	5.7 ± 1.3	5.3 ± 1.4	6.2 ± 0.9	0.029
Albumin (g/dL)	3.3 ± 0.4	3.2 ± 0.4	3.4 ± 0.5	0.425
Intact PTH (pg/mL)	235.0 (133.0 – 335.0)	262.0 (109.0 – 389.0)	231.0 (157.0 – 330.0)	0.973
CACS	549.7 (141.8 – 1221.2)	480.7 (142.5 – 1840.9)	618.7 (131.8 – 1074.9)	0.518
CVCS	2.0 (0.0 – 3.0)	2.0 (0.5 – 4.0)	2.0 (0.0 – 2.5)	0.231

AUC, area under the curve; HT, hypertension; DM, diabetes mellitus; DLp, dyslipidemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; Hb, hemoglobin; cCa, corrected calcium; P, phosphate; PTH, parathyroid hormone; CACS, coronary artery calcium score; CVCS, cardiac valvular calcification score. Values are presented as mean ± SD or median (interquartile range).

**Supplementary Table 4.** Clinical characteristics depending on the serum phosphate excursions among patients with CVCS

	All (n=18)	0 time (n=4)	3 times (n=14)	p
Age (year)	70.0 ± 9.2	78.3 ± 6.7	67.6 ± 8.5	0.018
Male (%)	15 (83.3)	4 (100.0)	11 (78.6)	0.446
Smoking (%)	11 (61.1)	3 (75.0)	8 (57.1)	0.485
HT (%)	18 (100.0)	4 (100.0)	14 (100.0)	-
DM (%)	8 (44.4)	2 (50.0)	6 (42.9)	0.618
DLp (%)	7 (38.9)	0 (0.0)	7 (50.0)	0.108
SBP (mmHg)	145.7 ± 20.3	144.3 ± 20.9	146.1 ± 20.9	0.875
DBP (mmHg)	67.6 ± 10.2	66.8 ± 6.7	67.8 ± 11.2	0.864
ACE-I/ARB (%)	11 (61.1)	2 (50.0)	9 (64.3)	0.515
Statin (%)	12 (66.7)	2 (50.0)	10 (71.4)	0.407
Lanthanum carbonate (%)	10 (55.6)	2 (50.0)	8 (57.1)	0.618
Calcium carbonate (%)	8 (44.4)	2 (50.0)	6 (42.9)	0.618
Sevelamer (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Bicalomer (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
Vitamin D (%)	7 (38.9)	2 (50.0)	5 (35.7)	0.515
Warfarin (%)	2 (11.1)	1 (25.0)	1 (7.1)	0.405
Hb (g/dL)	9.0 ± 1.1	9.2 ± 0.8	8.9 ± 1.3	0.705
cCa (mg/dL)	8.6 ± 0.4	8.3 ± 0.2	8.7 ± 0.4	0.053
P (mg/dL)	5.7 ± 1.2	4.3 ± 1.1	6.1 ± 1.0	0.005
Albumin (g/dL)	3.4 ± 0.5	3.4 ± 0.4	3.4 ± 0.5	0.979
Intact PTH (pg/mL)	235.0 (158.8 – 335.0)	161.0 (36.8 – 484.8)	239.0 (179.0 – 335.0)	0.442
CACS	510.1 (139.4 – 1122.0)	821.4 (219.1 – 1927.3)	495.8 (104.5 – 1058.7)	0.327
CVCS	2.0 (0.0 – 2.25)	1.0 (0.0 – 2.75)	2.0 (0.0 – 2.25)	0.721

AUC, area under the curve; HT, hypertension; DM, diabetes mellitus; DLp, dyslipidemia; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; Hb, hemoglobin; cCa, corrected calcium; P, phosphate; PTH, parathyroid hormone; CACS, coronary artery calcium score; CVCS, cardiac valvular calcification score. Values are presented as mean ± SD or median (interquartile range).