Clinical Kidney Journal

Clinical Kidney Journal, 2024, vol. 17, no. 10, sfae288

https://doi.org/10.1093/ckj/sfae288
Advance Access Publication Date: 4 October 2024
Original Article

ORIGINAL ARTICLE

The effects of dialysate calcium prescription on mortality outcomes in incident patients on hemodialysis

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ABSTRACT

Background. The appropriate prescription of dialysate calcium concentration for hemodialysis is debated. We investigated the association between dialysate calcium and all-cause, cardiovascular mortality and sudden cardiac death.

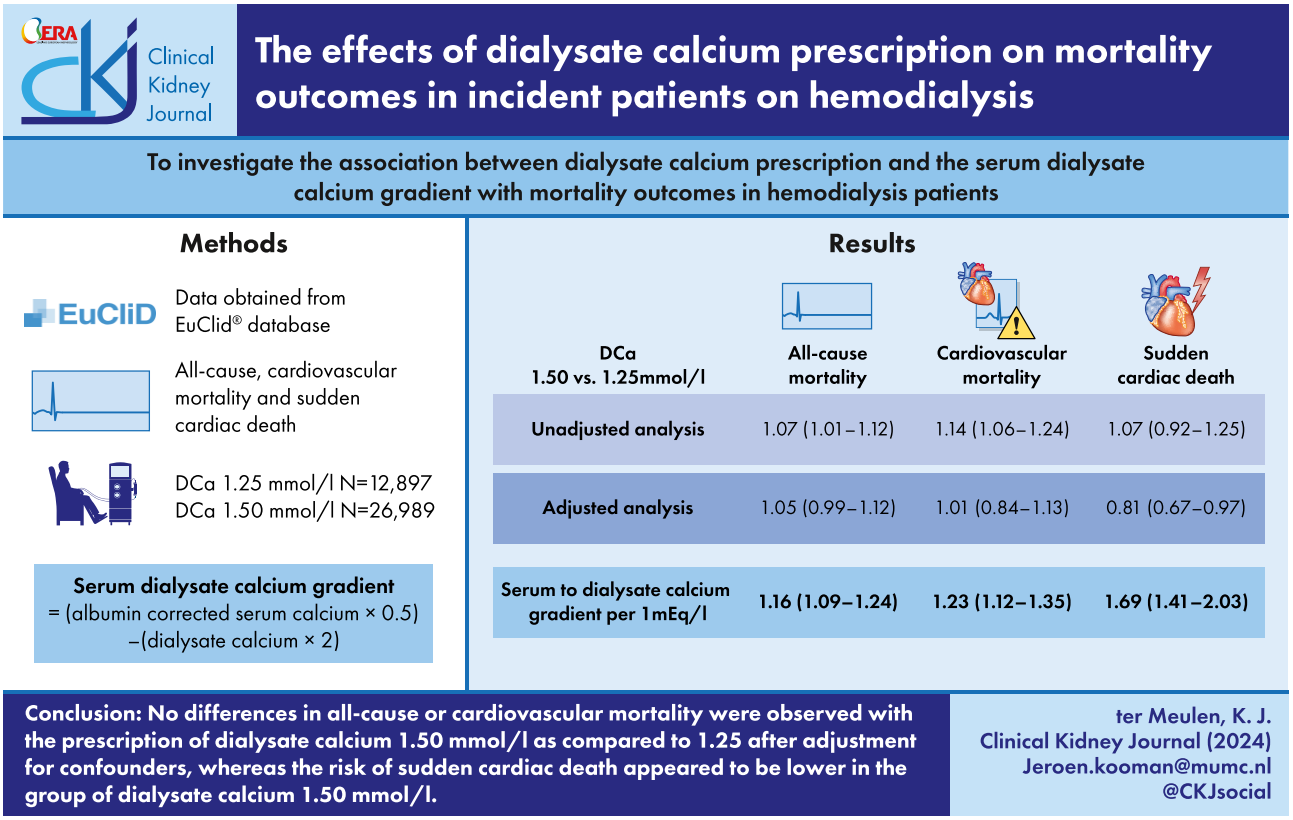
Methods. In this historical cohort study, we included adult incident hemodialysis patients who initiated dialysis between 1 January 2010 and 30 June 2017 who survived for at least 6 months (grace period). We evaluated the association between dialysate calcium 1.25 or 1.50 mmol/l and outcomes in the 2 years after the grace period, using multivariable Cox regression models. Moreover, we examined the association between the serum dialysate to calcium gradient and outcomes.

Results. We included 12 897 patients with dialysate calcium 1.25 mmol/l and 26 989 patients with dialysate calcium 1.50 mmol/l. The median age was 65 years, and 61% were male. The unadjusted risk of all-cause mortality was higher for dialysate calcium 1.50 mmol/l [hazard ratio (HR) 1.07, 95% confidence intervals (CI) 1.01–1.12]. However, in the fully adjusted model, no significant differences were noted (HR 1.05, 95% CI 0.99–1.12). Similar results were observed for the risk of cardiovascular mortality (HR 1.03, 95% CI 0.94–1.13). Adjusted risk of sudden cardiac death was lower for dialysate calcium 1.50 mmol/l (HR 0.81, 95% CI 0.67–0.97). Significant and positive associations with all outcomes were observed with larger serum-to-dialysate calcium gradients, primarily mediated by the serum calcium level.

Conclusions. In contrast to the unadjusted analysis that showed a higher risk for dialysate calcium of 1.50 mmol/l, after adjusting for confounders, there were no significant differences in the risk of all-cause and cardiovascular mortality between dialysate calcium concentrations of 1.50 and 1.25 mmol/l. After adjustment, a lower risk of sudden cardiac death was observed in patients with dialysate calcium 1.50 mmol/l. A higher serum-to-dialysate calcium gradient is associated with an increased risk for adverse outcomes.

Received: 11.6.2024; Editorial decision: 17.8.2024

GRAPHICAL ABSTRACT



Keywords: calcium, cardiovascular, chronic hemodialysis, dialysate, mortality

KEY LEARNING POINTS

What was known:

- Cardiovascular diseases are still an important risk factor for morbidity and mortality in hemodialysis patients despite all the improvements in techniques, medication, and medical care.
- A possible risk is the level of dialysate calcium concentration, where international guidelines even differ in their recommendations.

This study adds:

- We compared all-cause, cardiovascular mortality and sudden cardiac death among patients with dialysate calcium 1.25 and 1.50 mmol/l for 2 years in incident patients on hemodialysis.
- In contrast to the unadjusted analysis, no significant differences in all-cause or cardiovascular mortality were observed with the prescription of dialysate calcium 1.50 mmol/l compared to 1.25 after adjustment for confounders, whereas risk of sudden cardiac death appeared to be lower in the group of dialysate calcium 1.50 mmol/l.
- Association between serum dialysate calcium gradient and outcomes appears to be predominantly related to the effect of serum calcium.

Potential impact:

- This study supports the European Renal Best Practice recommendations that dialysate calcium prescription should be based on consideration of individual patient characteristics.

INTRODUCTION

Cardiovascular disease related to cardiovascular calcifications is a significant risk factor for morbidity and mortality in hemodialysis (HD) patients [1, 2]. Abnormalities in mineral metabolism, such as hyperphosphatemia in combination with deficiency of calcification inhibitors are key factors in their pathogenesis of calcifications [3]. The importance of calciprotein particles (CPP) has recently been acknowledged [4]. It is also suggested that dialysate calcium (DCa) prescription can contribute to the

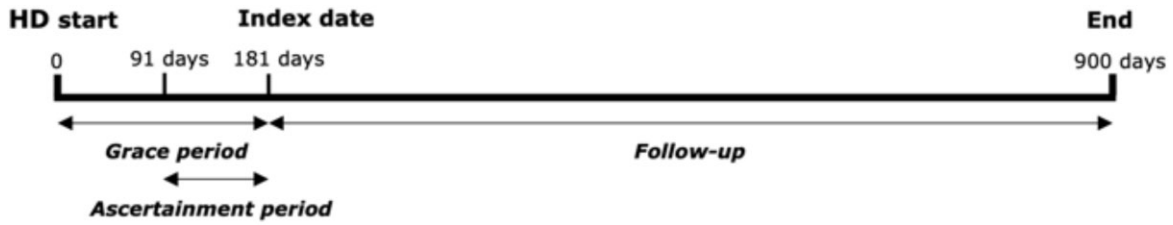


Figure 1: Study design. Grace period is the first 180 days. The ascertainment period is from day 91 to 180. Index date is set at 181 days. Follow-up period is up to 720 days after the index date.

progress of vascular calcification, with the latest evidence linking DCa to calcification propensity [5]. A DCa of 1.75 mmol/l has been related to increased vascular calcifications and arterial stiffness [6, 7], and was identified as a significant risk factor for all-cause mortality [8]. On the other hand, DCa levels below 1.25 mmol/l have been associated with an increased incidence of sudden cardiac death (SDC) [9], likely due to low ionized calcium levels and prolongation of the QT interval [10]. The most frequently prescribed DCa concentrations in clinical practice are 1.25 (DCa 1.25) and 1.50 (DCa 1.50) mmol/l. Few studies compared the relation between DCa 1.25 or 1.50 and clinical outcomes, and current guidelines differ in their recommendations. The Kidney Disease Outcomes Quality Initiative guidelines express a clear preference for DCa 1.25 [11], whereas the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines advise maintaining DCa prescription between 1.25 and 1.50 mmol [12]. They both state that the concentration can vary depending on the patient's parathyroid hormone level and calcium balance.

An important modifying factor in the relation between DCa and outcomes might be the gradient of serum calcium (SCa) and DCa (serum dialysate calcium gradient; SCa-DCa). Pun *et al.* showed that large SCa-DCa and low DCa were associated with an increased risk of sudden cardiac arrest [9]. Patients with a large SCa-DCa gradient may experience a higher risk of hemodynamic instability, arrhythmias due to rapid diffusive loss of calcium, and SCD, whereas those with a lower gradient might experience a higher risk of intradialytic calcium gain resulting in cardiovascular calcifications and subsequent mortality.

This observational study aimed to compare all-cause mortality, cardiovascular mortality, and SCD in incident patients on HD therapy treated with DCa 1.25 or DCa 1.50. Moreover, the association between the SCa-DCa gradient and outcomes was evaluated.

MATERIALS AND METHODS

Study design and participants

The study period was between 1 January 2010 and 31 December 2019. All adult incident patients who initiated HD between 1 January 2010 and 30 June 2017 were screened. The study design consisted of three periods: (i) the grace period, which began 180 days after the start of dialysis; (ii) the ascertainment period, which was set between 91 days after dialysis initiation and 180 days after; and (iii) the follow-up period, which was up to 2 years after the ascertainment period (Fig. 1). We included patients aged between 18 and 85 years who initiated HD in the recruitment period, survived the grace period, and provided consent to use their pseudo-anonymized data for secondary data analysis. The inclusion criteria necessitated a minimum of at least one HD treatment recorded in the grace, ascertainment, and follow-up periods. All treatments in the ascertainment period were required to utilize DCa 1.25 or 1.50 or 1.75 mmol/l, with at least 75% of sessions using one of these concentrations. In the Fresenius Medical Care Nephrocare network, no specific DCa concentration is required, but a DCa of 1.75 mmol/l is not recommended after the direct initiation period. It is, however, strongly recommended to individualize DCa prescription based on clinical and biochemical criteria, and the choice of phosphate and active vitamin D analogs [13].

Patients with misleading information on death (treatment recorded after death date), and missing information on vascular access or sex were excluded for data quality reasons. Considering the limited number, we ultimately excluded patients who had predominantly utilized DCa 1.75.

For this retrospective cohort study, data was extracted from European, Middle Eastern, and African countries registered in the European Clinical Database (EuCliD®). EuCliD® is an information technology tool managed by Fresenius Medical Care to monitor the quality of treatment in its centers [14]. All 663 participating centers are part of EuCliD®. The laboratory data, as well as treatment data, are automatically transferred in EuCliD®. To ensure the accuracy of the data provided by the participating countries, a continuous quality improvement program supported by digital transformation has been in use for several years [15]. The digitization of patient medical records and data warehousing technologies have standardized the data collection process and improved its efficiency, ensuring compliance with best clinical practices and the accuracy of the data reported.

The study protocol was reviewed by the local Medical Research Ethics Committee (METC) of the Maastricht University Medical Center, and they declared that Medical Research Involving Human Subjects Act (WMO) did not apply to this study and that an official approval by METC was not required (METC 2021–2621).

Exposure definition and outcome assessment

The DCa concentration most prescribed in the ascertainment period was defined as the exposure: DCa 1.25 or 1.50. Primary outcomes were all-cause mortality, cardiovascular mortality, and SCD, assessed during the follow-up period. In the case of death within the follow-up period, the patient was considered to be deceased; in case of death or a treatment beyond the follow-up period, the patient was considered alive at the end of the follow-up period; otherwise, the greatest date between the last treatment and the first cardiovascular hospitalization, if available, was considered the censoring date.

The reason of death is tracked in EuCliD® according to the International Classification of Diseases, tenth revision (ICD-10). Cardiovascular-related mortality was defined as any death recorded with an ICD-10 code within the range of I00–I99, while

sudden cardiac death was specifically defined as any death registered with the ICD-10 I46.

Measures and data management

Patient characteristics were assessed in the ascertainment period: demographic, anthropometric, lifestyle, comorbidities, dialysis-related parameters, blood biomarkers, hospitalizations, and medication use. Comorbidities were defined as any occurrence by the end of the ascertainment period. Specifically, cancer, cardiovascular, and liver diseases were stated according to the Charlson Comorbidity Index; diabetes was defined as any occurrence of suggestive ICD10 codes N08.3 or within the range of E08-E14 or prescription of antidiabetic drugs (occurrence of suggestive ATC code belonging to the therapeutic group A10).

We also considered the prescription of calcium-containing phosphate binders (ATC codes: A02AC, A12AA, V03AE04, V03AE07, V03AE09), vitamin D and analogs (ATC codes: H05BX02, A11CC), and calcimimetic agents (ATC code: H05BX01).

Quality control of the data was performed considering as missing any data that lied outside of pre-established range values (Supplemental Table S1).

The mean value in the ascertainment period was used for continuous variables.

SCa-DCa was based on the method by Pun *et al.* (albumin-corrected SCa $\times$ 0.5) $-$ (DCa $\times$ 2) [9]. SCa was corrected for serum albumin: [SCa (mg/dl) + 0.8 $\times$ (4 $-$ serum albumin (g/dl)].

Statistical analysis

Data were expressed as mean with standard deviation or median with interquartile range or percentage, as appropriate. Statistical analysis to determine the significance of differences was performed with one-way analysis of variance for normally distributed continuous variables, the Kruskal–Wallis test for non-normally distributed continuous variables, and the Pearson Chi-square test for dichotomous variables.

We calculated the incidence density and 95% confidence intervals (CI) of each outcome per 100 person-years (PY) based on the Poisson distribution. We utilized the Kaplan–Meier (KM) method for conducting survival analysis and the log-rank test to evaluate whether KM curves were statistically equivalent. For each outcome and exposure, we employed multivariable extended Cox regression models to account for non-proportional hazards (where required) to adjust for potential confounders. Model 1a represents the unadjusted model, whereas model 1b incorporates the country as random effect without adjustment. We added country indicators as random effect to account for differences in the prescription of dialysate calcium concentration. Model 2 builds on model 1b by adjusting for various factors, including age, sex, ethnicity, comorbidities (diabetes, cardiovascular disease, liver disease, and cancer), vascular access, treatment time, Kt/V, and total ultrafiltration volume per session. Model 3 extends the adjustments in model 2 by additionally incorporating variables such as serum hemoglobin, serum albumin, calcium-containing phosphate binders, vitamin D and analogs, and calcimimetic agents. Model 4 builds on model 3 and incorporates pre-dialytic corrected serum calcium and dialysate bicarbonate, as the latter may have an effect on the availability of calcium for intradialytic diffusion. The hazard ratios (HR) refer to DCa 1.50 versus DCa 1.25.

For the SCa-DCa gradient analysis, results until model 3 are reported. A secondary analysis was performed on patients with intact parathyroid hormone (iPTH) below 130 pg/ml as a threshold, according to the study performed by Neri *et al.* [16].

We included countries with at least 150 patients per exposure group for sensitivity analysis. We constructed a propensity score-matched cohort based on the likelihood of exposure in the same country. The potential confounding variables used for calculating the propensity score were those considered in model 3. We assessed covariate balance after matching by examining the effect size of the differences in clinical parameters across the matched samples. We modeled the risk of each outcome using Cox Proportional Hazard Regression models, stratified by country, and employed a robust covariance matrix estimate to account for matched-pair dependence.

All analyses were done using SAS 9.4®. A P value of $<.05$ was considered statistically significant. No correction was used for multiple testing.

RESULTS

Sample characteristics

A total of 86 595 patients were screened; among them, 39 886 patients from 22 countries and 663 dialysis centers were eligible to be included in the study. A large proportion of patients was excluded due to the absence of registered treatments during each period of the study. Specifically, 12 897 patients were included for DCa 1.25 and 26 989 patients for DCa 1.50 (Fig. 2). Demographic and clinical characteristics are described in Table 1. The median age was 65 years and 61% were male in both groups. The DCa 1.50 group exhibited a significantly longer mean follow-up time compared to the DCa 1.25 group (19.7 $\pm$ 7.4 versus 19.0 $\pm$ 7.7, $P < .001$). Furthermore, patients in the DCa 1.50 group had a significant lower rate of lost to follow-up (15% versus 21%, $P < .001$).

Incidence of outcomes

Within the DCa 1.25 group, we observed 2109 deaths (10.5/100 PY, 95% CI 10.0–10.9/100 PY), of which 43% attributed to cardiovascular causes ($n = 916$, 4.5/100 PY, 95% CI:4.3–4.9/100 PY) and 11% to SCD ($n = 233$, 1.2/100 PY, 95% CI 1.0–1.3/100 PY). On the other hand, within the DCa 1.50 group, we observed 4855 deaths (11.1/100 PY, 95% CI 10.8–11.5/100 PY), of which 47% were due to cardiovascular causes ($n = 2263$, 5.2/100 PY, 95% CI 5.0–5.4/100 PY) and 11% to SCD ($n = 538$, 1.2/100 PY, 95% CI 1.1–1.3/100 PY).

Effect of dialysate calcium (DCa)

Results are shown in Table 2. The significant unadjusted association with all-cause mortality was demonstrated with exposure to DCa 1.50 in respect to DCa 1.25 (HR 1.07, 95% CI 1.01–1.12), however, it lost its significance when country was included as random effect and it remained unsignificant in adjusted models (HR 1.05, 95% CI 0.99–1.12, fully adjusted model). A similar result was observed for cardiovascular mortality (HR 1.03, 95% CI 0.94–1.13, fully adjusted model). On the contrary, we found a significant association between the risk of SDC and DCa 1.50 in the adjusted models (HR 0.81, 95% CI 0.67–0.97, fully adjusted) that was not observed in the unadjusted model (HR 1.07, 95% CI 0.92–1.25).

Effect of serum dialysate calcium gradient (SCa-DCa)

Results are shown in Table 3. All models consistently indicated a significant association between all outcomes and a larger

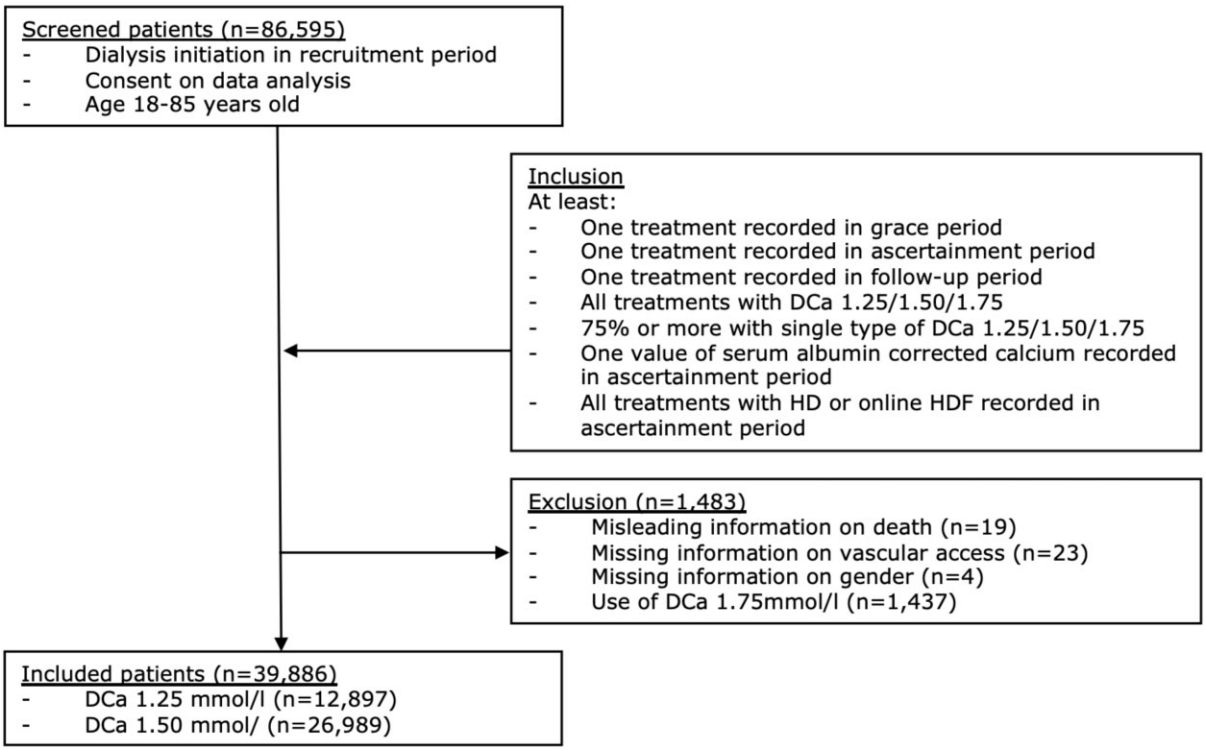


Figure 2: Patient flow chart. Grace period is the first 180 days after dialysis initiation; ascertainment period is day 91 to 180 after dialysis initiation; follow-up period is 720 days after the index date day 181.

SCa-DCa ($P < .001$). In the fully adjusted models, the HRs per 1 mEq/l of increase of SCa-DCa were 1.16 (95% CI 1.09–1.24) for all-cause and 1.23 (95% CI 1.12–1.35) for cardiovascular mortality, as well as 1.69 (95% CI 1.41–2.03) for SCD.

We also evaluated the association of the two gradient components and their interaction with each outcome (Table 4). We found a significant association between all outcomes and corrected SCa, but not with DCa. Besides, their interaction term was not significant for any outcomes, concluding that there was no significant evidence that the SCa-DCa was really associated with the outcomes except for the effect of its SCa component.

Secondary analysis on patients with intact parathyroid hormone (iPTH) below 130 pg/ml

Among the 17 407 patients with a detectable iPTH in the ascertainment period, we found 7438 patients with iPTH < 130pg/ml: 2296 patients in the DCa 1.25 group and 5142 patients in the DCa 1.50 group. Within the DCa 1.25 group, we observed 451 deaths (12.9/100 PY, 95% CI 11.8–14.2/100 PY), of which 44% attributed to cardiovascular causes ($n = 200$, 5.7/100 PY, 95% CI 5.0–6.6/100 PY) and 10% to SCD ($n = 47$, 1.4/100 PY, 95% CI 1.0–1.8/100 PY). On the other hand, within the DCa 1.50 group, we observed 1125 deaths (14.1/100 PY, 95% CI 13.3–15.0/100 PY), of which 46% attributed to cardiovascular causes ($n = 516$, 6.5/100 PY, 95% CI 5.9–7.1/100 PY) and 12% to SCD ($n = 134$, 1.7/100 PY, 95% CI 1.4–2.0/100 PY).

In this subgroup, we did not observe any significant associations between DCa and the different outcomes (Supplemental Table S2). The significant association between SCa-DCa and all-cause (HR 1.17, 95% CI 1.02–1.34) and cardiovascular mortality (HR 1.23, 95% CI 1.01–1.51) persisted even within these patients, but it was no longer significant with SCD. Last, the significant association between all outcomes and SCa found in the principal analysis was not confirmed in this subgroup.

Sensitivity analysis

We included nine countries with at least 150 patients per exposure group: Hungary, Poland, Portugal, Romania, Russia, Slovakia, Spain, Turkey, and the UK). The final matched patient cohort included 14 132 patients (7066 for each DCa group). The imbalance between the covariates after matching was minimal, as shown by the very small effect size estimates (Supplemental Figure S4). There was no significant effect found between exposure groups for all outcomes within this analysis. However, for SCD the HR remained of the same order of magnitude as that in the main analysis (Supplemental Table S3).

DISCUSSION

This large historical cohort study showed that, whereas DCa 1.50 was associated with an increased all-cause and cardiovascular mortality in unadjusted analysis, no significant differences in both parameters were observed after adjustment for confounders. Following adjustment, SCD was lower in patients using DCa 1.50, although the limited number of cases may have impacted the significance of this finding. Remarkably the cardiovascular diseases are more represented in the DCa 1.50 group.

Previous studies addressing the relation between DCa levels and outcomes in larger patient cohorts have yielded inconsistent results. In a study of 1182 incident patients on HD, DCa levels of 1.75 were associated with increased all-cause-, cardiovascular-, and infection-related mortality as compared to

Table 1: Demographic and clinical characteristics. Data are expressed as mean ± standard deviation or median with interquartile range, as appropriate. Frequencies are expressed in percentages. DCa: dialysate calcium concentration in mmol/l. BMI: body mass index. iPTH: intact parathyroid hormone. spKt/V: single pool fractional urea clearance. SBP: systolic blood pressure. DBP: diastolic blood pressure.

Patient characteristics	DCa 1.25	DCa 1.50	P value
Demographic			
Patients (*n*)	12 897	26 989	
Age (years)	65 (54.0, 74.0)	65 (55.0, 74.0)	.95
Sex (male)	7832 (61%)	16 444 (61%)	.70
BMI (kg/m^2)	27.2 ± 5.6	26.8 ± 5.4	<.001
Smoker	2596 (20%)	7042 (26%)	<.001
Comorbidities			
Diabetes mellitus	5069 (39%)	10 866 (40%)	.07
Aids	10 (0.1%)	35 (0.1%)	.15
Cardiovascular disease	3687 (29%)	10 134 (38%)	<.001
Liver disease	689 (5%)	2188 (8%)	<.001
Cancer	1045 (8%)	2504 (9%)	.001
Chronic pulmonary disease	1003 (8%)	2546 (9%)	<.001
Medication			
Calcium-containing phosphate binders	4943 (38%)	12 957 (48%)	<.001
Non-calcium-containing phosphate binders	2832 (22%)	5814 (22%)	.35
Vitamin D and analogs	5473 (42%)	11 778 (44%)	.02
Calcimimetic agents	542 (4%)	974 (4%)	.004
Laboratory values			
Blood hemoglobin (g/dl)	11.0 ± 1.3	11.1 ± 1.3	<.001
Serum albumin (g/dl)	3.7 ± 0.5	3.8 ± 0.5	<.001
Serum calcium (mg/dl)	8.9 ± 0.6	8.8 ± 0.6	<.001
Serum calcium corrected for albumin (mg/dl)	9.1 ± 0.7	8.9 ± 0.7	<.001
Serum phosphate (mg/dl)	4.9 ± 1.3	4.8 ± 1.2	<.001
Serum iPTH (pg/ml)	196.2 (109.6, 314.9)	182.0 (102.2, 291.8)	<.001
Serum potassium (mmol/l)	4.8 ± 0.7	4.9 ± 0.7	<.001
Serum bicarbonate (mmol/l)	22.8 ± 2.8	22.0 ± 2.8	<.001
Dialysis related			
Fistula	6953 (54%)	16 471 (61%)	<.001
Treatment time (min)	240 ± 14.7	243 ± 14.1	<.001
spKt/V	1.47 ± 0.34	1.51 ± 0.33	<.001
Ultrafiltration volume per session (ml)	2014 ± 847	2285 ± 803	<.001
Clinical parameters			
Predialysis SBP (mmHg)	140.1 ± 18.4	138.5 ± 17.7	<.001
Predialysis DBP (mmHg)	71.9 ± 11.0	71.8 ± 10.5	.30
Postdialysis SBP (mmHg)	132.1 ± 18.2	134.0 ± 18.2	<.001
Postdialysis DBP (mmHg)	70.2 ± 10.3	71.6 ± 9.7	<.001
Outcomes			
Follow-up in months	19.0 ± 7.7	19.7 ± 7.4	<.001
Patients lost to follow-up (n)	2727 (21%)	4072 (15%)	<.001
Serum dialysate calcium gradient (mEq/l)	2.1 ± 0.3	1.5 ± 0.3	<.001

DCa of 1.50 and 1.25–1.30, but there was no difference observed between the latter groups [8]. In a study of the REIN network, no difference in outcome was found between DCa levels ≤1.50 and >1.50, but DCa 1.50 was used in most dialysis centers and was not investigated separately [17]. The DOPPS cohort showed that higher DCa levels were related to mortality (RR 1.13 for every 1 mEq/l increase in DCa) [18], but no specific comparison between individual DCa levels was performed. By contrast, in a cross-sectional analysis of the Japanese DOPPS cohort including 3973 patients whom 66% were treated with DCa 1.50 and 21% with DCa 1.25, no significant differences in mortality were observed [19]. In an observational study in 299 patients comparing DCa of 1.75, 1.5, and 1.25 mmol/l, 5-year survival was higher in the DCa 1.25 group in univariate analysis, but not after adjustment for age and dialysis vintage [20]. Although in one single-center randomized trial in 128 patients a better survival was observed with a DCa 1.25 compared to DCa 1.50 [21]. A recent systematic review of 19 randomized clinical trials also did not find significant differences in mortality between studies with either low DCa (defined as 1.125 or 1.25 mmol/l) or high DCa defined as 1.5 or 1.75 mmol/l) but also noted that no RCT was designed to study hard outcomes. Moreover, the follow-up time of the studies was, in general, relatively short [22].

Differences in the total calcium load might partly explain differences between studies. For instance, in the 2005 DOPPS study, 80% of patients used calcium-containing phosphate binders versus up to 62% in the present sample, whereas in the 2005 DOPPS study 8% used non-containing phosphate binders versus 22% in the present study. Vitamin D therapy was prescribed in 52% in DOPPS versus up to 44% in the present study [18]. Interestingly, serum calcium levels were slightly, but significantly higher in patients treated with DCa 1.25 mmol/l, for which we do not have a good explanation as data on individualized treatment prescription was not available.

The fact that in the present study, after adjustment no significant differences in mortality were observed between patient

Table 2: Effect of dialysate calcium. Multivariable extended Cox regression models accounting for non-proportional hazard (where required). Data are expressed as HR with 95% CI. Model 1a: unadjusted model. Model 1b: model 1a plus country as random effect. Model 2: model 1b plus adjustment for age, sex, ethnicity, comorbidities (diabetes, cardiovascular disease, liver disease, and cancer), vascular access, treatment time, Kt/V, ultrafiltration volume per session. Model 3: model 2 plus blood hemoglobin, serum albumin, calcium-containing phosphate binders, active vitamin D and analogs, and calcimimetic agents. Model 4: model 3 plus dialysate bicarbonate and predialytic serum calcium level.

	All-cause mortality		Cardiovascular mortality		Sudden cardiac death	
DCa 1.50 vs. 1.25	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 1a	1.07 (1.01–1.12)	.01	1.14 (1.06–1.24)	<.001	1.07 (0.92–1.25)	.39
Model 1b	1.04 (0.97–1.10)	.29	1.03 (0.94–1.13)	.50	0.82 (0.69–0.99)	.03
Model 2	1.02 (0.95–1.08)	.63	0.997 (0.91–1.09)	.94	0.78 (0.65–0.94)	.008
Model 3	1.04 (0.97–1.10)	.30	1.01 (0.92–1.11)	.81	0.78 (0.65–0.94)	.008
Model 4	1,05 (0.99–1.12)	.14	1.03 (0.84–1.13)	.51	0.81 (0.67–0.97)	.02

Table 3: Effect of serum dialysate calcium gradient. Multivariable extended Cox regression models accounting for non-proportional hazard (where required). Data are expressed as HR with 95% CI. Model 3: fully adjusted model, country as random effect plus adjustment for age, sex, ethnicity, comorbidities (diabetes, cardiovascular disease, liver disease, and cancer), vascular access, treatment time, Kt/V, ultrafiltration volume per session, blood hemoglobin, serum albumin, calcium-containing phosphate binders, active vitamin D and analogs, and calcimimetic agents. Model 4: model 3 plus dialysate bicarbonate.

	All-cause mortality		Cardiovascular mortality		Sudden cardiac death	
SCa—DCa (per 1mEq/l increase)	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 3	1.16 (1.09–1.24)	<.001	1.23 (1.12–1.35)	<.001	1.69 (1.41–2.03)	<.001

Table 4: Effect of components of the serum dialysate calcium gradient. Multivariable extended Cox regression models accounting for non-proportional hazard (where required). The data are reported as p-values. Model 3: fully adjusted model, country as random effect plus adjustment for age, sex, ethnicity, comorbidities (diabetes, cardiovascular disease, liver disease, and cancer), vascular access, treatment time, Kt/V, ultrafiltration volume per session, blood hemoglobin, serum albumin, calcium-containing phosphate binders, active vitamin D and analogs, and calcimimetic agents. Model 4: model 3 plus dialysate bicarbonate.

	All-cause mortality *P* value	Cardiovascular mortality *P* value	Sudden cardiac death *P* value
Dialysate calcium (DCa)	.83	.46	.24
Corrected serum calcium (SCa)	.002	.02	.04
DCa*SCa	.73	.43	.33

cohorts treated with DCa 1.25 and 1.50 does not mean that in selected patients, different prescriptions of DCa may not have an important effect on (surrogate) outcomes. In a randomized trial in patients with a PTH below 100 mg/dl, Lu *et al*. observed different changes in the aortic calcification score over a one-year period when treated with a DCa of 1.25 versus 1.50 mmol/l [23]. This can be explained by the fact that in case of low bone turnover, the risk of vascular calcification may be higher as calcium is deposited at extraosseous sites. Still, in the secondary analysis in patients with iPTH < 130pg/dl, we observed no differences in association with all-cause and cardiovascular mortality or SCD. Regarding the risk of SCD, we are not aware of previous studies comparing DCa 1.25 and 1.50. A previous study showed an increased risk in patients treated with DCa levels below 1.25 [9]. Differences in SCD might be mediated by the effect of DCa and plasma ionized calcium on the QT interval, although in general, the isolated effect of DCa does not seem to be very large [8, 10, 24]. The effect of low DCa levels on the QT interval may, however, be enhanced by low dialysate potassium concentration [10], an interaction that was not addressed in the present study.

A larger SCa-DCa gradient was found to be significantly associated with increased risk of all-cause and cardiovascular mortality and SCD. Importantly, it appears that the primary determinant of this association is the SCa component rather than the DCa, given the fact that only the association with corrected SCa was found to be significantly related to the outcomes, but neither the DCa nor their interaction term. Indeed, several studies showed an association between higher mortality and higher SCa levels in patients on HD [19, 25, 26]. Nevertheless, we cannot exclude that some part of the relation between a large SCa-DCa gradient and outcomes is driven by the gradient per se, although the contribution of SCD to overall mortality was just 11%.

In the absence of serum ionized calcium levels, we followed the method of Pun *et al*. calculating the SCa-DCa gradient, in which total serum calcium levels are used. This explains why this value in our study, as well as in the study of Pun *et al*. invariably yields positive results with any DCa prescription [9]. In the absence of ionized calcium levels, we used this method because it is the only validated method using total serum calcium level to the best of our knowledge. It is based on the assumption that bound calcium dissipates rapidly during dialysis, making also total calcium levels an important driving force for diffusion. It is important to realize that a positive value of this SCa-DCa gradient does not provide information about the presence of a positive (i.e. calcium load) or negative intradialytic calcium mass balance (CaMB). Previous studies showed a generally negative to neutral CaMB with a DCa of 1.25 mmol/l in most studies, but not all, positive intradialytic CaMB with a DCa 1.5 mmol/l [27–29].

However, when CaMB is calculated using blood-based measurements, calcium loading is underestimated as the substantial exchangeable calcium pool, likely located at the bone surface area is not taken into account [30, 31]. Intradialytic CaMB is determined by, among others, the ionized calcium levels in serum and dialysate, which are also dependent on the serum and dialysate bicarbonate levels, the Gibbs–Donnan factor in plasma, and convective fluxes [28, 31]. As supported by studies assessing CaMB by dialysate-based measurements and taking the exchangeable calcium pool into account, it is likely that the substantial majority of patients will experience a positive diffusive CaMB during dialysis, which may even occur with the use of DCa 1.25 [5, 28, 30–32].

It is important to realize that DCa is an important, but by far not the only factor influencing total calcium balance in patients on HD [32]. Dietary intake, the use of calcium-based phosphate binders and use of active vitamin D levels all have a major effect that should be taken into account while prescribing DCa concentration [32]. It is our firm belief that DCa should be prescribed on an individualized basis, in which, given the potential for a long-term repeated vascular interdialytic calcium load and higher calcification propensity and subsequent risk of vascular calcification [5, 27, 31], DCa 1.50 might be reserved for selected indications such as a high risk for arrhythmias, especially in combination with high SCa-DCa gradients or frequent episodes of intra-dialytic hypotension in combination with a reduced systolic cardiac function [29]. However, outcome studies comparing fixed versus individualized DCa prescription urgently need to be conducted to evaluate the potential benefits of individualization.

The presented analysis was performed in a large cohort study with data from different countries in which various important confounders could be captured. There are various limitations as well. First, it is a retrospective observational study in which residual confounding cannot be excluded and specific indications for DCa prescriptions in individual patients and individual facilities practice patterns are not captured. Second, this study merely aimed to compare the effects of two specific, albeit most commonly used, DCa concentrations and did not study the interaction with other potentially relevant factors for patient outcomes. To minimize the effect of country on the outcome, we have used the country as a random effect in the main analysis. Given the strong impact of the country, it cannot be excluded next to demographic factors that practice patterns regarding DCa prescription will have had an effect on outcomes. In addition, a sensitivity analysis was performed, which confirmed the results of the main analysis.

With 2 years the follow-up time was relatively short whereas the clinical effects of intradialytic calcium loading may take more time to develop. Last, ionized calcium levels were not available in the database, whereas some non-differential bias in the measurement of plasma calcium and serum albumin levels cannot be excluded.

In conclusion, in unadjusted analysis, both all-cause and cardiovascular mortality were higher in the group with DCa 1.50. However, after adjustment for confounders, there was no significant difference in all-cause and cardiovascular mortality between treatment with DCa 1.50 and 1.25, whereas the risk for SCD appears to be higher in patients treated with DCa 1.25, although the limited numbers of cases may impact the significance of this finding. We suggest that DCa prescription should be based on consideration of individual patient characteristics that is in-line with European Renal Best Practice recommendations [33].

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

ACKNOWLEDGEMENTS

These results have not been published in whole or part, abstract had been presented as free communication at ERA-EDTA congress 2023 in Milan, Italy. The study protocol was reviewed by the local METC of the Maastricht University Medical Center, and they declared that Medical Research Involving Human Subjects Act (WMO) did not apply to this study and that an official approval by METC was not required.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to the datasets being captured from private electronic medical record systems that are restricted to use by only authorized employees of Fresenius Medical Care, but are available from L.N. (luca.neri@freseniusmedicalcarwe.com) on reasonable request. A reasonable request to access the datasets would include and require agreements to be established between Fresenius Medical Care and an external individual(s) institution.

CONFLICT OF INTEREST STATEMENT

The data were extracted from EuCliD®, which is managed by Fresenius Medical Care (FME). P.C., F.B., S.S., and L.N. are employees at FMC. S.S. holds stocks from FMC. K.t.Me., H.B., and J.K. received a speaker's fee from FMC. J.K. also received a speaker's fee from Baxter Healthcare.

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Received: 11.6.2024; Editorial decision: 17.8.2024