# Dialysate Calcium Concentration and the Risk of Sudden Cardiac Arrest in Hemodialysis Patients

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## Summary

**Background and objectives** The optimal dialysate calcium concentration to maintain normal mineralization and reduce risk of cardiovascular events in hemodialysis patients is debated. Guidelines suggest that dialysate Ca concentration should be lowered to avoid vascular calcification, but cardiac arrhythmias may be more likely to occur at lower dialysate Ca. Concurrent use of QT-prolonging medications may also exacerbate arrhythmic risk. This study examined the influence of serum Ca, dialysate Ca, and QT interval-prolonging medications on the risk of sudden cardiac arrest in a cohort of hemodialysis patients.

**Design, setting, participants, & measurements** This case-control study among 43,200 hemodialysis patients occurred between 2002 and 2005; 510 patients who experienced a witnessed sudden cardiac arrest were compared with 1560 matched controls. This study examined covariate-adjusted sudden cardiac arrest risk associations with serum Ca, dialysate Ca, serum dialysate Ca gradient, and prescription of QT-prolonging medications using logistic regression techniques.

**Results** Patients assigned to low Ca dialysate<2.5 mEq/L were more likely to be exposed to larger serum dialysate Ca gradient and had a greater fall in BP during dialysis treatment. After accounting for covariates and baseline differences, low Ca dialysate<2.5 mEq/L (odds ratio=2.00, 95% confidence interval=1.40–2.90), higher corrected serum Ca (odds ratio=1.10, 95% confidence interval=1.00–1.30), and increasing serum dialysate Ca gradient (odds ratio=1.40, 95% confidence interval=1.10–1.80) were associated with increased risk of sudden cardiac arrest, whereas there were no significant risk associations with QT-prolonging medications.

**Conclusions** Increased risk of sudden cardiac arrest associated with low Ca dialysate and large serum dialysate Ca gradients should be considered in determining the optimal dialysate Ca prescription.


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## Introduction

The appropriate management strategy for maintaining calcium balance in patients receiving hemodialysis is debated. Maintaining a positive calcium balance, where calcium intake exceeds calcium removal, can be an effective strategy for limiting hyperparathyroidism, but this practice may also predispose to soft tissue calcification and higher cardiovascular mortality. For this reason, current Kidney Disease Outcomes Quality Initiative (KDOQI) hemodialysis guidelines recommend that the dialysate calcium concentration be decreased as a means to maintain neutral or negative calcium balance and prevent vascular calcification (1). The recommendations also suggest that corrected serum calcium levels should be maintained at low to normal levels.

A potential harmful effect of reducing calcium concentrations in the dialysate and serum of hemodialysis patients is that excessive lowering may lead to an increased risk of cardiac rhythm disturbances and sudden cardiac arrest (SCA). SCA is known to be the leading cause of death among hemodialysis patients, accounting for one in every four deaths (2). Exposure to low calcium dialysate is associated with hypotension and QT interval prolongation, an indicator of enhanced arrhythmic risk (3,4). We previously reported that patients who received hemodialysis with a dialysate concentration of calcium<2.5 mEq/L had a higher risk of suffering an SCA than patients treated with higher dialysate calcium concentrations (5). However, it is unknown how the apparent risk of low calcium dialysate is influenced by other factors related to calcium balance. Therefore, we conducted this study to explore relationships among dialysate and serum calcium concentrations, concurrent exposure to QT-prolonging medications, and the risk of peridialytic SCA. Our hypothesis was that the risk of SCA increases as the serum-to-dialysate calcium gradient increases, and the risk is further magnified among patients who are exposed to QT-prolonging medications.

## Materials and Methods

The methods and resources used to identify the study cohort have been described in detail elsewhere (5). They are summarized below.

### Patient Population and Data Source

We examined patient data from patients who underwent long-term hemodialysis treatment from January 1, 2002 to January 1, 2005 in 565 outpatient dialysis clinics of a large dialysis organization in the United States. (DaVita Inc.; formerly Gambro Healthcare). These data include information on demographic characteristics, laboratory parameters, medication use, treatment-to-treatment–specific dialysis care, and clinical outcomes, including occurrence of adverse events within hemodialysis facilities. Using this resource, we had access to the records of over 43,000 hemodialysis patients who dialyzed over the 4-year study period.

### Study Design

We used a case-control study design to compare risk factors among in-clinic SCA patients (defined as patients who experienced an SCA within the facility of the outpatient hemodialysis clinic) and selected matched controls. Using an existing database of all adverse events occurring within the dialysis clinic facility, we identified a cohort of SCA patients by event narrative review and adjudication of qualifying events by three study physicians. We limited the case cohort to only patients who had been receiving outpatient dialysis for at least 90 days before SCA to allow for sufficient lead time for examination of the factors relating to the dialysis prescription and practice before the event. The overall SCA rate was very similar to other published event rates of in-clinic SCA (6,7).

We used a frequency-matching strategy (8) to select controls from among approximately 43,000 patients who did not experience an in-clinic adverse event during the study period. In frequency matching, control patients are chosen to ensure that the frequency of a potential confounding factor is the same as found in the case group. To reduce the influence of nonmodifiable demographic factors on our analysis, the following frequency-matching criteria were used, each measured at the time of the SCA event: age, dialysis vintage (number of years receiving hemodialysis), and calendar year of treatment. Approximately three controls were randomly selected for every case patient from the entire population of available patients. Controls were assigned an index date corresponding to the SCA event date recorded for case patients to allow for matching by these variables.

### Clinical Demographic and Comorbid Characteristics

Demographic variables used for the purpose of this analysis were patient sex, age, race (black, white, Hispanic, or other as reported to DaVita), and years on dialysis. We recorded history of preexisting medical conditions using organ-based groupings of international classification of diseases clinical modification (International Classification of Diseases, Ninth Revision) codes recorded in the clinical database. We supplemented this information with additional data available on the Medical Evidence Form 2728 of the United States Renal Data System. Blood samples were drawn by uniform techniques in all clinics and measured in a central laboratory. Serum albumin, creatinine, potassium calcium, phosphorus, hemoglobin, intact parathyroid hormone, and urea nitrogen levels were measured at least monthly.

### Dialysis-Specific Data and Medication Use

Dialysis-specific data included composition of the dialysate (potassium and calcium concentration) that was prescribed on the day of the cardiac arrest event or index date. Other parameters included intradialytic ultrafiltration volume expressed as percentage of postdialysis weight removed during the course of treatment and dialysis medications administered to patients. Detailed medication data were cataloged in the clinical database, and standard medication classifications were used to determine prescription by drug class. Drug classes specifically examined included calcium channel blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, $\beta$-blockers, aspirin, statins, and other antiarrhythmic medications. Medications were classified as QT-prolonging if they were listed in the database of drugs that prolong the QT interval maintained by the University of Arizona Center for Education and Research on Therapeutics and published online at http://www.qtdrugs.org. Only medications prescribed to patients at the time of the event (cases) or index date (controls) were considered.

### Calculation of Corrected Serum Calcium and Serum Dialysate Calcium Gradients

We reported albumin-corrected serum calcium variables using the following equation: corrected calcium in milligrams per deciliter=(0.8×(4−serum albumin level in milligrams per deciliter)+serum calcium). For this study, we defined the serum dialysate calcium gradient as the difference between the predialysis corrected total serum calcium level minus the dialysate calcium level (both measured in milliequivalents per liter). Serum calcium levels were converted from milligrams per deciliter to milliequivalents per liter by multiplying by 0.5.

### Statistical Analyses

Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and the Pearson chi-squared test for categorical variables. All continuous variables are described as medians with 25th and 75th percentiles unless otherwise specified. Categorical variables are expressed as percentages.

We used multivariable logistic regression models that were developed to evaluate the covariate-adjusted association of dialysate and serum calcium concentrations and exposure to QT-prolonging medications with SCA. Covariates included in the model were selected based on statistically significant associations with SCA in univariate logistic regression models and factors known to be influential based on prior studies and clinical insight (5,6,9). Restricted cubic spline transformations were applied to continuous measures, and the univariable association of the transformed variable with SCA was compared with a linear association using logistic models. When the linearity assumptions were violated, variables were transformed as appropriate (10).

All tests were two-sided and carried out using SAS 9.1 (SAS Institute, Cary, NC). Results were declared significant at a $P$ value$<0.05$.

## Results

After applying exclusion criteria, the study cohort consisted of 2070 hemodialysis patients (510 SCA patients

compared with 1560 control patients). There was a very slight imbalance in the intended ratio of case patients to control patients (1:3) because of the exclusion of patients with <90-day dialysis vintage. Figure 1 shows the underlying distribution of the last recorded dialysate calcium assignment in the cohort. The majority of patients was assigned to a dialysate calcium concentration of 2.5 mEq/L, with 7.7% assigned to dialysate calcium<2.5 mEq/L and 17.4% assigned to dialysate calcium>2.5 mEq/L. Table 1 examines the baseline characteristics of the cohort by last dialysate calcium concentration assignment (<2.5, 2.5, and >2.5 mEq/L). Patients prescribed low calcium dialysate (<2.5 mEq/L) were younger, had longer dialysis vintages, and were significantly more likely to be black and have a history of hypertension. They also had a significantly lower reported prevalence of coronary artery disease compared with patients assigned to calcium dialysate≥2.5 mEq/L. Otherwise, there were no significant differences in patient demographics or comorbid conditions between the groups. Patients assigned the low dialysate calcium concentration had higher serum phosphorus (median 5.5 versus 5.1 versus 4.9, respectively), higher corrected serum calcium values (median 10.1 versus 9.5 versus 9.2, respectively), and larger serum dialysate gradients (3.0 versus 2.3 versus 1.7 mEq/L, respectively). There were no significant differences in last recorded dialysate potassium concentration assignments between the three groups. There was a greater prevalence of vitamin D use among low dialysate calcium recipients (80.7%) compared with high dialysate calcium recipients (68.1%, $P$=0.003). There was an increased prevalence of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use in the low calcium dialysate group. The use of concurrent QT-prolonging medications was prevalent overall (46%), but there were no significant differences between the groups. There were no other significant differences in other laboratory measures or other aspects of the dialysis prescription, including the urea reduction ratio and fluid removal targets between the groups. Consistent with previous reports, patients assigned to low calcium dialysate had the greatest fall in mean arterial BP through the treatment, with a median 7-mmHg fall between pre- and postdialysis BP ($P$=0.004).

Table 2 shows the unadjusted and adjusted relationships between measures of calcium homeostasis, QT-prolonging medications, and risk of SCA. Significant unadjusted associations with SCA were observed with predialysis corrected serum calcium levels (odds ratio [OR]=1.10 per 1 mg/dl increase, 95% CI=1.00–1.20), exposure to low calcium dialysate<2.5 mEq/L (OR=2.00, 95% CI=1.40–2.80), and larger serum-to-dialysate calcium gradients (OR=1.40, 95% CI=1.10–1.60). The unadjusted association between exposure to QT-prolonging medications and SCA approached but did not reach statistical significance ($P$=0.06). In an adjusted model accounting for factors significantly associated with risk of SCA, there also was no observed relationship with QT-prolonging medication exposure. However, the significant relationship between serum calcium, low calcium dialysate<2.5, and serum-to-dialysate calcium gradient persisted in the fully adjusted model (Table 2). Of note, in the adjusted analysis, we found a direct linear relationship between the serum-to-dialysate calcium gradient and the risk of SCA. Each 1 mEq/L increase in the serum-to-dialysate calcium gradient was associated with a nearly 50% increase in the odds of cardiac arrest (adjusted OR=1.40 per 1 mEq/L increase in calcium gradient, 95% CI=1.10–1.80, $P$=0.002).

Finally, we examined whether the detrimental association of the serum dialysate calcium gradient was constant or unevenly distributed across the spectrum of predialysis serum calcium and dialysate calcium levels by looking for interactions among these variables. Using both simplified and adjusted models, the interaction terms calcium

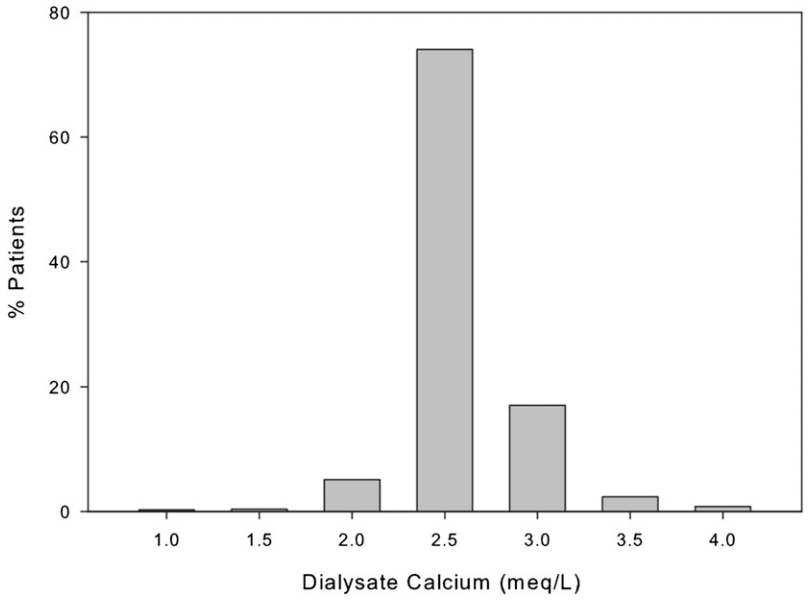


**Figure 1. | Distribution of dialysate calcium assignment in the study cohort.**

**Table 1. Baseline characteristics of the cohort by dialysate calcium assignment**

| Variable | <2.5 meq/L (*n*=159) | 2.5 meq/L (*n*=1550) | >2.5 meq/L (*n*=361) | *P* Value |
|---|---|---|---|---|
| Demographic variables | | | | |
| Age at index or event date (median, Q1, Q3) | 62.0 (53.0, 69.0) | 66.0 (57.0, 76.0) | 64.0 (53.0, 75.0) | 0.002 |
| Dialysis vintage in yr (median, Q1, Q3) | 4.5 (2.2, 7.6) | 2.4 (1.0, 5.2) | 3.0 (1.1, 6.8) | <0.001 |
| Black (%) | 52.8 | 37.2 | 42.7 | <0.001 |
| Male (%) | 45.3 | 52.5 | 53.2 | 0.20 |
| CAD | 22.0 | 32.6 | 32.1 | 0.02 |
| CHF (%) | 27.0 | 35.0 | 30.2 | 0.13 |
| Diabetes (%) | 48.4 | 56.6 | 50.7 | 0.18 |
| Hypertension (%) | 93.7 | 87.0 | 85.6 | 0.04 |
| Arrhythmia (%) | 13.2 | 12.1 | 12.2 | 0.91 |
| Hyperlipidemia | 10.1 | 7.0 | 5.0 | 0.12 |
| PVD | 15.1 | 19.5 | 18.6 | 0.05 |
| Smoker | 4.4 | 3.5 | 4.2 | 0.17 |
| Valvular heart disease (%) | 2.5 | 1.1 | 1.1 | 0.06 |
| Medications prescribed at time of event (%) | | | | |
| ACEi or ARB | 59.5 | 46.3 | 48.6 | 0.003 |
| Antiarrhythmic medication | 16.5 | 16.3 | 14.8 | 0.39 |
| BBL | 53.8 | 52.5 | 45.3 | 0.71 |
| QT-prolonging medication | 51.9 | 44.9 | 46.1 | 0.26 |
| Calcium supplement medication | 34.8 | 42.5 | 38.8 | 0.12 |
| Vitamin D | 80.7 | 72.8 | 68.1 | 0.003 |
| Last recorded laboratory values (median value, Q1, Q3) | | | | |
| Hemoglobin (g/dl) | 11.8 (10.8, 12.4) | 11.7 (10.9, 12.6) | 11.8 (10.8, 12.6) | 0.64 |
| Potassium (meq/L) | 4.6 (4.0, 5.1) | 4.7 (4.2, 5.3) | 4.7 (4.1, 5.3) | 0.15 |
| Phosphorus (meq/L) | 5.5 (4.6, 6.4) | 5.1 (4.1, 6.3) | 4.9 (4.0, 6.1) | 0.05 |
| Creatinine (mg/dl) | 8.4 (6.2, 9.7) | 7.4 (5.7, 9.6) | 8.0 (6.1, 10.1) | 0.06 |
| Bicarbonate (meq/L) | 22 (20, 26) | 22 (19, 25) | 21.0 (18.0, 24.0) | 0.01 |
| URR | 70.9 (66.0, 75.0) | 72.0 (67.0, 75.9) | 72.0 (68.0, 75.9) | 0.28 |
| Albumin (g/L) | 3.8 (3.3, 4.1) | 3.7 (3.3, 4.0) | 3.7 (3.4, 4.0) | 0.05 |
| Corrected serum calcium (mg/dl) | 10.1 (9.4, 10.7) | 9.5 (9.0, 10.0) | 9.2 (8.8, 9.8) | <0.001 |
| Dialysis prescription parameters | | | | |
| Potassium dialysate assignment (%; Meq/L) | | | | 0.21 |
| <2.0 | 8.9 | 12.8 | 7.2 | |
| 2.0 | 76.6 | 66.6 | 72.1 | |
| >2.0 | 14.6 | 20.6 | 20.6 | |
| Calcium gradient (median, Q1, Q3) | 3.0 (2.7, 3.4) | 2.3 (2.0, 2.5) | 1.7 (1.4, 2.0) | <0.001 |
| Fluid removed % DW mean 90 (median, Q1, Q3) | 3.5 (2.8, 4.3) | 3.5 (2.7, 4.4) | 3.7 (2.8, 4.7) | 0.88 |
| Dialysis BP (mmHg) | | | | |
| Predialysis BP | 144/79 | 144/77 | 142/77 | |
| Postdialysis BP | 134/72 | 136/73 | 138/75 | |
| Intradialytic fall in mean arterial BP (median, IQR) | 7 (−6, 23) | 2 (−6, 21) | 0 (−7, 16) | 0.004 |

Q, quartile; CAD, coronary artery disease; CHF, congestive heart failure; PVD, peripheral vascular disease; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BBL, β-blocker; URR, urea reduction ratio; DW, dry weight; IQR, interquartile range.

gradient × serum calcium and calcium gradient × dialysate calcium did not meet significance ($P$=0.70 and $P$=0.12, respectively). This result suggests that higher or lower predialysis serum calcium or dialysate calcium levels did not alter the association between the calcium gradient on SCA risk. Other plausible interactions with the serum dialysate gradient that were tested included the dialysate potassium assignment and QT medication use. These interaction terms were also not significant.

## Discussion

The choice of dialysate calcium concentration has important management implications in hemodialysis

**Table 2. Unadjusted and adjusted associations between relevant factors related to calcium homeostasis and risk of sudden cardiac arrest**

| Parameter | Unadjusted OR (95% CI) | *P* Value | Adjusted[a] OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Predialysis corrected serum calcium (per 1 mg/dl increase) | 1.10 (1.00–1.20) | 0.05 | 1.10 (1.00–1.30) | 0.05 |
| Dialysate calcium<2.5 meq/L | 2.00 (1.40–2.80) | <0.001 | 2.00 (1.40–2.90) | <0.001 |
| Serum-to-dialysate calcium gradient (per 1 meq/L increase) | 1.40 (1.10–1.60) | <0.001 | 1.40 (1.10–1.80) | 0.002 |
| QT medication exposure | 1.20 (1.00–1.50) | 0.06 | 1.00 (0.80–1.30) | 0.80 |

[a]Adjusted for history of coronary artery disease or congestive heart failure; number of years on dialysis; prescription of calcium-containing medication, vitamin D, antiarrhythmic medication, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and β-blockers; potassium dialysate assignment and percent fluid removed during treatment; and serum potassium, bicarbonate, creatinine, albumin, and hemoglobin values.

patients. Maintaining calcium balance could have short- and long-term effects on cardiac function. Much of the recent debate on the ideal dialysate calcium concentration has focused on optimizing the total body calcium load to prevent vascular calcification, which is well established as a cardiac risk factor among hemodialysis patients (11). However, reducing calcium load by lowering dialysate calcium levels may have the unintended consequence of decreased hemodynamic stability and the potential to promote arrhythmias. The association between lower dialysate calcium levels and increased hypotension is well known (3), but this study is the first to our knowledge to specifically identify associations between calcium dialysate concentration, serum calcium concentration, and risk of SCA. In this study, we determined that increases in the serum-to-dialysate calcium gradient proportionally increased the risk of peridialytic SCA. This associated risk was observed across the entire spectrum of predialysis serum calcium levels and among all dialysate calcium assignments. We did not observe a significantly increased risk among patients who were prescribed QT interval-prolonging medications or any evidence of an interaction effect between serum or dialysate calcium levels and exposure to these medications. This lack of an association between SCA and these medications is similar to findings recently reported by Jadoul *et al.* (12) in the multinational Dialysis Outcomes and Practice Patterns Study cohort.

Excess SCA risk resulting from rapid or aggressive lowering of serum calcium levels might result from two physiologic processes. First, rapid lowering of serum calcium levels on dialysis may lead to prolongation of the QT interval and subsequent fatal ventricular arrhythmias because of torsade de pointes. Multiple authors have documented prolongation of the corrected QT interval occurring during hemodialysis treatment, and several studies have shown an association between intradialytic fall in serum calcium, low calcium dialysate, and QT prolongation (4,13,14). Second, serum ionized calcium levels regulate the contractility of vascular smooth muscle cells and cardiac myocytes. Development of hypocalcemia during hemodialysis treatment can lead to hypotension because of decreased vascular resistance and cardiac output, which in turn, may reduce coronary blood and cause myocardial ischemia. These transient responses could compound the effects of subclinical dialysis-induced myocardial ischemia, which is increasingly recognized as an important risk factor for cardiac events (15). Consistent with previous reports, we observed a substantial drop in BP during the dialysis treatment in those patients prescribed lower calcium dialysate and those patients exposed to a greater serum dialysate calcium gradient (3,16).

Both the current KDOQI (1) and Kidney Disease Improving Global Outcomes (17) guidelines have offered an opinion-based recommendation of 2.5 mEq/L dialysate calcium concentration, weighing the long-term goals of maintaining bone and vascular health by neutral calcium balance with the effects of dialysate calcium on hyperparathyroidism and cardiac function. Although our study was designed to explore only one aspect of the multifaceted risks and benefits associated with dialysate calcium assignment, we offer more concrete evidence that calcium dialysate less than 2.5 mEq/L and large serum dialysate calcium gradients occurring at any dialysate calcium concentration are associated with sudden death. The guidelines also suggest that dialysate calcium concentrations should be individualized whenever possible based on the patient's clinical setting but do not give suggestions regarding which patients to target or how treatment should be modified. Our study suggests a possible method to guide dialysate calcium assignment using the serum-to-dialysate calcium gradient, which is easily calculated from readily available laboratory data. For example, patients at high risk for SCA (such as those with advanced age, at the extremes of dialysis vintage, and known cardiac disease) could be identified for special attention. Calculation of the serum-to-dialysate gradient in these patients could further identify patients who might be at particularly high risk of arrhythmic events, suggesting a need to avoid lowering dialysate calcium levels.

There are several limitations of our study. First, we did not have data on serum ionized calcium levels. Because only unbound calcium is dialyzable, ionized calcium would be a better measure of the diffusible serum calcium to dialysate calcium gradient and overall dialyzer calcium flux. Nevertheless, there is evidence that bound calcium dissociates rapidly, making total serum calcium

the effective driving force for diffusion (18). Additionally, because ionized calcium levels are not routinely monitored in outpatient dialysis clinics, calculation of the total serum calcium to dialysate calcium gradient may be a more practical measurement to assess SCA risk and to direct subsequent dialytic management. Second, although we took into account the prescription of calcium supplements and vitamin D medications in our analysis, relatively few patients were prescribed calcimimetics during the study time period. Therefore, we were not able to assess any association of these hypocalcemic medications on the risk of SCA or any interacting effects with dialysate calcium. Third, we purposely examined only witnessed and verified SCA events occurring in the outpatient dialysis clinic. Although this limits the generalizability of our findings, we used this limitation to increase the reliability of our findings compared with studies relying on cause of death reporting alone, which may misrepresent the true incidence of SCA. Also, it should be noted that, although we observed a two-fold increased relative risk of SCA associated with low calcium dialysate, the incremental increase in absolute risk is small when considering the overall incidence of in-clinic SCA (estimated to be between four and seven events per 100,000 dialysis treatments) (5,6). It is possible that exposure to low calcium dialysate and a larger calcium gradient also increases the risk of events occurring in the hours after outpatient dialysis treatment, but our study findings do not directly address risk for these out-of-clinic events. Finally, we cannot eliminate the possibility that our findings reflect an inherent indication or selection bias because of unmeasured confounders. Specifically, we did not have data regarding other factors that may have been considered in establishing a dialysate prescription, such as evidence of arterial calcification and electrocardiogram data, although we accounted for a diverse and detailed set of covariates associated with dialysate calcium assignment.

In conclusion, the use of low calcium dialysate and greater serum dialysate calcium gradients associates with a significantly increased risk of SCA. Although confirmation of our findings is needed, our observations are consistent with recognized links among electrolyte disturbances and arrhythmic events. In the absence of a prospective clinical trial, reducing these risk exposures may be a reasonable approach to combat the epidemic of sudden death in vulnerable hemodialysis patients.

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**Disclosures**

None.

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