HHS Public Access

Author manuscript

Hemodial Int. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

Hemodial Int. 2016 July ; 20(3): 421–431. doi:10.1111/hdi.12382.

Cinacalcet, Dialysate Calcium Concentration, and Cardiovascular Events in the EVOLVE trial

Patrick H. Pun, MD, MHS[1], **Safa Abdalla, MD**[3], **Geoffrey A. Block, MD**[4], **Glenn M. Chertow, MD, MPH**[3], **Ricardo Correa-Rotter, MD**[5], **Bastian Dehmel, MD**[11], **Tilman B. Drüeke, MD**[6], **Jürgen Floege, MD**[7], **William G. Goodman, MD**[11], **Charles A. Herzog, MD**[8], **Gerard M. London, MD**[9], **Kenneth W. Mahaffey, MD**[3], **Sharon M. Moe, MD**[9], **Patrick S. Parfrey, MD**[2], **David C. Wheeler, MD**[10], and **John P. Middleton, MD**[1]

[1]Duke University School of Medicine, Durham NC 27710

[2]Health Sciences Center, St. John's, Newfoundland, Canada A1B 3V6

[3]Stanford University School of Medicine, Palo Alto, California 94304

[4]Denver Nephrology, Denver, Colorado 20230

[5]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico D.F. 140100

[6]Inserm Unit 1088, UFR Médecine/Pharmacie, Université de Picardie, 80037 Amiens, France

[7]Universitätsklinikum der RWTH Aachen, 52074 Aachen, Germany

[8]University of Minnesota, Minneapolis, Minnesota 55415

[9]Hôpital Manhès, Paris, France91712; [9]Indiana University School of Medicine and Roudebush Veterans Administration Medical Center, Indianapolis, Indiana 46202

[10]University College London, London, United Kingdom NW32PF

[11]Amgen, Inc, Thousand Oaks, California 91320

Abstract

Background—Among patients receiving hemodialysis, abnormalities in calcium regulation have been linked to an increased risk of cardiovascular events. Cinacalcet lowers serum calcium concentrations through its effect on parathyroid hormone secretion and has been hypothesized to reduce the risk of cardiovascular events. In observational cohort studies, prescriptions of low dialysate calcium concentration and larger observed serum–dialysate calcium gradients have been associated with higher risks of in-dialysis facility or peri-dialytic sudden cardiac arrest. We performed this study to examine risks associated with dialysate calcium and serum-dialysate gradients among participants in the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial.

Address for Correspondence: Patrick H Pun, MD, MHS. Duke University Medical Center, PO Box 2747, Durham, NC, 27710; Patrick.pun@duke.edu; telephone (919) 660-6865; fax (919) 684-4476.

Conflict of Interest Disclosure: Full list of disclosures for authors supplied separately.

Methods—In EVOLVE, 3883 hemodialysis patients were randomized 1:1 to cinacalcet or placebo. Dialysate calcium was administered at the discretion of treating physicians. We examined whether baseline dialysate calcium concentration or the serum–dialysate calcium gradient modified the effect of cinacalcet on the following adjudicated endpoints: 1) primary composite endpoint (death or first non-fatal myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event); 2) cardiovascular death; and 3) sudden death.

Results—In EVOLVE, use of higher dialysate calcium concentrations was more prevalent in Europe and Latin America compared to North America. There was a significant fall in serum calcium concentration in the cinacalcet group; dialysate calcium concentrations were changed infrequently in both groups. There was no association between baseline dialysate calcium concentration or serum–dialysate calcium gradient and the endpoints examined. Neither the baseline dialysate calcium nor the serum–dialysate calcium gradient significantly modified the effects of cinacalcet on the outcomes examined.

Conclusions—The effects of cinacalcet on cardiovascular death and major cardiovascular events are not altered by the dialysate calcium prescription and serum-dialysate calcium gradient.

INTRODUCTION

Patients with end stage kidney disease are subject to an extraordinarily high risk of cardiovascular disease-related death; sudden cardiac death, the most common cause of death for patients with end stage kidney disease treated with hemodialysis, occurs at a rate 30 times greater than the general population.[1] Among the many risk exposures that are prevalent in patients receiving hemodialysis, factors related to disordered mineral metabolism such as hyperphosphatemia, hypercalcemia, and secondary hyperparathyroidism have been associated with increased likelihood of cardiovascular events in observational studies. [2] Putative mechanisms include adverse hemodynamic events and alterations in vascular compliance due to arterial calcification. [3, 4]

Processes that pertain to the dialytic removal of calcium have been reported to prompt hypotension, cardiac arrhythmias, and an increased risk of sudden death, most likely through disturbances in electrical conduction in the heart due to decreases in blood calcium concentration. [5–7] Prior studies indicate that the risk of sudden cardiac arrest in the immediate peri-dialytic period is two-fold higher among patients managed with dialysate calcium concentrations <2.5 mEq/L (<1.25 mmol/L). [7] Moreover, the likelihood of sudden cardiac arrest increased proportionally as a function of the difference in calcium concentration between serum and dialysate, a relationship that was more pronounced as the dialysate calcium level was reduced.

The calcimimetic agent cinacalcet (Sensipar®/ Mimpara®) treats secondary hyperthyroidism by inhibiting parathyroid hormone (PTH) secretion and lowering serum calcium. The randomized, placebo-controlled Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial examined the effect of cinacalcet on death and cardiovascular events among hemodialysis patients with moderate-to-severe secondary hyperparathyroidism. Overall, cinacalcet did not significantly reduce the risk of death or major cardiovascular events compared to placebo (relative hazard in patients randomized to

cinacalcet group *versus* placebo group=0.93; 95% confidence interval, 0.85 to 1.02; p=0.11). Analysis adjusted for baseline characteristics showed a nominally significant reduction in risk.[8] Because of the calcium-lowering effect of cinacalcet, and prior observations of cardiovascular risk associated with dialysate calcium, we sought to determine whether variations in baseline dialysate calcium concentration or the serum-dialysate calcium gradient modified the effects of cinacalcet on death and cardiovascular events among participants in the EVOLVE trial.

METHODS

Study Population and Design

In the EVOLVE trial, 3883 patients with secondary hyperparathyroidism receiving hemodialysis were randomized 1:1 to either cinacalcet or placebo. All patients received conventional therapies for chronic kidney disease mineral bone disorder (CKD-MBD) (i.e., instructions for dietary phosphorus restriction, phosphate binders, and vitamin D sterols).[9] Eligible participants were on hemodialysis three times per week with plasma PTH concentrations ≥ 300 pg/mL (31.8 pmol/L), serum calcium phosphate product ≥ 45 mg^2/dL^2 (3.63 $mmol^2/L^2$), and serum calcium ≥ 8.4 mg/dL (2.1 mmol/L). The dose of study drug was titrated once every 4 weeks during the first 20 weeks and every 8 weeks during the subsequent follow-up period (from a starting dose of 30 mg to a maximum dose of 180 mg daily), depending on blood levels of PTH and calcium. The dialysis prescription (including dialysate electrolyte composition) and all other medications including phosphate binders, vitamin D sterols and calcium supplements were administered at the discretion of treating clinicians. Information on the dialysate prescription was collected at approximately 6-month intervals. The trial was led by an academic Executive Committee and sponsored by Amgen, Inc. Institutional Review Board or Ethics Committee approval was obtained at all participating sites; all patients gave informed consent.

Study Endpoints

For the purpose of these analyses, we examined whether baseline dialysate calcium or the serum–dialysate calcium gradient (determined from the difference between the last recorded dialysate and pre-dialysis serum calcium concentrations) modified the effect of cinacalcet on the following three endpoints: 1) primary composite endpoint (time to all-cause death or first non-fatal myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event); 2) cardiovascular death (one of the key secondary endpoints); and 3) sudden death. All cardiovascular endpoints were adjudicated by an independent Clinical Events Committee.

Calculation of corrected serum calcium and serum-dialysate calcium gradients

For patients with albumin levels less than 4 mg/dL, serum calcium was reported as a corrected value by the central laboratory using the following equation: corrected calcium in mg/dL= (0.8 × (4 − serum albumin in mg/dL) + serum calcium). Serum calcium concentrations were converted from mg/dL to mEq/L by multiplying by 0.5. For this study, we defined the serum-dialysate calcium gradient as the difference between total corrected

serum calcium concentration minus dialysate calcium concentration in mEq/L, measured at baseline.

Statistical Analysis

We used generalized estimating equations to test the difference between the treatment arms in dialysate calcium prescription, serum calcium and serum-dialysate calcium gradient over time. We used multivariable proportional hazards (Cox) regression analysis to evaluate associations among baseline dialysate calcium concentrations or the serum–dialysate calcium gradients and outcomes (primary composite endpoint, cardiovascular death, and sudden death). We adjusted for baseline characteristics, including age, sex, race (white, black, other), geographic region, history of diabetes mellitus, and history of cardiovascular diseases, among other factors. Covariates were selected by a process of backward elimination from a list of biologically plausible baseline covariates that were also associated with endpoints in univariate analyses. We tested for effect modification by baseline dialysate calcium concentration and the serum–dialysate calcium gradient using multiplicative interaction terms. The effect of cinacalcet *versus* placebo was evaluated using the intention-to-treat principle. All inference tests were performed without adjusting for multiple comparisons. As the effects of randomization to cinacalcet *versus* placebo on the primary composite endpoint did not reach statistical significance in an unadjusted log-rank test, subsequent comparisons yielding 2-tailed p-values <0.05 were deemed nominally significant. We conducted all statistical analyses at Stanford University using SAS 9.3 (Cary, NC, USA).

RESULTS

Table 1 shows baseline characteristics of patients in EVOLVE treated with different dialysate calcium concentrations assigned to receive either cinacalcet or placebo. Differences between placebo and cinacalcet groups have been previously described.[10] Nearly half of all study participants were prescribed dialysate calcium concentrations of 2.5 mEq/L, and the use of different dialysate calcium concentrations at baseline (categorized as <2.5, 2.5 or ≥ 2.5 mEq/L) did not differ between the cinacalcet and placebo groups. Patients treated with lower dialysate calcium were older and were more likely to be black and female. Among patients prescribed lower dialysate calcium, the prevalence of baseline vitamin D sterol use was higher, the use of calcium-based phosphate binders was lower, and the proportion of patients with a history of cardiac disease (heart failure, coronary artery disease and arrhythmia) was higher.

Regional Differences in Dialysate Calcium Prescription

Table 2 shows baseline prescribing patterns of dialysate calcium by geographic region. There were marked differences, with a predominance of higher dialysate calcium usage in Europe and Latin America (high calcium dialysate >2.5 mEq/L used in 59% of patients from the combined regions), and a predominance of lower dialysate calcium usage in the United States (≤2.5 mEq/L used in 96% of patients; <2.5 mEq/L used in 21% of patients).

Changes in serum and dialysate calcium over time

There was a small increase in prescriptions for dialysate calcium >2.5 mEq/L over the course of the trial and a decline in the use of 2.5 mEq/L prescriptions. There were no significant differences in dialysate calcium prescribing patterns between treatment groups (Figure 1).

Median serum calcium concentrations did not differ between treatment groups at baseline, but serum calcium declined in patients randomized to cinacalcet, with the separation most pronounced at 52 weeks (9.3 mg/dl in the cinacalcet group, 9.9 mg/dl in the placebo group). Concordant with changes in serum calcium, the serum–dialysate calcium gradient also showed separation over time between treatment groups; the group assigned to cinacalcet had a fall in the serum–dialysate gradient as compared to the group assigned to placebo and the difference was maximal at 52 weeks and narrowed over time (Figure 2).

As reported previously, there was a slight decrease in the use of vitamin D sterols and an increase in the use of calcium-containing phosphate binders over time in the group randomized to cinacalcet. [8]

Baseline dialysate calcium, serum–dialysate calcium gradient and cardiovascular endpoints

Nine hundred thirty-eight (48.2%) of the group randomized to cinacalcet experienced the primary composite endpoint, compared to 952 (49.2%) in the placebo group. There were 377 (19.4%) cardiovascular deaths and 109 (5.6%) sudden deaths in the cinacalcet arm compared to 391 (20.2%) cardiovascular deaths and 115 (5.9%) sudden deaths in the placebo arm. Associations among dialysate calcium concentration, serum-dialysate calcium gradients and study endpoints were examined. In unadjusted analyses, the risk of all outcomes was significantly increased among patients exposed to higher serum-dialysate calcium gradients, and the risk of the primary composite outcome was increased among patients exposed to low calcium dialysate <2.5 mEq/L. However, after adjustment for other baseline factors and treatment assignment, no associations among these factors and the primary composite endpoint, cardiovascular death, and sudden death were observed. (Table 3)

Effect modification by the serum–dialysate calcium gradient and the dialysate calcium concentration

Figures 3 and 4 shows the relative hazard of the primary composite outcome, cardiovascular death and sudden death comparing cinacalcet *versus* placebo across the quintiles of baseline serum–dialysate calcium gradient and baseline dialysate calcium prescription. There was no significant modification of the effect of cinacalcet on outcomes by the serum–dialysate calcium gradient (Figure 3). Examination of outcomes by dialysate calcium concentration is shown in Figure 4; there was no significant interaction (effect modification) by dialysate calcium strata.

DISCUSSION

In this study, we examined the prescription of dialysate calcium in a large multi-national randomized clinical trial comparing the calcimimetic cinacalcet and placebo along with conventional therapy for CKD-MBD. There were large regional differences in baseline dialysate calcium prescription. Despite a significant decline in serum calcium concentration among patients randomized to cinacalcet, relatively few patients had their dialysate calcium prescriptions changed over the course of the trial. The baseline dialysate calcium concentration and baseline serum–dialysate calcium gradient were not associated with the primary composite endpoint (death or first non-fatal myocardial infarction, hospitalization for unstable angina, heart failure or peripheral vascular event), cardiovascular death or sudden death after adjustment for covariates. Moreover, we found that neither dialysate calcium nor the serum-dialysate calcium gradient modified the effect of cinacalcet on outcomes.

The ideal dialysate calcium concentration has prompted a long-standing debate, particularly with the development of newer agents used in the treatment of chronic kidney disease mineral bone disease (CKD-MBD), including non-calcium-containing phosphate binders and the calcimimetic cinacalcet. It has been evident for decades that persons with longstanding and/or severe kidney disease are likely to develop complications related to calcification of soft tissues. Many tissues can become calcified in patients with CKD, but involvement of heart valves and arteries has been the most extensively studied. Since dialysate calcium concentration is one of the key factors determining dialysis and total body calcium balance, current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that dialysate calcium concentration be carefully titrated in an effort to maintain neutral or negative calcium balance and to prevent vascular calcification.[11] However, others including the Kidney Disease: Improving Global Outcomes (KDIGO) Mineral and Bone Disorder workgroup have expressed concern that exposure to low calcium dialysate has been associated with secondary hyperparathyroidism, intradialytic hypotension, and cardiac arrhythmias including sudden cardiac arrest, leading to uncertainty on the “ideal” dialysate calcium concentration and whether or not individualization of dialysate calcium provides significant overall benefits.[12, 13]

This lack of consensus on the ideal dialysate calcium is manifest by substantial variation in prescribing habits around the world. More than 50% of all baseline prescriptions in EVOLVE were for a dialysate calcium >2.5 mEq/L in Europe, Australia, Latin America and Russia (>80% of all prescriptions in Australia and Russia), whereas in North America, a dialysate calcium concentration of 2.5 mEq/L was most frequently prescribed (>75% of all prescriptions) with more than one in five patients prescribed dialysate calcium concentrations <2.5 mEq/L. The use of lower dialysate calcium in North America and higher dialysate calcium in other regions confirms earlier reports; reasons for these regional preferences are uncertain, but may be related to frequent use of high-dose vitamin D sterols in the United States.[14–16]

The availability of cinacalcet to manage secondary hyperparathyroidism offers new opportunities and challenges in the management of calcium homeostasis. Cinacalcet inhibits

parathyroid hormone release, resulting in a fall in serum calcium. The decline in serum calcium can influence clinical decision-making with respect to dialysate calcium concentration. On one hand, for patients who begin with normal or low serum calcium concentrations, declining serum calcium concentrations might prompt an increase in dialysate calcium. On the other hand, for patients with hypercalcemia, cinacalcet may provide a means to lower serum calcium concentrations without lowering dialysate calcium. In the EVOLVE trial, treating physicians were not blinded to serum calcium concentrations and were allowed to alter dialysis prescriptions at their discretion. Although the median serum calcium decreased by nearly 1 mg/dL in the cinacalcet arm, the dialysate calcium prescription was rarely changed, with no discernible difference in prescription changes for dialysate calcium between the cinacalcet and placebo groups. This may reflect a resistance to modification of dialysate calcium in favor of other means of altering serum calcium concentrations (changes in oral calcium supplementation or vitamin D sterols). While we observed an increase in the use of calcium-containing phosphate binder use in the cinacalcet arm, the effects on serum calcium concentration may have been offset by a concomitant decrease in vitamin D sterol use. It is also possible that lack of changes to dialysate calcium resulted from clinical inertia or uncertainty regarding the clinical significance of changes in serum calcium. Indeed, although both hypo- and hypercalcemia have been associated with adverse outcomes in observational studies, the optimal serum calcium concentration has not been determined prospectively.

Several studies have shown associations among intradialytic fall in serum calcium, low calcium dialysate, and electrocardiographic QT prolongation, a marker of arrhythmic risk. [6, 17] In a case-control study of prevalent patients receiving hemodialysis, dialysate calcium <2.5 mEq was associated with a doubling in the odds of peri-dialytic in-facility sudden cardiac arrest.[7] In addition, a larger calcium “gradient,” determined by the difference between the most recent serum and the prescribed dialysate calcium concentrations, was also associated with an increased risk of in-facility cardiac arrest in this study (odds ratio 1.40, 95% CI 1.10 to 1.80 per 1 mEq/L increase). A recent study examining the outcomes in dialysis units that lowered default dialysate calcium from 2.5 mEq/L to less than 2.5 mEq also suggested an increase in heart failure hospitalization and intradialytic hypotension.[18] While our unadjusted analyses showed a similar significant adverse association between low dialysate calcium and high calcium gradients with cardiovascular events, the association did not persist after adjustment for covariates. This could suggest that effect sizes observed in previous studies might be reduced after further adjustment for residual confounding.

We found that neither the dialysate calcium concentration nor the dialysate–serum calcium gradient significantly influenced the effects of cinacalcet. Additionally, although the decline in serum calcium concentration was limited to some extent by increased prescription of calcium-containing phosphate binders, it is important to note that the results herein suggest that the hypocalcemic effects of cinacalcet do not increase the risk of sudden death. If there is a benefit of cinacalcet on sudden death or other cardiovascular endpoints, these effects may be independent of effects on serum calcium, perhaps reflecting salutary effects of PTH lowering.

Several important limitations should be considered. First, we did not have data on serum ionized calcium. Ionized calcium would be a better measure of the diffusible serum calcium-to-dialysate gradient and overall dialyzer calcium flux, since only unbound calcium is dialyzable. Nevertheless, there is evidence that bound calcium dissociates rapidly, making total serum calcium the effective driving force for diffusion[19] and thus, the difference between total serum calcium and dialysate calcium levels would be expected to be proportional to the diffusible calcium gradient. Second, in order to avoid indication bias and confounding associated with changes in serum and dialysate calcium, we considered only baseline concentrations when testing for effect modification. As such, the exposure of some patients may have been misclassified, if during the majority of their months on study they were treated with a different dialysate calcium concentration relative to baseline. However, since relatively few patients had their dialysate calcium concentrations changed, substantial misclassification is unlikely. Third, the power of the trial was limited by extensive non-adherence to the randomized assignment as well as by co-interventions that lowered PTH (parathyroidectomy, kidney transplantation and use of commercial cinacalcet). In turn, the power to detect a meaningful interaction (effect modification) is reduced. While we have no evidence of effect modification by either dialysate calcium or the serum–dialysate calcium gradient, it is possible that one exists; yet we were unable to detect it. Finally, the results could have been influenced by co-interventions that were not carefully tracked (e.g., use of over-the-counter calcium supplements and/or oral vitamin D sterols, changes in dietary calcium).

In summary, this study demonstrates major regional differences in the prescription of dialysate calcium. We observed no association between dialysate calcium or the serum–dialysate calcium gradient and the primary composite endpoint, cardiovascular death, or sudden death. We observed relative hypocalcemia induced by cinacalcet, with infrequent up-titration of the dialysate calcium. Despite relative hypocalcemia associated with cinacalcet, the risk of sudden cardiac death was not increased. Finally, we found that the effects of cinacalcet were not modified by the dialysate calcium or the serum–dialysate calcium gradient, although the power to detect such an interaction was low. There is continued uncertainty with respect to the optimal dialysate calcium concentration, with or without conventional and newer therapeutics for CKD-MBD.

Acknowledgments

Sources of Funding: The EVOLVE trial was supported by Amgen. SA and GMC received grant funding from Amgen to conduct secondary data analysis using EVOLVE data. PHP was also supported by grant (1K23DK098281-01) from the National Institute of Diabetes and Digestive and Kidney Diseases.

The EVOLVE trial was funded by Amgen. This work was also supported by grant funding (1K23DK098281-01) from the National Institute of Diabetes and Digestive and Kidney Diseases (Dr. Pun).

References

1. Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011; 80(6):572–586. [PubMed: 21750584]

2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004; 15(8):2208–2218. [PubMed: 15284307]

3. Suzuki T, Yonemura K, Maruyama Y, Takahashi T, Takita T, Furuhashi M, Hishida A. Impact of serum parathyroid hormone concentration and its regulatory factors on arterial stiffness in patients undergoing maintenance hemodialysis. Blood Purif. 2004; 22(3):293–297. [PubMed: 15166491]

4. London GM, Marchais SJ, Guerin AP, Metivier F. Arteriosclerosis, vascular calcifications and cardiovascular disease in uremia. Current opinion in nephrology and hypertension. 2005; 14(6): 525–531. [PubMed: 16205470]

5. van der Sande FM, Cheriex EC, van Kuijk WH, Leunissen KM. Effect of dialysate calcium concentrations on intradialytic blood pressure course in cardiac-compromised patients. Am J Kidney Dis. 1998; 32(1):125–131. [PubMed: 9669433]

6. Severi S, Grandi E, Pes C, Badiali F, Grandi F, Santoro A. Calcium and potassium changes during haemodialysis alter ventricular repolarization duration: in vivo and in silico analysis. Nephrol Dial Transplant. 2008; 23(4):1378–1386. [PubMed: 18045821]

7. Pun PH, Horton JR, Middleton JP. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. Clinical journal of the American Society of Nephrology : CJASN. 2013; 8(5):797–803. [PubMed: 23371957]

8. Investigators ET, Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012; 367(26): 2482–2494. [PubMed: 23121374]

9. Chertow GM, Pupim LB, Block GA, Correa-Rotter R, Drueke TB, Floege J, et al. Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): rationale and design overview. Clin J Am Soc Nephrol. 2007; 2(5):898–905. [PubMed: 17702710]

10. Chertow GM, Correa-Rotter R, Block GA, Drueke TB, Floege J, Goodman WG, et al. Baseline characteristics of subjects enrolled in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial. Nephrol Dial Transplant. 2012; 27(7):2872–2879. [PubMed: 22529163]

11. Uhlig K, Berns JS, Kestenbaum B, Kumar R, Leonard MB, Martin KJ, et al. KDOQI US commentary on the 2009 KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of CKD-Mineral and Bone Disorder (CKD-MBD). Am J Kidney Dis. 2010; 55(5):773–799. [PubMed: 20363541]

12. Messa P, Sherman RA. Should Dialysate Calcium be Individualized? Semin Dial. 2014; 27(1):4–7. [PubMed: 24400799]

13. Kidney Disease: Improving Global Outcomes CKDMBDWG. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009; (113):S1–130.

14. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2005; 67(3):1179–1187. [PubMed: 15698460]

15. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, et al. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006; 114(10):e385–484. [PubMed: 16935995]

16. Tentori F, Albert JM, Young EW, Blayney MJ, Robinson BM, Pisoni RL, et al. The survival advantage for haemodialysis patients taking vitamin D is questioned: findings from the Dialysis Outcomes and Practice Patterns Study. Nephrol Dial Transplant. 2009; 24(3):963–972. [PubMed: 19028748]

17. Genovesi S, Dossi C, Vigano MR, Galbiati E, Prolo F, Stella A, Stramba-Badiale M. Electrolyte concentration during haemodialysis and QT interval prolongation in uraemic patients. Europace. 2008; 10(6):771–777. [PubMed: 18287086]

18. Brunelli SM, Sibbel S, Do TP, Cooper K, Bradbury BD. Facility Dialysate Calcium Practices and Clinical Outcomes Among Patients Receiving Hemodialysis: A Retrospective Observational Study. Am J Kidney Dis. 2015; 66(4):655–665. [PubMed: 26015274]

19. Gotch F, Levin NW, Kotanko P. Calcium balance in dialysis is best managed by adjusting dialysate calcium guided by kinetic modeling of the interrelationship between calcium intake, dose of vitamin D analogues and the dialysate calcium concentration. Blood Purif. 2010; 29(2):163–176. [PubMed: 20093823]

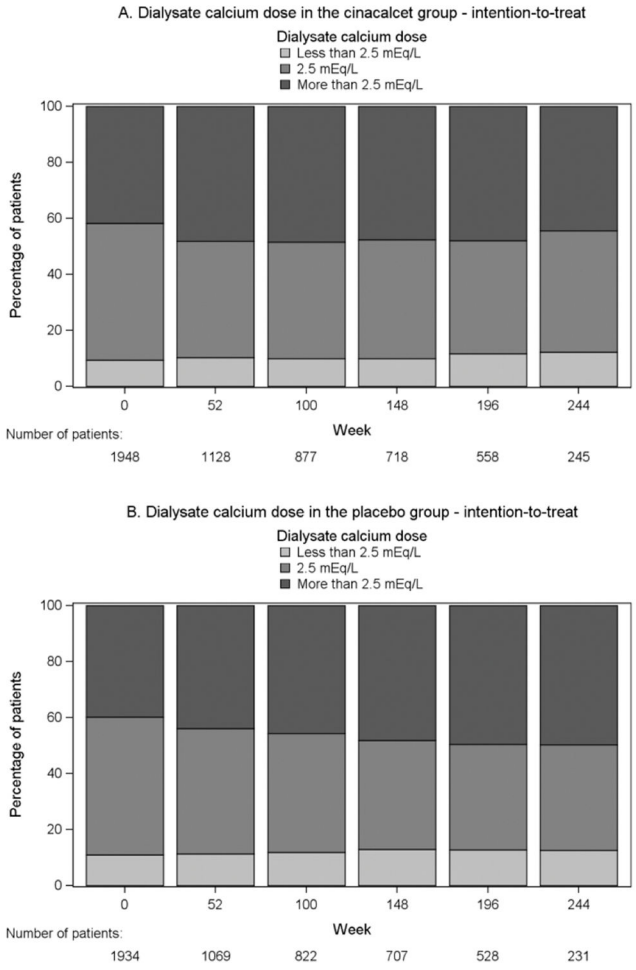

Figure 1.

Dialysate Calcium Concentration over the course of the trial in cinacalcet (Panel A) and placebo (Panel B) treated groups.

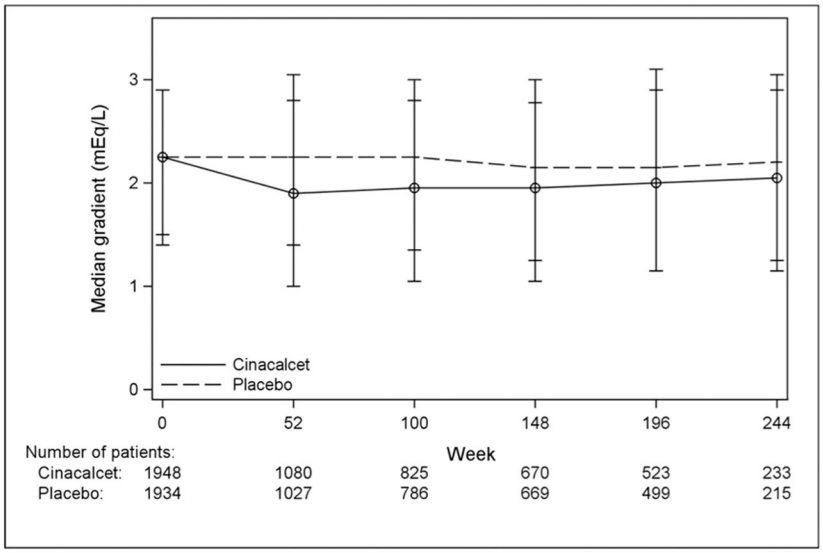

Figure 2.

Median Serum-Dialysate Gradient over time (bars represent the range between 10th and 90th percentiles)

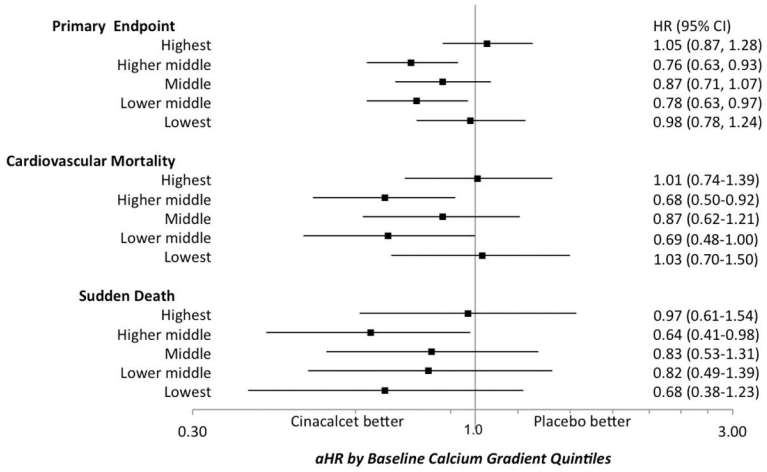

Figure 3.

Forest plots of covariate-adjusted relative hazard and 95% CI for the primary composite outcome, cardiovascular mortality and sudden cardiac death by baseline serum-to-dialysate calcium gradient quintile groups (Lowest quintile <1.75 mEq/L; Low middle quintile 1.75–2.10 mEq/L; middle quintile = 2.11–2.35 mEq/L; higher middle quintile = 2.36–2.65 mEq/L; highest quintile >2.65 mEq/L). Interactions with the continuous baseline calcium gradient variable were p=0.663 for the primary composite endpoint, p=0.826 for the cardiovascular mortality endpoint and p=0.771 for the sudden death endpoint.

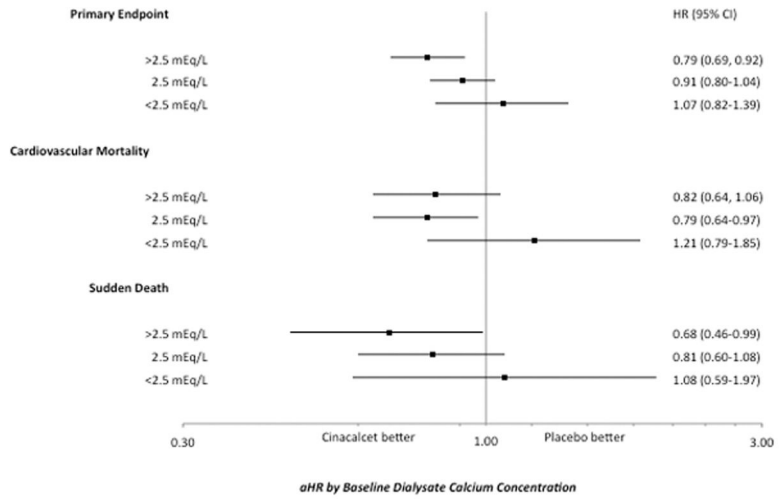

Figure 4.

Forest plots of covariate-adjusted HR and 95% CI for the primary composite outcome, cardiovascular mortality and sudden cardiac death by baseline dialysate calcium prescription. Interactions with the dialysate calcium variable were p=0.117 for the primary composite endpoint, p=0.205 for the cardiovascular mortality endpoint, and p=0.434 for the sudden death endpoint.

Table 1

Baseline characteristics of patients by treatment assignment, based on dialysate calcium concentration category. (P10, P90= 10th, 90th percentile)

Treatment Assignment (N)	**Placebo (1935)**			**Cinacalcet (1948)**		
Dialysate calcium concentration at baseline (N)	**Less than 2.5 mEq/L (211)**	**2.5 mEq/L (952)**	**More than 2.5 mEq/L (771)**	**Less than 2.5 mEq/L (184)**	**2.5 mEq/L (949)**	**More than 2.5 mEq/L (815)**
Age (years)						
Median	55	55	53	59	57	53
P10, P90	36,73	35,73	34,73	39,77	35,75	34,72
Sex (% female)	48%	38%	39%	45%	42%	40%
Race						
Black	51%	29%	5%	48%	29%	6%
White	40%	46%	77%	41%	46%	75%
Other	9%	25%	18%	11%	25%	19%
BMI (Kg/m^2)						
Median	27	27	26	27	27	25
P10, P90	21,40	21,37	20,34	20,37	21,38	20,34
Dialysis vintage (months)						
Median	36	43	53	44	39	55
P10, P90	11, 113	9,136	12, 164	9,119	8,124	10,165
Type of access						
Permanent catheter	15%	13%	8%	15%	15%	7%
Fistula or graft *	85%	87%	92%	85%	85%	93%
Baseline antiarrhythmic use **	5%	3%	4%	3%	3%	4%
Baseline calcium-based phosphate binder use	44%	49%	61%	42%	50%	60%
Baseline vitamin D use	75%	60%	55%	76%	64%	50%
History of coronary heart disease ***	38%	34%	25%	37%	34%	23%
History of cardiac arrhythmia	16%	15%	14%	18%	15%	12%
History of diabetes	50%	40%	21%	43%	42%	21%
History of heart failure	38%	27%	16%	30%	27%	17%
Albumin (g/dl)						
Median	3.6	3.6	3.7	3.6	3.7	3.7

Treatment Assignment (N)	Placebo (1935)			Cinacalcet (1948)		
Dialysate calcium concentration at baseline (N)	**Less than 2.5 mEq/L (211)**	**2.5 mEq/L (952)**	**More than 2.5 mEq/L (771)**	**Less than 2.5 mEq/L (184)**	**2.5 mEq/L (949)**	**More than 2.5 mEq/L (815)**
P10, P90	3.2,4.1	3.2,4.1	3.2,4.2	3.2,4.0	3.2,4.1	3.2,4.1
Serum creatinine (mg/dl)						
Median	9.0	9.7	10.4	9.5	9.5	10.4
P10, P90	6.1,13.9	6.4,13.7	7.4,14.2	6.3,13.2	6.3,13.6	7.2,14.2
Corrected serum calcium (mg/dl)						
Median	9.8	9.8	9.8	9.9	9.8	9.7
P10, P90	9.0,10.7	9.0,10.6	9.0,10.9	9.1,10.7	9.1,10.7	8.9,10.8
Serum bicarbonate (mEq/L)						
Median	21.7	21.4	19.0	21.7	21.4	19.2
P10, P90	16.9, 26.3	16.6, 26.4	14.9, 23.5	15.7, 26.8	16.1, 26.1	15.3, 23.2
Serum potassium (mEq/L)						
Median	4.8	4.9	5.2	4.9	4.9	5.2
P10, P90	3.9, 5.9	4.0, 5.9	4.2, 6.3	4.0, 5.9	4.0, 5.9	4.3, 6.3

* Includes arteriovenous fistula, graft or other non-catheter

** Includes baseline use of amiodarone or other antiarrhythmic medication

*** Includes history of coronary artery disease, myocardial infarction, revascularization, coronary artery bypass graft, and percutaneous coronary intervention.

Table 2

Dialysate calcium assignment at baseline by region

Dialysate calcium Concentration (N)	Australia (149)	Canada (146)	Europe (1188)	Latin America (687)	Russia (283)	United States (1430)
Less than 2.5 mEq/L	15%	8%	5%	1%	0%	21%
2.5 mEq/L	0%	81%	40%	34%	1%	75%
2.5 – 3 mEq/L	83%	11%	45%	32%	32%	2%
More than 3 mEq/L	2%	1%	10%	34%	66%	2%

Table 3

Hazard ratio of the primary composite end point for the serum-dialysate calcium gradient, adjusting for treatment assignment and other important covariates.

	Primary Composite Endpoint		Cardiovascular Death		Sudden Cardiac Death	
Variable	**Hazard Ratio (95% CI)**	**P value**	**Hazard Ratio (95% CI)**	**P value**	**Hazard Ratio (95% CI)**	**P value**
Serum-dialysate calcium gradient (per 1 mEq/L increase)						
Unadjusted	1.39 (1.28, 1.50)	<0.0001	1.33 (1.17, 1.33)	<0.0001	1.38 (1.14, 1.67)	0.0009
Covariate-adjusted *	1.00 (0.91, 1.10)	0.976	1.08 (0.92, 1.27)	0.320	1.09 (0.87, 1.37)	0.453
Covariate+treatment assignment adjusted **	1.00 (0.91, 1.10)	0.970	1.08 (0.92, 1.27)	0.324	1.09 (0.87, 1.37)	0.451
Dialysate calcium (ref = 2.5mEq/L)						
Unadjusted						
< 2.5 mEq/L	1.27 (1.10, 1.47)	0.001	1.22 (0.98, 1.53)	0.081	1.19 (0.86, 1.65)	0.303
> 2.5 mEq/L	0.75 (0.68, 0.82)	<0.0001	0.81 (0.68, 0.94)	0.006	0.71 (0.56, 0.90)	0.004
Covariate-adjusted *						
< 2.5 mEq/L	1.10 (0.94, 1.27)	0.238	1.06 (0.85, 1.30)	0.643	1.05 (0.74, 1.47)	0.800
> 2.5 mEq/L	1.06 (0.94, 1.21)	0.341	1.06 (0.84, 1.35)	0.6256	0.87 (0.63, 1.19)	0.377
Covariate+treatment assignment adjusted **						
< 2.5 mEq/L	1.09 (0.94, 1.27)	0.259	1.06 (0.83, 1.34)	0.659	1.03 (0.74, 1.45)	0.847
> 2.5 mEq/L	1.07 (0.94, 1.22)	0.298	1.06 (0.85, 1.31)	0.622	0.87 (0.63, 1.20)	0.389

* Adjusted for age, geographic region, race, tobacco use, dialysis vintage, vascular access, baseline systolic blood pressure, baseline comorbidities (coronary artery disease, cardiac arrhythmia, diabetes, heart failure, transient ischemic attack, retinopathy, revascularization, baseline medication use (statin, vitamin D), baseline laboratory data (albumin, HDL, parathyroid hormone)

** Adjusted for factors listed above plus treatment assignment (cinacalcet vs. placebo)