Nephrol Dial Transplant, 2024, **39**, 637–647
https://doi.org/10.1093/ndt/gfad213
Advance access publication date: 30 September 2023

Hypocalcemia and cardiovascular mortality in cinacalcet users

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ABSTRACT

Background. Calcimimetics are widely used in hemodialysis patients and influence serum calcium levels. Although the Kidney Disease: Improving Global Outcomes guidelines argued that low calcium levels induced by calcimimetics may be harmless, large observational studies investigating the association between hypocalcemia and mortality are scarce. We investigated the association between serum calcium levels and cardiovascular mortality in calcimimetics users using the nationwide Japanese registry for dialysis patients.

Methods. In this 9-year prospective cohort study, the baseline data were collected at the end of 2009. We enrolled patients on maintenance hemodialysis or hemodiafiltration. We employed three models (baseline, time-dependent and time-averaged) to conduct Cox proportional hazard regression analyses.

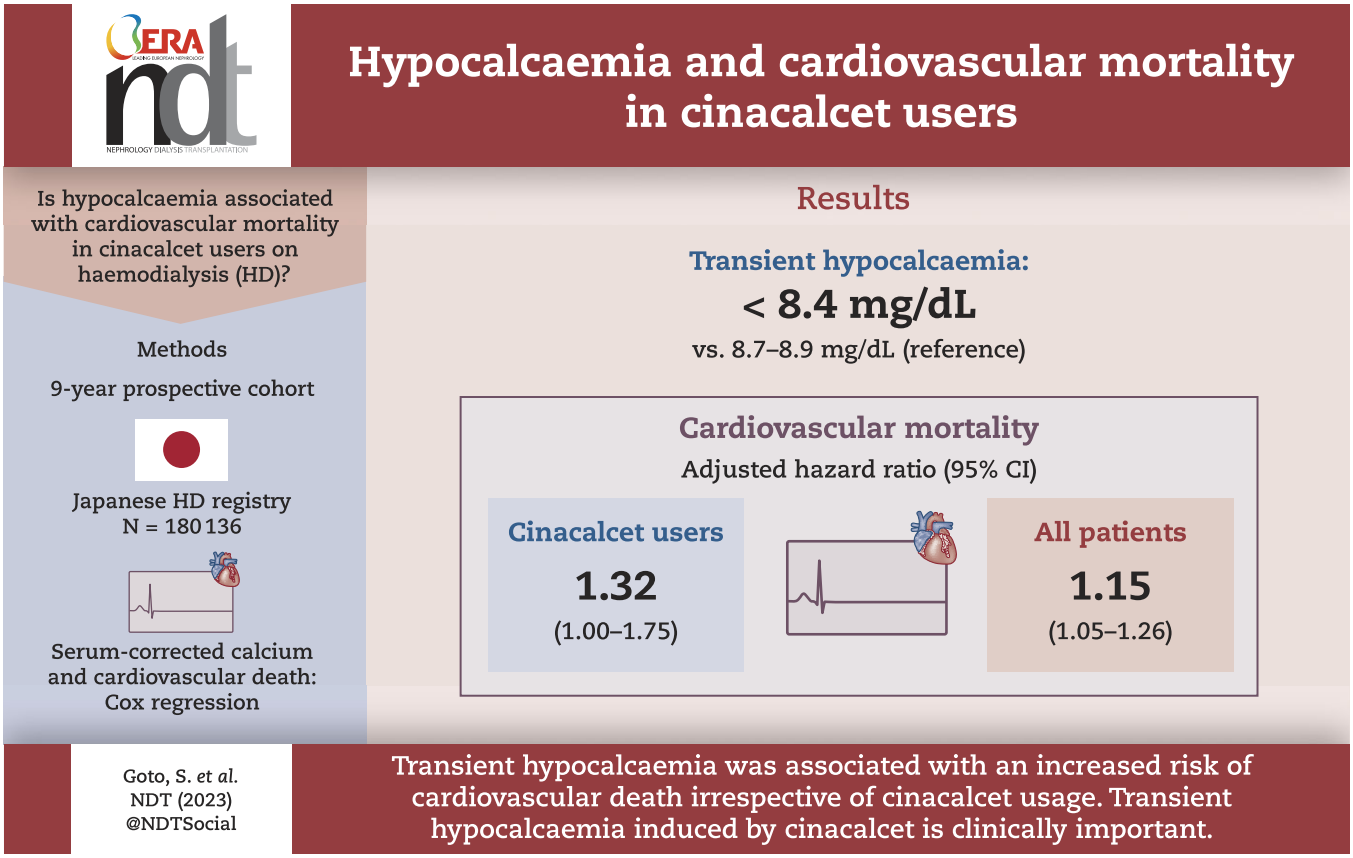
Results. Cinacalcet was prescribed to 12.7% ($N = 22\,853$) at baseline. The median observation period was 98 (interquartile range 40–108) months and 108 (interquartile range 59–108) months in the whole cohort ($N = 180\,136$) and in cinacalcet users, respectively. Three-quarters of survivors at the end of 2019 had continued calcimimetic therapy for 10 years, corresponding to a mean annual dropout rate of 2.9%. Hypocalcemia was not associated with cardiovascular mortality in the baseline or time-averaged model. In the time-dependent model, however, the lowest calcium decile (corrected calcium <8.4 mg/dL) was significantly associated with higher cardiovascular mortality than the reference (corrected calcium 8.7–8.9 mg/dL) in both cinacalcet users and all patients [hazard ratio (95% confidence interval) 1.32 (1.00, 1.75) and 1.15 (1.05, 1.26), respectively]. Hypocalcemia was especially associated with sudden death and death due to hemorrhagic stroke, heart failure and ischemic heart disease. Higher rate of fatal and non-fatal cardiovascular events was observed in hypocalcemic patients regardless of cinacalcet usage.

Conclusions. Our findings suggest that transient hypocalcemia was associated with an increased risk of cardiovascular death independent of cinacalcet usage. We should pay attention to hypocalcemia transiently induced by cinacalcet.

Keywords: calcimimetics, calcium, cardiovascular, hemodialysis, PTH

Received: April 7, 2023; Editorial decision: August 26, 2023

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- The wide use of calcimimetics may have increased the incidence of hypocalcemia in patients with dialysis.
- Some researchers argued that cinacalcet-induced hypocalcemia may be harmless.
- However, there is no large observational study supporting this argument.

This study adds:

- In a large cohort of the Japanese nationwide registry, hypocalcemia was not associated with cardiovascular mortality in the baseline or time-averaged model.
- In the time-dependent model, however, hypocalcemia was significantly associated with cardiovascular mortality in both cinacalcet users and in all patients.
- Cardiovascular mortality associated with hypocalcemia was especially observed regarding sudden death and death due to hemorrhagic stroke, as well as death due to heart failure and ischemic heart disease.

Potential impact:

- Transient hypocalcemia was associated with an increased risk of cardiovascular death independent of cinacalcet usage.
- We should pay attention to hypocalcemia induced by cinacalcet.

INTRODUCTION

Bone-related mineral disorder, a component of chronic kidney disease–bone mineral disorder (CKD-MBD), is an important risk factors in hemodialysis patients because numerous papers have demonstrated that abnormal serum calcium, phosphorus and parathyroid hormone (PTH) levels are associated with mortality [1–4]. Therefore, the control of these parameters is expected to improve clinical outcomes and various treatments including phosphate binders, vitamin D receptor activators (VDRAs) and calcimimetics are indicated for the disorder.

Calcimimetics are one of the medications for CKD-MBD. Cinacalcet has been available since 2004 in the USA and has drastically changed the treatment strategy for CKD-MBD. The agent allows for better control of PTH levels and the rate of parathyroidectomy (PTx) decreases after the introduction of cinacalcet [5]. Some studies have also suggested that calcimimetics may reduce mortality, cardiovascular events and fracture in

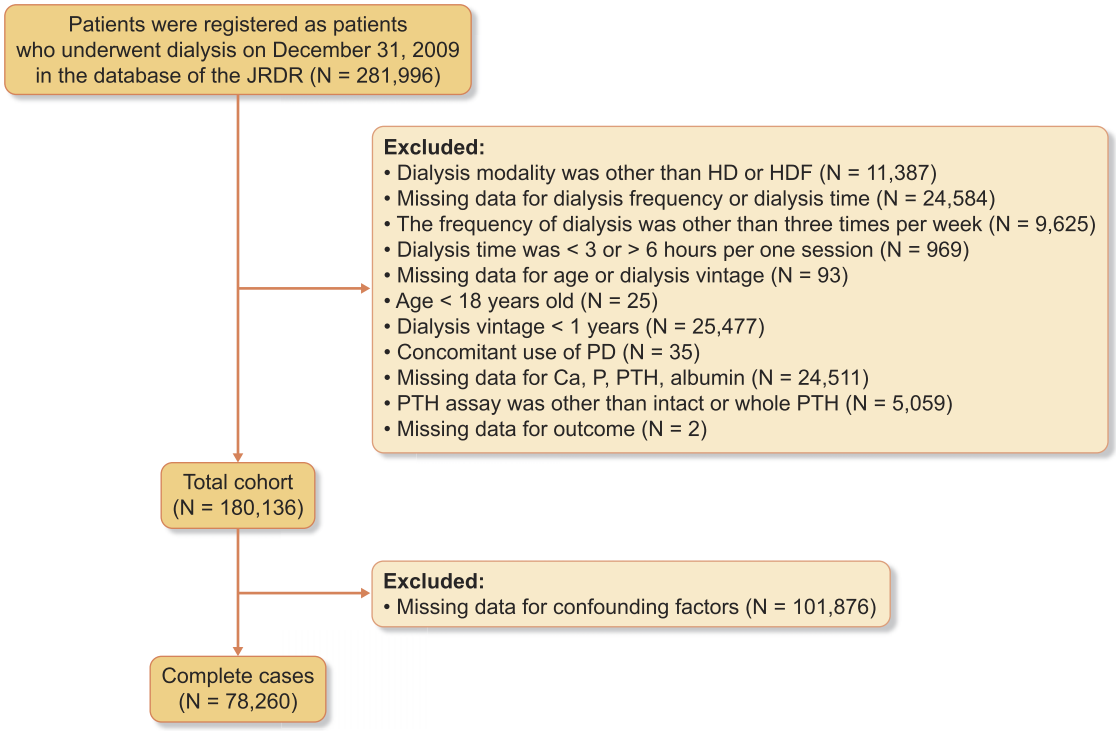


Figure 1: Flow diagram. HD, hemodialysis; HDF, hemodiafiltration; Ca, calcium; P, phosphorus.

elderly hemodialysis patients [6–8]. Because of these benefits, calcimimetics have been widely used in hemodialysis patients [5]. However, the wide use of calcimimetics may have increased the incidence of hypocalcemia in patients on dialysis [6, 9, 10]. Although some researchers have argued that cinacalcet-induced hypocalcemia may be harmless [11, 12], there is no large observational study supporting this argument. Although heart failure is sometimes observed after surgical PTx [13, 14], such an association has not been reported in medical PTx by calcimimetics.

This prospective study aimed to assess the risk of hypocalcemia in calcimimetics users by investigating the association between serum calcium levels and mortality using the database of the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR), a nationwide registry of data on dialysis patients in Japan.

MATERIALS AND METHODS

Data source, study population and study design

The data in this study were obtained from the database of the JRDR. The detailed protocol of this survey has been described elsewhere [15]. Briefly, the Japanese Society for Dialysis Therapy (JSDT) sent questionnaires to all dialysis facilities in Japan at the end of each year and prospectively surveyed demographic and clinical data of dialysis patients in Japan. Cardiovascular deaths and comorbidities were captured by chart review. The response rate exceeded 95% every year.

The study population in this study was selected from patients whose data was collected at the end of 2009. We enrolled those patients on maintenance hemodialysis or hemodiafiltration three times per week, with treatment time between 3 and six 6 h per session, who were aged 18 years or older and whose dialysis vintage was 1 year or longer. We excluded patients who received combined therapy with peritoneal dialysis, who did not have data on calcium, phosphorus, PTH and albumin, in whom the method of measuring PTH was not either intact PTH assay or whole PTH assay, and whose outcome was unknown (Fig. 1).

The current study is a 9-year prospective cohort study in which the baseline is at the end of 2009. Patients were censored at end of 2018, kidney transplantation or at loss to follow-up. For the assessment of adherence to calcimimetics, we used the prescription data at the end of 2019, when the calcimimetic use was surveyed again. The study protocol was approved by the Ethics Committee of the JSDT (approval number 54) and was conducted in accordance with the Helsinki Declaration. The study was exempt from the need to obtain informed consent from participants, which was also approved by the Ethics Committee of the JSDT.

Definition

If serum albumin levels were <4 g/dL, serum calcium levels were corrected using the following formula: corrected calcium = serum calcium (mg/dL) + [4 − serum albumin (g/dL)]. If the PTH assay was whole, whole PTH levels were multiplied by 1.7 to obtain equivalent values measured by an intact PTH assay [16]. Performance status was graded according to the Eastern Cooperative Oncology Group Performance Status classification [17]. Cardiovascular death was defined as death due to heart failure, pulmonary edema, ischemic heart disease, arrhythmia, endocarditis, valvular disease, other cardiac diseases, subarachnoid hemorrhage, cerebral hemorrhage, cerebral infarction, other cerebrovascular diseases or sudden death. In addition, since the code for cause of death was revised in the database of JRDR in 2017 and aortic aneurysm and other vascular diseases were newly coded [18], these causes were treated as cardiovascular death after 2017. Five main causes of cardiovascular death were

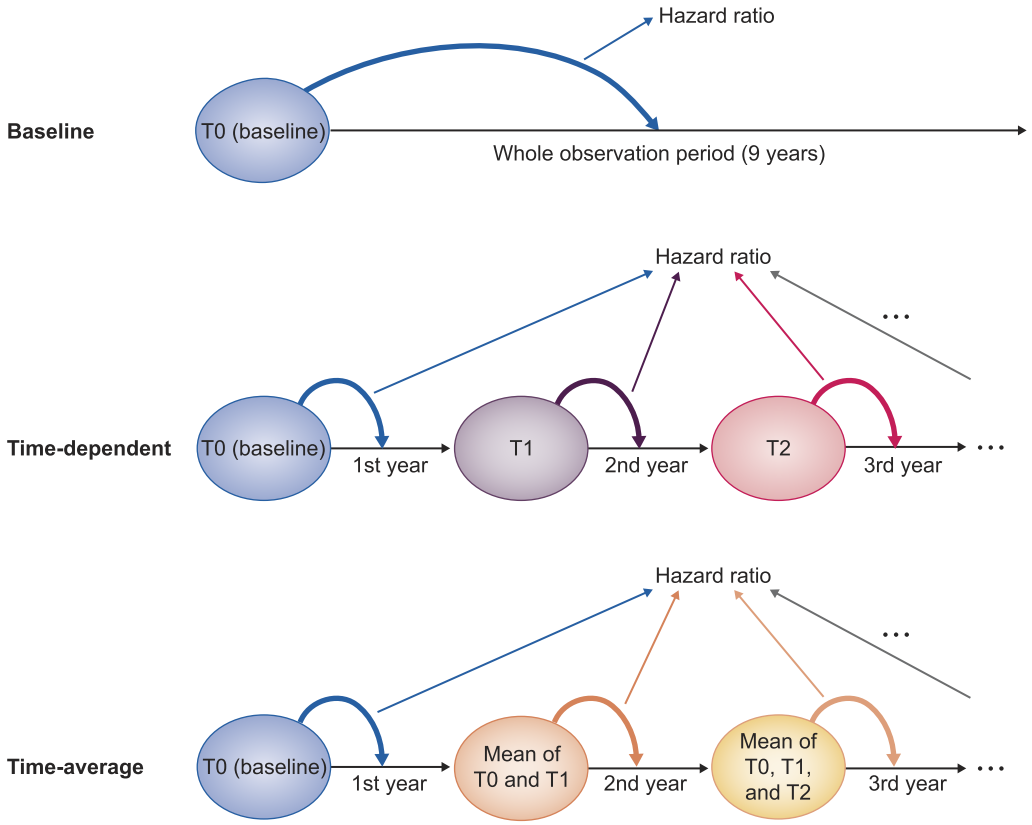


Figure 2: Outline of the baseline model, time-dependent model and time-averaged model.

defined as heart failure, ischemic heart disease, sudden death, hemorrhagic stroke and cerebral infarction. Among these causes, death due to pulmonary edema and arrhythmia was categorized into "heart failure" and "sudden death," respectively. "Hemorrhagic stroke" included subarachnoid hemorrhage and cerebral hemorrhage.

Statistical analysis

Data were presented as mean and standard deviation for continuous variables with a normal distribution, median and interquartile range (IQR) for continuous variables with a skewed distribution, or number and percentage for categorical variables.

Multivariate Cox proportional hazards regression analysis was used to assess the association between all-cause or cardiovascular mortality, and serum calcium levels in cinacalcet users or all patients. The data in our study did not include cinacalcet use after baseline. The baseline in our study was the end of 2009 as cinacalcet became available in 2008 in Japan, with the prescription of cinacalcet increasing after 2009 [5]. Since calcimimetics including etelcalcetide would be prescribed to some patients who did not take cinacalcet at baseline, we could not adjudicate never-users of calcimimetics. Therefore, we could not analyze the patients not receiving calcimimetics in this study. For this analysis, we employed three types of models used in the previous study [1]: (i) baseline models adjusted for baseline covariates; (ii) time-dependent models adjusted for time-varying covariates, where the follow-up time was divided into 1-year intervals because data were collected annually in this study; and (iii) time-averaged models, where the follow-up time was divided as time-dependent models and mean values of variables up to that time were used as time-varying covariates (Fig. 2). The same analyses were performed to assess the association between all-cause or cardiovascular mortality and phosphorus, intact PTH and calcium × phosphorus product. Adjusted variables in these analyses were age, sex, dialysis vintage, dialysis time, dialysis modality (hemodialysis or hemodiafiltration), body mass index (BMI), Kt/V, normalized protein catabolic rate (nPCR), the primary cause of renal failure (glomerulonephritis, diabetes, hypertension, polycystic kidney disease, others and unknown), history of myocardial infarction, cerebral hemorrhage, cerebral infarction, amputation, hip fracture, PTx and percutaneous ethanol injection therapy (PEIT), calcium, phosphorus, intact PTH, albumin, creatinine, C-reactive protein (CRP), hemoglobin, magnesium, alkaline phosphatase (ALP), CKD-MBD-related medications (calcium carbonate, sevelamer chloride, lanthanum carbonate, other phosphate binders, oral VDRA, intravenous VDRA, and cinacalcet), dialysate calcium concentration (<2.75, 2.75–<3.0, ≥3.0 mEq/L, and acetate-free), and performance status. Of these variables, dialysis time, BMI, Kt/V, nPCR, calcium, phosphorus, intact PTH, albumin, creatinine, CRP and hemoglobin were used as time-varying covariates in the time-dependent and time-averaged models. The time-varying covariates were treated as missing values at the time when the frequency of hemodialysis per week was anything other than three times. CRP was log-transformed to normalize the distribution. Serum calcium, phosphorus, intact PTHa and calcium × phosphorus product levels were divided into deciles (Supplementary data, Table S1) and serum magnesium level was divided into quintiles (<2.4, 2.4–<2.6, 2.6–<2.8, 2.8–<3.0, ≥3.0 mg/dL) because U-shaped associations between these variables and mortality were reported [1, 19]. The Cox proportional hazard assumption was tested by the Schoenfeld residual

method. If it was violated for some covariates, we employed Cox proportional hazard model including interaction term between analysis time and each covariate violating it. Furthermore, we conducted five sensitivity analyses. First, multiple imputations were conducted. The missing values were imputed by fully conditional chained equations. We created five imputed datasets and combined them using Rubin's rules. Second, conventional Cox proportional hazards regression analysis was conducted in patients who had no history of PTx or PEIT. Third, competing risk regression analyses (Fine and Gray models) were conducted. In the analysis, non-cardiovascular death was considered as a competing event. Fourth, conventional Cox proportional hazards regression analysis was conducted in a population including patients with dialysis vintage of <1 year. Fifth, the same analysis was conducted between baseline and 2016 to eliminate the effect of etelcalcetide use. In addition, similar analysis was conducted in patients with or without PTH suppressive therapy (VDRA or cinacalcet) at baseline in order to assess whether the association between serum intact PTH levels and cardiovascular mortality was similar or not among patients with or without PTH suppressive therapy.

Restricted cubic spline models were used to show potentially non-linear associations of serum calcium, phosphorus, intact PTH and calcium × phosphorus product levels with the risk of cardiovascular mortality and all-cause mortality. To eliminate the influence of outliers, we excluded values above the 99th percentile and below the 1st percentile of the independent variables. The number of knots in each model was determined based on the Akaike Information Criterion. Furthermore, we conducted a *post hoc* analysis to examine the association between serum calcium levels and five main causes of cardiovascular death (heart failure, ischemic heart disease, sudden death, hemorrhagic stroke and cerebral infarction) in all patients to clarify the mechanism of discrepancy between the time-dependent model and the time-averaged model regarding the risks of cardiovascular mortality associated with low calcium levels.

Since the JSDT surveyed cardiovascular hospitalization in 2017, we used the data to assess the association with fatal and non-fatal cardiovascular event. Logistic regression analysis was used for the assessment.

In the comparison of each baseline variable, a standardized difference <10% was considered to denote a negligible difference between groups. *P*-value <.05 was considered statistically significant. All statistical analyses were performed using Stata/MP 14.2 software for Windows (Stata, College Station, TX, USA).

RESULTS

Table 1 and Supplementary data, Table S2 show baseline characteristics of patients in complete cases and the whole cohort. Cinacalcet was prescribed in 12.7% of patients and 65.8% of cinacalcet users were treated for ≥1 year in the whole cohort. The standardized differences between complete cases and non-complete cases were <10% except for dialysate calcium in cinacalcet users and all patients and Kt/V in cinacalcet users.

During the 9-year follow-up period, 3961 cardiovascular deaths (9159 all-cause deaths) occurred in cinacalcet users and 39 260 cardiovascular deaths (93 462 all-cause deaths) occurred, 1917 patients received kidney transplantation and 293 patients were lost to follow-up in all patients in the whole cohort. The median observational period was 98 (IQR 40–108) months and 108 (IQR 59–108) months in the whole cohort and in cinacalcet users, respectively. Regarding adherence to calcimimetics, 74.7% of survivors at the end of 2019 had continued calcimimetic therapy for 10 years. Thus, mean annual dropout rate was estimated to be 2.9%.

Tables 2–4 and Supplementary data, Tables S3 and S4 show the results of the Cox proportional hazard regression analysis assessing the association between calcium and cardiovascular

Table 1: Baseline characteristics of cinacalcet users in complete cases and number of missing values in the whole cohort.

	All cinacalcet users (N = 10 849)	No. of missing values in the whole cohort (%)
Age (years)	60.7 ± 11.8	0
Men (%)	58.8	0
Dialysis vintage (months)	139 (90–203)	0
Dialysis time (h/week)	12.4 ± 1.3	0
Hemodiafiltration (%)	11.4	0
BMI (kg/m^2)	21.5 ± 4.1	22 350 (12.4)
Kt/V	1.51 ± 0.29	7344 (4.1)
nPCR (g/kg/day)	0.93 ± 0.17	7111 (3.9)
Cause of kidney failure (%)		3 (<0.1)
Glomerulonephritis	57.6	
Diabetes	17.3	
Hypertension	4.4	
Polycystic kidney disease	4.1	
Others	7.0	
Unknown	9.5	
Past history (%)		
Myocardial infarction	6.5	17 419 (9.7)
Cerebral hemorrhage	4.7	17 694 (9.8)
Cerebral infarction	11.0	17 861 (9.9)
Amputation	2.0	16 503 (9.2)
Fracture	1.8	17 965 (10.0
PTx	8.2	15 198 (8.4)
PEIT	4.3	16 038 (8.9)
Laboratory test		
Corrected calcium (mg/dL)	9.5 ± 0.9	0
Phosphorus (mg/dL)	5.5 ± 1.4	0
Intact PTH (pg/mL)	175 (110–285)	0
Albumin (g/dL)	3.8 ± 0.3	0
Creatinine (mg/dL)	11.7 ± 2.7	42 (<0.1)
CRP (mg/dL)	0.1 (0–0.3)	34 029 (18.9)
Hemoglobin (g/dL)	10.8 ± 1.2	953 (0.5)
Magnesium (mg/dL)	2.7 ± 0.4	54 493 (30.3)
ALP (IU/L)	281 ± 172	4863 (2.7)
Medication (%)		
Calcium carbonate	55.3	7559 (4.2)
Sevelamer	53.4	8306 (4.6)
Lanthanum carbonate	26.2	9209 (5.1)
Other phosphate binders	5.2	10 804 (6.0)
Oral VDRA	20.4	8758 (4.9)
Intravenous VDRA	65.1	14 582 (8.1)
Dialysate calcium (%)		7215 (4.0)
<2.75 mEq/L	39.7	
2.75—<3.0 mEq/L	8.8	
≥3.0 mEq/L	46.4	
Acetate-free dialysis	5.1	
Performance status (%)		13 960 (7.7)
Grade 0	56.0	
Grade 1	30.9	
Grade 2	8.2	
Grade 3	3.3	
Grade 4	1.5	

Data in column 2 are presented as mean ± standard deviation, median (IQR) or %.

Table 2: Hazard ratios or subhazard ratios and 95% confidence intervals for cardiovascular mortality according to serum calcium levels in cinacalcet users (time-dependent model).

	Cox proportional hazard regression analysis	Cox proportional hazard regression analysis after multiple imputations	Cox proportional hazard regression analysis in patients without PTx or PEIT	Competing-risk regression analysis
Ca (mg/dL)				
<8.4	1.32 (1.00, 1.75)*	1.38 (1.12, 1.70)*	1.34 (1.00, 1.79)*	1.33 (1.00, 1.77)*
8.4–<8.7	1.05 (0.79, 1.39)	1.06 (0.85, 1.31)	1.04 (0.77, 1.41)	1.06 (0.79, 1.42)
8.7–<8.9	ref	ref	ref	ref
8.9–<9.1	1.22 (0.93, 1.59)	1.32 (1.08, 1.61)*	1.25 (0.94, 1.65)	1.19 (0.90, 1.57)
9.1–<9.3	1.14 (0.88, 1.48)	1.25 (1.02, 1.52)*	1.14 (0.86, 1.50)	1.12 (0.86, 1.47)
9.3–<9.5	1.05 (0.81, 1.37)	1.06 (0.87, 1.30)	1.11 (0.85, 1.47)	1.02 (0.77, 1.34)
9.5–<9.7	1.18 (0.91, 1.53)	1.21 (0.99, 1.48)	1.18 (0.90, 1.55)	1.09 (0.83, 1.43)
9.7–<9.9	1.19 (0.91, 1.55)	1.19 (0.97, 1.46)	1.20 (0.91, 1.58)	1.09 (0.83, 1.44)
9.9–<10.3	1.31 (1.02, 1.67)*	1.35 (1.12, 1.63)*	1.30 (1.01, 1.69)*	1.22 (0.95, 1.58)
≥10.3	1.42 (1.12, 1.82)*	1.53 (1.27, 1.84)*	1.45 (1.12, 1.87)*	1.15 (0.89, 1.48)

Ca, calcium.
*$P < .05$.

Table 3: Hazard ratios or subhazard ratios and 95% confidence intervals for cardiovascular mortality according to serum calcium levels in cinacalcet users (time-averaged model).

	Cox proportional hazard regression analysis	Cox proportional hazard regression analysis after multiple imputations	Cox proportional hazard regression analysis in patients without PTx or PEIT	Competing-risk regression analysis
Ca (mg/dL)				
<8.4	0.93 (0.66, 1.31)	0.96 (0.76, 1.21)	0.89 (0.62, 1.26)	0.75 (0.53, 1.07)
8.4–<8.7	0.91 (0.70, 1.20)	0.88 (0.72, 1.08)	0.93 (0.70, 1.24)	0.87 (0.66, 1.15)
8.7–<8.9	ref	ref	ref	ref
8.9–<9.1	0.88 (0.70, 1.11)	1.01 (0.86, 1.18)	0.87 (0.68, 1.11)	0.88 (0.70, 1.12)
9.1–<9.3	0.96 (0.77, 1.19)	1.00 (0.86, 1.17)	0.94 (0.75, 1.18)	0.94 (0.75, 1.17)
9.3–<9.5	1.08 (0.88, 1.33)	1.11 (0.96, 1.30)	1.09 (0.87, 1.36)	1.04 (0.83, 1.29)
9.5–<9.7	0.89 (0.72, 1.11)	0.98 (0.84, 1.14)	0.89 (0.71, 1.12)	0.87 (0.70, 1.09)
9.7–<9.9	1.16 (0.93, 1.44)	1.13 (0.97, 1.33)	1.16 (0.92, 1.46)	1.04 (0.83, 1.31)
9.9–<10.3	1.06 (0.85, 1.31)	1.10 (0.94, 1.29)	1.09 (0.87, 1.36)	0.93 (0.74, 1.17)
≥10.3	1.08 (0.85, 1.37)	1.12 (0.95, 1.33)	1.08 (0.85, 1.39)	0.84 (0.65, 1.08)

Ca, calcium.
$P < .05$.

Table 4: Hazard ratios or subhazard ratios and 95% confidence intervals for cardiovascular mortality according to serum calcium levels in all patients including cinacalcet users (time-dependent model).

	Cox proportional hazard regression analysis	Cox proportional hazard regression analysis after multiple imputations	Cox proportional hazard regression analysis in patients without PTx or PEIT	Competing-risk regression analysis
Ca (mg/dL)				
<8.4	1.15 (1.05, 1.26)*	1.08 (1.01, 1.16)*	1.14 (1.03, 1.25)*	1.19 (1.08, 1.31)*
8.4–<8.7	1.00 (0.92, 1.09)	0.98 (0.92, 1.05)	0.98 (0.89, 1.07)	1.01 (0.92, 1.11)
8.7–<8.9	ref	ref	ref	ref
8.9–<9.1	1.08 (0.99, 1.18)	1.09 (1.02, 1.15)*	1.07 (0.98, 1.16)	1.09 (1.00, 1.19)*
9.1–<9.3	1.10 (1.01, 1.19)*	1.07 (1.01, 1.13)*	1.07 (0.99, 1.16)	1.10 (1.01, 1.20)*
9.3–<9.5	1.15 (1.06, 1.24)*	1.13 (1.06, 1.19)*	1.14 (1.05, 1.24)*	1.14 (1.04, 1.24)*
9.5–<9.7	1.20 (1.11, 1.31)*	1.18 (1.11, 1.25)*	1.19 (1.09, 1.29)*	1.18 (1.08, 1.28)*
9.7–<9.9	1.23 (1.13, 1.34)*	1.21 (1.14, 1.29)*	1.22 (1.11, 1.33)*	1.19 (1.09, 1.31)*

Ca, calcium.
*$P < .05$.

mortality in cinacalcet users and all patients. In the baseline and time-averaged models, hypocalcemia was not associated with cardiovascular mortality. In the time-dependent model, however, the lowest calcium decile (corrected calcium <8.4 mg/dL) was significantly associated with higher cardiovascular mortality compared with the reference (corrected calcium 8.7–<8.9 mg/dL) in both cinacalcet users and all patients [hazard ratio (95% confidence interval), 1.32 (1.00, 1.75) and 1.15 (1.05, 1.26), respectively]. Similar results were obtained in analysis after multiple imputations, analysis for subjects without a history

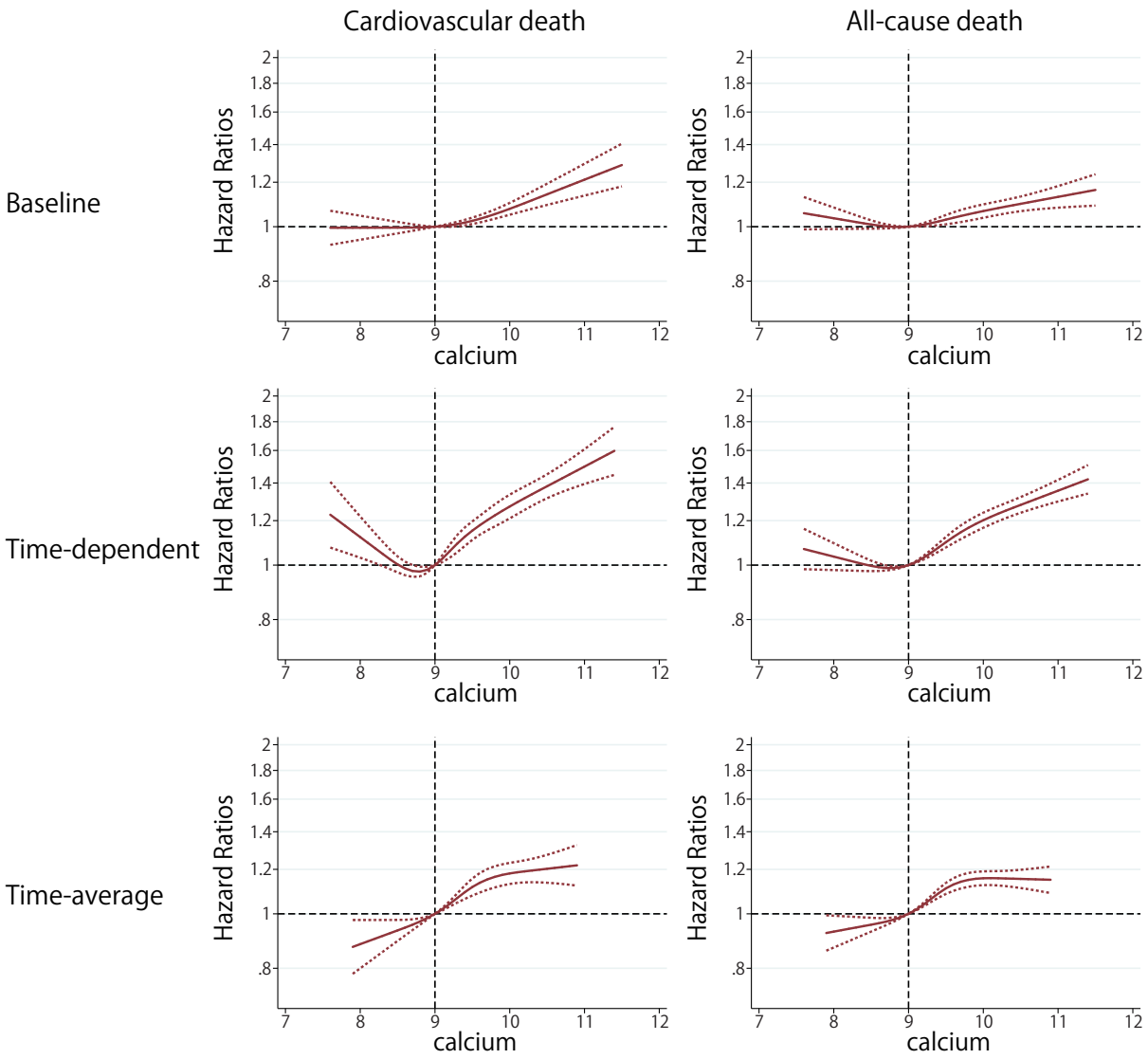


Figure 3: Relationship between calcium and cardiovascular mortality in all patients.

of PTx or PEIT, and competing risk regression analysis. In addition, similar trends were observed in population including patients with dialysis vintage of <1 year or when the study period was restricted until 2016 (data not shown). Although the Cox proportional hazard assumption was violated for some covariates, we confirmed that the associations between serum calcium levels and cardiovascular were not changed in the Cox proportional hazard model including interaction term between analysis time and each covariate violating it. In the analysis for the association with fatal and non-fatal cardiovascular events, the lowest calcium decile was associated with higher rate of cardiovascular events in all patients (Supplementary data, Table S5). These results were similar in cinacalcet users.

In restricted cubic spline models, the association between calcium and cardiovascular mortality was U-shape in the time-dependent model, while the association was positively linear in the time-averaged model in all patients including cinacalcet users (Fig. 3). Similar trends were observed in cinacalcet users (data not shown).

Figure 4 shows the association between serum calcium levels and five main causes of cardiovascular death (heart failure, ischemic heart disease, sudden death, hemorrhagic stroke and cerebral infarction) in all patients. The number and proportion of these causes in complete cases were as follows: 9117 deaths (53.3%) due to heart failure, 1958 deaths (11.5%) due to ischemic heart disease, 1832 sudden deaths (10.7%), 1757 deaths (10.3%) due to hemorrhagic stroke and 1094 deaths (6.4%) due to cerebral infarction. In the time-dependent model, the associations with heart failure, ischemic heart disease, sudden death or hemorrhagic stroke were U-shaped with increased risk in the range of hypocalcemia. In contrast, the association regarding cerebral infarction was linear, with low calcium levels having a low hazard ratio. In the time-averaged model, similar linear associations were observed regarding heart failure, cerebral infarction and sudden death. The sigmoid relationship was observed for ischemic heart disease. No association with serum calcium levels was observed for hemorrhagic stroke. In time-averaged model, hypercalcemia was associated with increased mortality caused by heart failure, ischemic heart disease and cerebral infarction, but not sudden

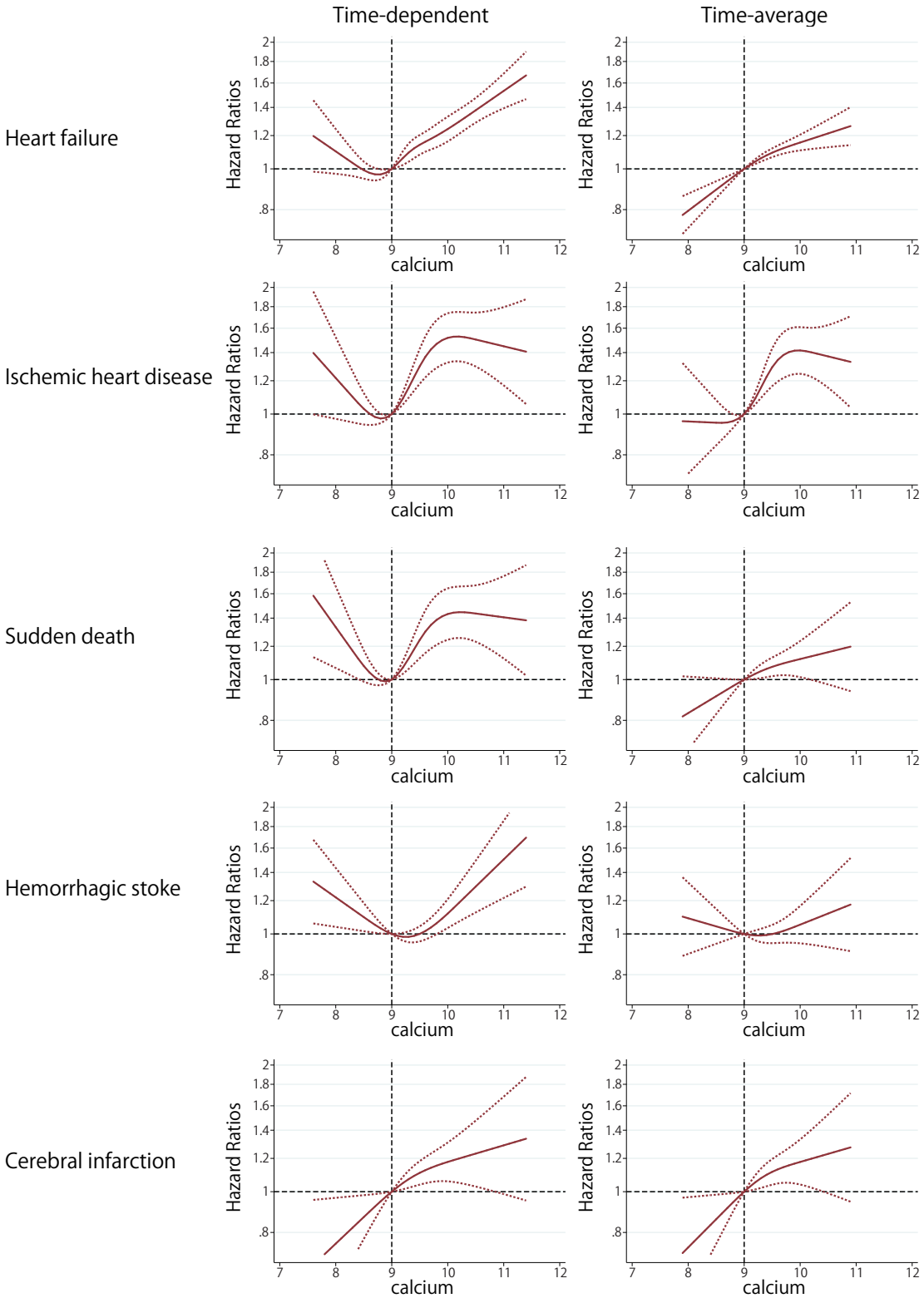


Figure 4: Relationship between calcium and five main causes of cardiovascular death in all patients in the time-dependent model and in the time average model.

death or death by hemorrhagic stroke (Supplementary data, Table S6).

The cardiovascular mortality risk across ranges of phosphorus, intact PTH and calcium × phosphorus is shown in Supplementary data, Figs S1–S3 and Tables S7–S12. Unlike baseline and time-dependent models, low phosphorus levels in the time-averaged model were associated with lower mortality risk, and high phosphorus levels were associated with higher mortality risk compared with the reference in both cinacalcet users and all patients. The associations for calcium × phosphorus

were similar to those for phosphorus. Low intact PTH levels were not associated with an increased risk of mortality. High intact PTH levels were associated with increased cardiovascular mortality risk in the time-dependent and time-averaged model in all patients. Similar trends were observed in patients with or without PTH suppressive therapy (Supplementary data, Table S13).

Associations regarding all-cause mortality are shown in Supplementary data, Figs S1–S3 and Table S14. Although most associations had a similar trend to cardiovascular mortality, the risk associated with low calcium levels was attenuated.

DISCUSSION

Hypocalcemia is commonly observed in patients treated with calcimimetics. The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Event (EVOLVE) trial has shown that 58.6% of participants developed at least one episode of hypocalcemia [12]. Although some case reports reported that this hypocalcemia caused serious adverse events [20, 21], prospective studies have shown that calcimimetics-induced hypocalcemia was usually self-limited, and serious adverse events were very rare [22, 23]. In the EVOLVE trial, low calcium levels did not increase the onset of the composite endpoint of death and cardiovascular event [12]. The Kidney Disease: Improving Global Outcomes guidelines argued that hypocalcemia due to calcimimetics may be harmless [11]. However, in our study, the cardiovascular mortality risk of hypocalcemia was increased in cinacalcet users in the time-dependent model. These results suggest that transient hypocalcemia induced by cinacalcet may be a risk of cardiovascular death.

Whether hypocalcemia is a risk factor for mortality in hemodialysis patients is controversial. Hypocalcemia is associated with increased mortality in patients with heart failure [24, 25]. Heart failure has been reported to be one of the most common causes of early readmission after PTx [13]. A large cohort study has demonstrated that hypocalcemia was associated with excess mortality in dialysis patients [26]. However, an old meta-analysis showed that low calcium levels were associated with decreased mortality risk [4]. In our study, hypocalcemia was associated with increased cardiovascular mortality in the time-dependent model, while the time-averaged model showed that hypocalcemia was associated with decreased cardiovascular mortality in hemodialysis patients. These findings suggest that transient hypocalcemia may increase the risk of cardiovascular mortality and maintaining low calcium levels may possibly decrease this risk in patients who survive even with hypocalcemia. As low calcium levels are often treated resulting in normal or high calcium, leading to normal time-averaged calcium levels, a time-averaged model cannot capture transient hypocalcemia. If the risk is observed around time spent at a low calcium level, it would be better captured in a time-dependent model.

We examined the association between serum calcium levels and the five main causes of cardiovascular death to clarify the mechanism for the discrepancy between the models regarding the risks of cardiovascular mortality associated with low calcium levels. The observed increased risk of death due to ischemic heart disease and sudden death in the range of hypocalcemia may be attributed to fatal arrhythmia induced by hypocalcemia. This finding is consistent with the existing evidence demonstrating that hypocalcemia is a risk factor for QTc interval prolongation, which may result in fatal arrhythmia [27]. QTc interval prolongation is frequently found after intracerebral hemorrhage [28, 29], which may be one of the reasons for the increased risk of death due to hemorrhagic stroke associated with hypocalcemia. Furthermore, several studies have shown that low calcium levels were associated with large hematoma volume of intracerebral hemorrhage [30, 31] and hypocalcemia may induce impaired coagulation [32, 33]. These results are in line with our findings. Taken together, the increased cardiovascular mortality risk of hypocalcemia in the time-dependent model may be induced by increased fatal arrhythmia and fatal hemorrhagic stroke.

In the time-averaged model, we observed a high risk of cerebral infarction but not hemorrhagic stroke in the range of relative hypercalcemia. Since time-averaged models allow us to examine the cumulative effects of mineral parameters, reducing the influence of their fluctuation, this finding reflects that consistently high serum calcium levels may have contributed to the development of atherosclerotic disease in hemodialysis patients. This hypothesis is in line with the result that serum calcium levels were also positively associated with death from ischemic heart disease.

This study has several limitations. First, the follow-up data on the use of calcimimetics following the baseline assessment was obtained only once, at the end of 2019. However, the mean annual dropout rate of calcimimetics therapy was estimated to be only 2.9%. Therefore, we think hypocalcemia was induced by cinacalcet treatment. Second, target ranges for CKD-MBD markers are different across countries. The PTH target range in Japan is lower than that in other countries. Therefore, caution is warranted in extrapolating the present findings. Third, since this study was an observational not an interventional study, doctors tried to keep calcium levels within target ranges. As a result, hypocalcemia in the first decile was mild, especially in the time-averaged model. Therefore, the hazard ratio in this range may not be applicable to patients with severe hypocalcemia. Fourth, cardiovascular deaths and comorbidities were identified by medical personnel such as physicians, surgeons, nurses, clinical engineers and trained abstractors of facilities, and data validation has not been performed. Fifth, our study could not assess serum potassium, which is an important risk factor for arrhythmia and sudden cardiac death. However, potassium may not distort the association between calcium and cardiovascular mortality because serum potassium levels were reported not to be correlated with serum calcium levels [34, 35]. Sixth, although we adjusted important confounders, there might be residual confounding. Although there are several limitations in this study, it has strengths. To the best of our knowledge, this study is the largest study, with the longest follow-up time, assessing the relationship between calcium levels and mortality in hemodialysis patients treated with cinacalcet. Since cinacalcet is used widely, this study will provide us with useful evidence for many hemodialysis patients.

In conclusion, hypocalcemia in the time-dependent model was associated with an increased risk of cardiovascular death in hemodialysis patients with cinacalcet. These findings suggest that transient hypocalcemia induced by cinacalcet is found to be harmful.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

ACKNOWLEDGEMENTS

We thank the members of the Committee of Renal Data Registry of the JSDT and the personnel at the participating institutions involved in this survey. The data reported in this study have been supplied by the JRDR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the JSDT.

FUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

S.G. was responsible for the research idea and study design, and contributed to the analysis and drafting of the manuscript. H.F., M.T., T.H., M.A., K.N. and S.N. contributed to the concept of design, analysis, interpretation of data and revision of the manuscript.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the JSDT but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the JSDT.

CONFLICT OF INTEREST STATEMENT

S.G. reports receiving honoraria from Kyowa Kirin, Sanwa Kagaku Kenkyusho, Kissei and Astellas, and scholarship grants from Kyowa Kirin, Bayer and Chugai. H.F. reports receiving speaker fees as honoraria from Kyowa Kirin, Bayer, Kissei and Astellas, and receiving scholarship grants from Kyowa Kirin, Bayer and Chugai. M.T. reports receiving honoraria from Kyowa Kirin, Torii, Kissei, Ono, Bayer, Daiichi Sankyo, Sanwa Kagaku Kenkyusho, Astellas and Mitsubishi Tanabe. T.H. reports receiving honoraria from Kyowa Kirin, Ono, Sanwa Kagaku Kenkyusho, Kissei, Astellas, Chugai and Torii, and receiving research funding from Kyowa Kirin, Kissei, Chugai, Sanwa Kagaku Kenkyusho and Torii. M.A. reports receiving research funding from Kyowa Kirin and Torii. K.N. reports receiving honoraria from Kyowa Kirin and receiving research funding from Kyowa Kirin. S.N. reports receiving honoraria from Kyowa Kirin, Chugai, Bayer Yakuhin, Kissei, Astellas and Torii, and receiving scholarship grants from Kyowa Kirin, Bayer and Chugai.

REFERENCES

1. Taniguchi M, Fukagawa M, Fujii N *et al.* Serum phosphate and calcium should be primarily and consistently controlled in prevalent hemodialysis patients. *Ther Apher Dial* 2013;**17**:221–8. https://doi.org/10.1111/1744-9987.12030
2. Nakai S, Akiba T, Kazama J *et al.* Effects of serum calcium, phosphorous, and intact parathyroid hormone levels on survival in chronic hemodialysis patients in Japan. *Ther Apher Dial* 2008;**12**:49–54. https://doi.org/10.1111/j.1744-9987.2007.00540.x
3. Fernández-Martín JL, Martínez-Camblor P, Dionisi MP *et al.* Improvement of mineral and bone metabolism markers is associated with better survival in hemodialysis patients: the COSMOS study. *Nephrol Dial Transplant* 2015;**30**:1542–51. https://doi.org/10.1093/ndt/gfv099
4. 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. https://doi.org/10.1186/1471-2369-14-88
5. 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**:98–109. https://doi.org/10.2215/CJN.12941213
6. Chertow GM, Block GA, Correa-Rotter R *et al.* Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012;**367**:2482–94. https://www.nejm.org/doi/10.1056/NEJMoa1205624
7. Parfrey PS, Drüeke TB, Block GA *et al.* The effects of cinacalcet in older and younger patients on hemodialysis: the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial. *Clin J Am Soc Nephrol* 2015;**10**:791–9. https://doi.org/10.2215/CJN.07730814
8. Moe SM, Abdalla S, Chertow GM *et al.* Effects of cinacalcet on fracture events in patients receiving hemodialysis: the EVOLVE trial. *J Am Soc Nephrol* 2015;**26**:1466–75. https://doi.org/10.1681/ASN.2014040414
9. Chonchol M, Locatelli F, Abboud HE *et al.* A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet HCl in participants with CKD not receiving dialysis. *Am J Kidney Dis* 2009;**53**:197–207. https://doi.org/10.1053/j.ajkd.2008.09.021
10. St Peter WL, Li Q, Liu J *et al.* Cinacalcet use patterns and effect on laboratory values and other medications in a large dialysis organization, 2004 through 2006. *Clin J Am Soc Nephrol* 2009;**4**:354–60. https://doi.org/10.2215/CJN.05241008
11. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2017;**7**:1–59. https://doi.org/10.1016/j.kisu.2017.04.001
12. Floege J, Tsirtsonis K, Iles J *et al.* Incidence, predictors and therapeutic consequences of hypocalcemia in patients treated with cinacalcet in the EVOLVE trial. *Kidney Int* 2018;**93**:1475–82. https://doi.org/10.1016/j.kint.2017.12.014
13. Kravietz AM, Buicko JL, Parreco JP *et al.* Thirty-day readmissions following parathyroidectomy: evidence from the National Readmissions Database, 2013-2014. *Am J Otolaryngol* 2018;**39**:82–7. https://doi.org/10.1016/j.amjoto.2018.01.006
14. Zhang W, Xue F, Bu Q *et al.* Hypocalcemic cardiomyopathy after parathyroidectomy in a patient with uremia: a case report and literature review. *J Int Med Res* 2020;**48**:300060520942115. https://journals.sagepub.com/doi/10.1177/0300060520942115
15. Nakai S, Iseki K, Itami N *et al.* Overview of regular dialysis treatment in Japan (as of 31 December 2009). *Ther Apher Dial* 2012;**16**:11–53. https://doi.org/10.1111/j.1744-9987.2011.01050.x
16. 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**:247–88. https://doi.org/10.1111/1744-9987.12058
17. Oken MM, Creech RH, Tormey DC *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;**5**:649–55. https://doi.org/10.1097/00000421-198212000-00014

18. Nitta K, Masakane I, Hanafusa N *et al.* Annual dialysis data report 2017, JSDT Renal Data Registry. *Ren Replace Ther* 2019;**5**:53. https://doi.org/10.1186/s41100-019-0248-1
19. Sakaguchi Y, Fujii N, Shoji T *et al.* Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis. *Kidney Int* 2014;**85**:174–81. https://doi.org/10.1038/ki.2013.327
20. Novick T, McMahon BA, Berliner A *et al.* Cinacalcet-associated severe hypocalcemia resulting in torsades de pointes and cardiac arrest: a case for caution. *Eur J Clin Pharmacol* 2016;**72**:373–5. https://doi.org/10.1007/s00228-015-1989-6
21. Koubar SH, Qannus AA, Medawar W *et al.* Hungry bone syndrome two weeks after starting cinacalcet: a call for caution. *CEN Case Rep* 2018;**7**:21–23. https://doi.org/10.1007/s13730-017-0284-z
22. Block GA, Martin KJ, de Francisco AL *et al.* Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 2004;**350**:1516–25. https://doi.org/10.1056/NEJMoa031633
23. Wetmore JB, Gurevich K, Sprague S *et al.* A randomized trial of cinacalcet versus vitamin D analogs as monotherapy in secondary hyperparathyroidism (PARADIGM). *Clin J Am Soc Nephrol* 2015;**10**:1031–40 https://doi.org/10.2215/CJN.07050714
24. Miura S, Yoshihisa A, Takiguchi M *et al.* Association of hypocalcemia with mortality in hospitalized patients with heart failure and chronic kidney disease. *J Card Fail* 2015;**21**:621–7. https://doi.org/10.1016/j.cardfail.2015.04.015.
25. Jensen AC, Polcwiartek C, Søgaard P *et al.* The association between serum calcium levels and short-term mortality in patients with chronic heart failure. *Am J Med* 2019;**132**:200–8. https://doi.org/10.1016/j.amjmed.2018.10.006
26. Rivara MB, Ravel V, Kalantar-Zadeh K *et al.* Uncorrected and albumin-corrected calcium, phosphorus, and mortality in patients undergoing maintenance dialysis. *J Am Soc Nephrol* 2015;**26**:1671–81. https://doi.org/10.1681/ASN.2014050472
27. Heemskerk CPM, Pereboom M, van Stralen K *et al.* Risk factors for QTc interval prolongation. *Eur J Clin Pharmacol* 2018;**74**:183–91. https://doi.org/10.1007/s00228-017-2381-5
28. Qin G, Dai C, Feng S *et al.* Changes of electrocardiogram and myocardial enzymes in patients with intracerebral hemorrhage. *Dis Markers* 2022;**2022**:9309444. https://doi.org/10.1155/2022/9309444
29. Takeuchi S, Nagatani K, Otani N *et al.* Electrocardiograph abnormalities in intracerebral hemorrhage. *J Clin Neurosci* 2015;**22**:1959–62. https://doi.org/10.1016/j.jocn.2015.04.028
30. Inoue Y, Miyashita F, Toyoda K *et al.* Low serum calcium levels contribute to larger hematoma volume in acute intracerebral hemorrhage. *Stroke* 2013;**44**:2004–6. https://doi.org/10.1161/STROKEAHA.113.001187
31. Morotti A, Charidimou A, Phuah CL *et al.* Association between serum calcium level and extent of bleeding in patients with intracerebral hemorrhage. *JAMA Neurol* 2016;**73**:1285–90. https://doi.org/10.1001/jamaneurol.2016.2252
32. Fukuda T, Nakashima Y, Harada M *et al.* Effect of whole blood clotting time in rats with ionized hypocalcemia induced by rapid intravenous citrate infusion. *J Toxicol Sci* 2006;**31**:229–34. https://doi.org/10.2131/jts.31.229
33. Fujita Y, Doi K, Harada D *et al.* Modulation of physiological hemostasis by irrigation solution: comparison of various irrigation solutions using a mouse brain surface bleeding model. *J Neurosurg* 2010;**112**:824–8. https://doi.org/10.3171/2009.7.JNS09561
34. Kim T, Rhee CM, Streja E *et al.* Racial and ethnic differences in mortality associated with serum potassium in a large hemodialysis cohort. *Am J Nephrol* 2017;**45**:509–21. https://doi.org/10.1159/000475997
35. Kovesdy CP, Regidor DL, Mehrotra R *et al.* Serum and dialysate potassium concentrations and survival in hemodialysis patients. *Clin J Am Soc Nephrol* 2007;**2**:999–1007. https://doi.org/10.2215/CJN.04451206

Received: April 7, 2023; Editorial decision: August 26, 2023