

The Effects of Cinacalcet in Older and Younger Patients on Hemodialysis: The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial

Patrick S. Parfrey,* Tilman B. Drüeke,[†] Geoffrey A. Block,[‡] Ricardo Correa-Rotter,[§] Jürgen Floege,^{||} Charles A. Herzog,[¶] Gerard M. London,^{**} Kenneth W. Mahaffey,^{††} Sharon M. Moe,^{††} David C. Wheeler,^{§§} Yumi Kubo,^{|||} Bastian Dehmel,^{|||} William G. Goodman,^{|||} and Glenn M. Chertow^{††} for the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators

Abstract

Background and objectives The calcimimetic cinacalcet reduced the risk of death or cardiovascular (CV) events in older, but not younger, patients with moderate to severe secondary hyperparathyroidism (HPT) who were receiving hemodialysis. To determine whether the lower risk in younger patients might be due to lower baseline CV risk and more frequent use of cointerventions that reduce parathyroid hormone (kidney transplantation, parathyroidectomy, and commercial cinacalcet use), this study examined the effects of cinacalcet in older (≥ 65 years, $n=1005$) and younger (< 65 years, $n=2878$) patients.

Design, setting, participants, & measurements Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) was a global, multicenter, randomized placebo-controlled trial in 3883 prevalent patients on hemodialysis, whose outcomes included death, major CV events, and development of severe unremitting HPT. The age subgroup analysis was prespecified.

Results Older patients had higher baseline prevalence of diabetes mellitus and CV comorbidity. Annualized rates of kidney transplantation and parathyroidectomy were >3 -fold higher in younger relative to older patients and were more frequent in patients randomized to placebo. In older patients, the adjusted relative hazard (95% confidence interval) for the primary composite (CV) end point (cinacalcet versus placebo) was 0.70 (0.60 to 0.81); in younger patients, the relative hazard was 0.97 (0.86 to 1.09). Corresponding adjusted relative hazards for mortality were 0.68 (0.51 to 0.81) and 0.99 (0.86 to 1.13). Reduction in the risk of severe unremitting HPT was similar in both groups.

Conclusions In the EVOLVE trial, cinacalcet decreased the risk of death and of major CV events in older, but not younger, patients with moderate to severe HPT who were receiving hemodialysis. Effect modification by age may be partly explained by differences in underlying CV risk and differential application of cointerventions that reduce parathyroid hormone.

Clin J Am Soc Nephrol 10: 791–799, 2015. doi: 10.2215/CJN.07730814

Introduction

Cardiovascular (CV) events occur frequently in patients with CKD (1). Age-adjusted rates of CV death in patients with ESRD are ≥ 10 times higher than in the general population (2). The cause of cardiovascular disease (CVD) in CKD is multifactorial, but mineral and bone disorder (MBD), including secondary hyperparathyroidism (sHPT), hyperphosphatemia, and vascular calcification, have been implicated (3). Arterial medial calcification is associated with arteriosclerosis, increased pulse wave velocity, left ventricular hypertrophy, diastolic dysfunction, and ultimately heart failure (4). Arterial intimal calcification advances with the progression of atherosclerosis and may predispose to atherosclerotic events, including myocardial infarction, angina, stroke, and peripheral vascular disease (5).

The calcimimetic cinacalcet (Sensipar/Mimpara; Amgen) modulates the activity of the calcium-sensing receptor in parathyroid tissue (6) and reduces serum concentrations of parathyroid hormone (PTH) (7). In addition, calcimimetic-induced upregulation of the calcium-sensing receptor in vascular smooth muscle and endothelial cells may attenuate the progression of vascular calcification (8–10). In patients receiving hemodialysis, cinacalcet may slow the progression of vascular and cardiac-valve calcification (11).

The efficacy of cinacalcet in the prevention of CV events was examined in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial, a global randomized controlled trial (RCT) in which 3883 patients with moderate to severe sHPT who were receiving hemodialysis were randomly assigned

*Department of Medicine, Health Sciences Center, St. John's, Newfoundland, Canada; [†]French Institute of Health and Medical Research Unit 1088, Faculty of Medicine and Pharmacy, University of Picardie, Amiens, France; [‡]Denver Nephrology, Denver, Colorado; [§]Department of Nephrology and Mineral Metabolism, Salvador Zubirán National Institute of Health Sciences and Nutrition, Mexico City, Mexico; ^{||}Department of Nephrology, RWTH Aachen University Hospital, Aachen, Germany; [¶]Department of Internal Medicine, University of Minnesota, Minneapolis, Minnesota; ^{**}Service of Nephrology, Manhès Hospital, Paris, France; ^{††}Department of Medicine, Stanford University School of Medicine, Palo Alto, California; ^{‡‡}Department of Medicine, Indiana University School of Medicine and Roudebush Veterans Administration Medical Center, Indianapolis, Indiana; ^{§§}Centre for Nephrology, University College London, United Kingdom; and ^{|||}Amgen Inc, Thousand Oaks, California

Correspondence:

Dr. Patrick S. Parfrey, Health Sciences Centre, Memorial University, St. John's, NF A1B 3V6, Canada. Email: pparfrey@mun.ca

to either cinacalcet or placebo, in addition to conventional therapy, which included phosphate binders and vitamin D sterols in most patients (12). The unadjusted relative hazard (cinacalcet versus placebo) for the primary composite outcome (time to death for any cause or major CV events) was not statistically significant, although the relative hazard adjusted for baseline covariates was nominally statistically significant (0.88; 95% confidence interval [95% CI], 0.79 to 0.97). Patients randomized to cinacalcet also experienced lower rates of parathyroidectomy (PTX) and the composite outcome of severe unremitting hyperparathyroidism (HPT) (severe HPT with hypercalcemia or PTX) (12,13).

In a prespecified subgroup analysis, the effect of cinacalcet on the primary outcome was more pronounced in older patients. The treatment \times age (continuous) interaction was significant ($P=0.03$) (12). We hypothesized that lower risks of death and CVD in younger patients and more frequent use of co-interventions that reduce PTH, including kidney transplantation and PTX, might explain the observed findings.

Materials and Methods

Study Setting

EVOLVE was a global, multicenter, randomized placebo-controlled trial of cinacalcet, during which enrolled patients received conventional therapy for sHPT. Between August 2006 and January 2008, 3883 adult patients on hemodialysis were enrolled from 5755 individuals who were screened. Patients were followed for up to 64 months. The trial design and procedures (14), baseline characteristics of trial participants (15), inclusion/exclusion criteria, Consolidated Standards of Reporting Trials diagram, sample size estimate, results of the primary composite and the secondary end points, and adverse event rates were previously reported (12).

The EVOLVE trial was sponsored by Amgen Inc. An academically led executive committee supervised the trial design and operations. An independent data monitoring committee reviewed safety data and interim analyses for efficacy. All primary and secondary end points were adjudicated by an independent clinical events classification group. The study was approved by institutional review boards at participating study sites and the authors adhered to the Declaration of Helsinki in the conduct of this trial (ClinicalTrials.gov NCT00345839).

Study Population

Eligible participants received hemodialysis three times per week with plasma PTH concentrations ≥ 300 pg/ml (31.8 pmol/L), serum calcium phosphate product ≥ 45 mg²/dl² (3.63 mmol²/L²), and serum calcium ≥ 8.4 mg/dl (2.1 mmol/L). Written informed consent was obtained from all patients.

Study Design

Randomization. Randomization was stratified by country and diabetes status using fixed blocks. Treatment assignment was blinded to investigators, trial participants, and the sponsor.

Subgroup Analyses. To determine treatment effect modifiers, the following seven factors were prespecified for subgroup analysis: age (<65 and ≥ 65 years), sex, race, geographic region, baseline plasma PTH, and baseline use of

vitamin D. Only age was associated with a significant treatment interaction (12).

Biochemical Determinations. Biochemical markers of CKD-MBD were measured throughout the trial, including plasma PTH and serum concentrations of total calcium, phosphorus, total alkaline phosphatases, and bone-specific alkaline phosphatase. All determinations were done in central laboratories using established methods (15).

Outcomes. The primary composite end point was the time to death of any cause or the first nonfatal CV event (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular disease). Detailed definitions are provided in Supplemental Table 1. Outcomes associated with the progression of HPT included PTX and development of severe unremitting HPT.

There were no protocol-specified criteria, either biochemical or otherwise, that prompted surgical PTX. We defined severe unremitting HPT as time to the first occurrence of any of the three following events: (1) plasma PTH >1000 pg/ml with serum total calcium >10.5 mg/dl (2.6 mmol/L) on two consecutive occasions, or (2) plasma PTH >1000 pg/ml and serum total calcium >10.5 mg/L (2.6 mmol/L) on one occasion with prescription of commercial cinacalcet within 2 months, or (3) surgical PTX (13).

Statistical Analyses

All end point data were collected and analyzed using the intention-to-treat principle. The following analyses were performed for prespecified age categories of ≥ 65 years and <65 years. Kaplan–Meier product-limit estimates of the event-free survival time were computed and compared between treatment groups using a two-sided log-rank test stratified by country and history of diabetes mellitus (yes/no). The relative hazard (cinacalcet versus placebo) and 95% CIs were calculated using Cox proportional-hazards regression models, also stratified according to country and history of diabetes mellitus. We conducted multivariable analyses in which we adjusted for baseline covariates using a stepwise selection procedure. For the primary composite end point, we conducted prespecified companion analyses in which data were censored at the time of kidney transplantation, PTX, or off-protocol initiation of commercial cinacalcet, alone or in combination. The primary analysis (unadjusted log-rank test) did not reach statistical significance (12). The analyses presented herein are not adjusted for multiplicity and P values <0.05 are considered nominally significant. Data on adverse events were collected while patients were taking the study drug (12). Statistical analyses were performed using SAS software (version 9.2; SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

There were 2878 (74%) patients aged <65 years and 1005 (26%) aged ≥ 65 years (Table 1). The prevalence of white race, diabetes mellitus, and CVD (including heart failure, peripheral vascular disease, coronary artery revascularization, myocardial infarction, stroke, and atrial fibrillation) was higher in older patients, as was the use of vitamin D sterols, antiplatelet agents, and statins.

Exposure and Adherence

In patients randomized to cinacalcet, duration of exposure (median 16 months; 10th and 90th percentile range, 2–49 months) and median daily dose (46 mg; 10th and 90th percentile range, 26–109 mg) were lower in older patients (23 months; 10th and 90th percentile range, 2–52 months) relative to younger patients (58 mg; 10th and 90th percentile range, 29–136 mg) (Supplemental Table 2). In patients randomized to placebo, the maximum dose level was reached in 76% of older patients and 81% of younger patients. Reasons for discontinuation are provided in Supplemental Table 3.

Biochemical Markers of and Concomitant Medications for CKD-MBD

Baseline biochemical markers by age group are provided in Table 1. The absolute reduction in PTH after use of cinacalcet was similar in both age groups and was sustained over time. Baseline use of vitamin D sterols and phosphate binders by treatment group (stratified by age) is provided in Supplemental Table 4.

Use of Kidney Transplantation, PTX, and Commercial Cinacalcet in the Placebo Group

Among patients randomized to placebo, exposure to severe HPT was limited by cointerventions to a greater extent in younger patients. The annualized transplantation rate (percentage per year) was 2.0 (95% CI, 1.3 to 2.9) in older patients and 7.1 (95% CI, 6.4 to 7.9) in younger patients. By year 3, 6.2% of older patients had been transplanted compared with 20% of younger patients (Figure 1A).

Corresponding annualized PTX rates were 1.7 (95% CI, 1.1 to 2.6) and 5.2 (95% CI, 4.6 to 5.8). By year 3, 3.7% of older patients had PTX compared with 15.6% of younger patients (Figure 1B). The annualized rates of commercial cinacalcet use were similar in both age groups (Figure 1C).

By year 3, 32% of older patients had received one or more of these cointerventions compared with 50% of younger patients.

The Effects of Cinacalcet

Primary End Point. The effect of cinacalcet on the primary composite end point was more pronounced in patients aged ≥ 65 years, compared with patients aged < 65 years ($P=0.01$) (Figure 2A). In older patients, the relative hazard adjusted for baseline covariates (cinacalcet versus placebo) for the primary composite end point was 0.70 (95% CI, 0.60 to 0.81); in younger patients, the relative hazard was 0.97 (95% CI, 0.86 to 1.09). The relative hazard by decade is provided in Figure 3. Annualized event rates and relative hazards for components of the primary composite end point are shown in Table 2. Event rates were substantially higher in older patients. The differential treatment effect by age was observed for mortality, myocardial infarction, and peripheral vascular disease, but not for unstable angina.

Mortality. The adjusted relative hazard for all-cause mortality in older patients was 0.68 (95% CI, 0.58 to 0.81); in younger patients, the relative hazard was 0.99 (95% CI, 0.86 to 1.13) (Figure 2B).

Severe Unremitting HPT. Few parathyroidectomies were undertaken in older patients (Figure 1B); the effect of cinacalcet on abrogating the provision of PTX was evident only in the younger patients. When we considered the composite

outcome of severe unremitting HPT, rates were higher in younger patients, although the effect of cinacalcet was similar in older (relative hazard, 0.46; 95% CI, 0.31 to 0.69) and younger patients (0.43; 95% CI, 0.36 to 0.51) (Figure 2C).

Analyses with Censoring by PTH-Lowering Events

When we censored data for patients after kidney transplantation, the relative hazard for the primary composite end point was 0.74 (95% CI, 0.63 to 0.86) in older patients and 0.95 (95% CI, 0.84 to 1.07) in younger patients. When censoring data after PTX, corresponding results were 0.72 (95% CI, 0.62 to 0.84) and 0.97 (95% CI, 0.87 to 1.10). When censoring data after the start of commercial cinacalcet, corresponding results were 0.70 (95% CI, 0.60 to 0.83) and 0.97 (95% CI, 0.85 to 1.09). Censoring at the time of any of these three events—all of which would be expected to correct or treat sHPT—yielded a relative hazard of 0.70 (95% CI, 0.59 to 0.82) in older patients and 0.89 (95% CI, 0.78 to 1.02) in younger patients.

Side Effects

In patients randomized to cinacalcet, exposure-adjusted rates of nausea, vomiting, and hypocalcemia were similar across age groups (Supplemental Table 5).

Discussion

In the EVOLVE trial, we previously showed a nominally statistically significant benefit of cinacalcet on the primary composite end point in older compared with younger patients with moderate to severe sHPT who were receiving hemodialysis (12). Here we show that all-cause mortality was also significantly reduced in the older patients. The annualized mortality rate was 20.4% in patients randomized to placebo and 15.9% in patients randomized to cinacalcet. Because older and younger patients on hemodialysis differ in many ways, we aimed to explore these differences in detail. The absence of a treatment effect in younger patients contrasts with the 30% reduction in the risk of the primary composite end point and the 32% reduction in the risk of death in older patients. This effect modification by age can be explained by one of several factors, such as a true difference in the treatment effect, bias introduced by differential application of cointerventions (including kidney transplantation, PTX, and provision of commercial cinacalcet), differential susceptibility to the effects of sHPT for which cinacalcet is prescribed, or lower event rates in younger patients, thereby reducing statistical power. Very high rates of discontinuation of the study drug were known to have lowered the trial's power well below what had been anticipated (12).

Our results demonstrate differential application of PTH-lowering interventions, with kidney transplantation and PTX performed > 3 times more frequently in younger patients. Analyses in which we accounted for PTH-lowering therapies failed to show a significant benefit in younger patients, although the 95% CIs of the relative hazards were more closely aligned with those observed in older patients. Younger patients had substantially less CV comorbidity than older patients at baseline, and diminished CV risk was confirmed by the markedly lower CV event rates experienced during the trial in this age group.

The effect of alterations in mineral metabolism induced by cinacalcet on calcification of either intimal or medial

Table 1. Baseline characteristics by age group and by treatment arm

| Characteristic | Age <65 yr (n=2878) | | Age ≥65 yr (n=1005) | |
|--|-----------------------------------|--------------------------------|----------------------------------|-------------------------------|
| | Cinacalcet (N ₁ =1418) | Placebo (N ₁ =1460) | Cinacalcet (N ₁ =530) | Placebo (N ₁ =475) |
| Age (yr) ^a | 50 (32, 61) | 50 (33, 61) | 71 (66, 80) | 71 (66, 80) |
| Women ^b | 569 (40) | 574 (39) | 240 (45) | 195 (41) |
| Race or ethnic group^a | | | | |
| White | 771 (54) | 785 (54) | 353 (67) | 331 (70) |
| Black | 321 (23) | 341 (23) | 88 (17) | 87 (18) |
| Other | 326 (23) | 334 (23) | 89 (17) | 57 (12) |
| Region^a | | | | |
| United States | 520 (37) | 534 (37) | 195 (37) | 181 (38) |
| Europe | 387 (27) | 407 (28) | 211 (40) | 183 (39) |
| Latin America | 292 (21) | 302 (21) | 53 (10) | 40 (8) |
| Russia | 128 (9) | 126 (9) | 15 (3) | 14 (3) |
| Australia | 43 (3) | 45 (3) | 31 (6) | 30 (6) |
| Canada | 48 (3) | 46 (3) | 25 (5) | 27 (6) |
| Dialysis vintage (mo) ^a | 47 (9, 156) | 48 (11, 159) | 40 (7, 106) | 39 (9, 116) |
| Current dialysis access^a | | | | |
| Fistula | 1062 (75) | 1073 (74) | 363 (69) | 317 (67) |
| Graft | 172 (12) | 205 (14) | 75 (14) | 78 (16) |
| Permanent catheter | 151 (11) | 155 (11) | 80 (15) | 67 (14) |
| Other | 33 (2) | 27 (2) | 12 (2) | 13 (3) |
| BP (mmHg) | | | | |
| Systolic | 140 (111, 177) | 140 (111, 178) | 140 (110, 175) | 141 (111, 175) |
| Diastolic ^a | 80 (60, 100) | 80 (63, 100) | 72 (56, 89) | 73 (60, 89) |
| Tobacco use^a | | | | |
| Never | 774 (55) | 829 (57) | 312 (59) | 269 (57) |
| Current | 279 (20) | 289 (20) | 33 (6) | 31 (7) |
| Former | 363 (26) | 341 (23) | 185 (35) | 175 (37) |
| Diabetes ^a | 414 (29) | 422 (29) | 240 (45) | 226 (48) |
| Heart failure ^a | 281 (20) | 294 (20) | 169 (32) | 162 (34) |
| Peripheral vascular disease ^a | 181 (13) | 194 (13) | 132 (25) | 128 (27) |
| Coronary artery bypass graft ^a | 58 (4) | 68 (5) | 77 (15) | 86 (18) |
| Percutaneous coronary intervention ^a | 79 (6) | 81 (6) | 51 (10) | 51 (11) |
| Myocardial infarction ^a | 138 (10) | 132 (9) | 101 (19) | 112 (24) |
| Stroke ^a | 99 (7) | 132 (9) | 63 (12) | 61 (13) |
| Transient ischemic attack ^a | 54 (4) | 40 (3) | 46 (9) | 34 (7) |
| Amputation | 86 (6) | 89 (6) | 35 (7) | 40 (8) |
| Atrial fibrillation ^a | 82 (6) | 109 (8) | 120 (23) | 116 (24) |
| Parathyroidectomy ^c | 79 (6) | 71 (5) | 12 (2) | 16 (3) |
| Fracture | 265 (19) | 292 (20) | 117 (22) | 95 (20) |
| iPTH (pg/ml) ^a | 732 (373, 1756) | 747 (379, 1799) | 608 (338, 1565) | 580 (322, 1316) |
| Corrected serum calcium (mg/dl) ^a | 9.7 (9.0, 10.7) | 9.8 (9.0, 10.7) | 9.9 (9.1, 10.8) | 9.9 (9.1, 10.8) |
| Serum phosphorus (mg/dl) ^a | 6.4 (5.1, 8.5) | 6.4 (5.0, 8.6) | 5.9 (4.8, 7.8) | 5.7 (4.7, 7.7) ^b |
| Serum total alkaline phosphatases (μg/L) ^a | 111 (66, 259) | 110 (65, 246) | 98 (63, 214) | 105 (65, 193) |
| Serum bone alkaline phosphatases ≥21 (μg/L) ^a | 820 (58) | 811 (56) | 247 (47) | 232 (49) |
| Serum albumin (g/dl) ^a | 3.7 (3.2, 4.1) | 3.7 (3.2, 4.1) | 3.6 (3.1, 4.0) | 3.6 (3.1, 4.0) |
| Medication use | | | | |
| Vitamin D sterol ^a | 821 (56) | 832 (57) | 335 (63) | 322 (68) |
| Calcium-containing phosphate binder ^c | 770 (54) | 795 (55) | 267 (50) | 230 (48) |
| Noncalcium-containing phosphate binder | 484 (34) | 514 (35) | 190 (36) | 183 (39) |
| β-adrenergic antagonists | 690 (49) | 669 (46) | 255 (48) | 209 (44) |
| RAS inhibitors | 651 (46) | 633 (43) | 222 (42) | 194 (41) |
| Antiplatelet agents ^a | 455 (32) | 489 (34) | 279 (53) | 247 (52) |
| Statins ^a | 395 (28) | 400 (27) | 252 (48) | 214 (45) |

Data are presented as the median (10th and 90th percentiles) or *n* (%) unless otherwise indicated. Percentages are based on N₁. Significance of the differences between each age group, combining those randomized to placebo and to cinacalcet, are indicated by lettered footnotes. iPTH, intact parathyroid hormone; RAS, renin-angiotensin system.

^a*P* value <0.001.

^b*P* value <0.05.

^c*P* value <0.01.

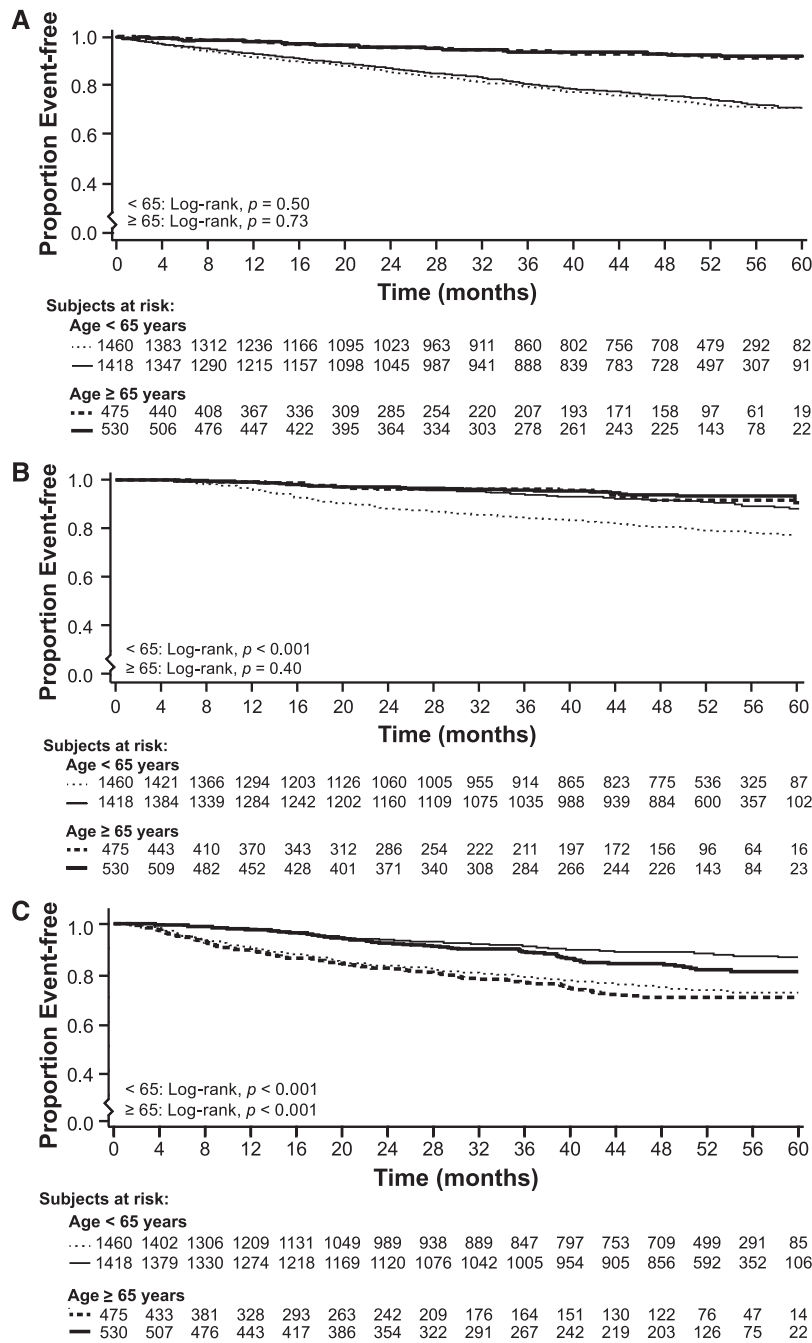


Figure 1. | Kaplan-Meier time-to-event curves for cointerventions that reduce parathyroid hormone (PTH). Time to kidney transplantation (A), parathyroidectomy (B), and use of commercial cinacalcet (C) in the groups randomized to placebo (dotted line, <65 years; dashed line, ≥65 years) and to cinacalcet (solid line, <65 years; bold line, ≥65 years) by age group.

lesions may be diminished in younger patients. Advanced age and diabetes mellitus are consistent risk factors for the presence and progression of coronary artery calcifications (16). Medial thickness and calcification are increased in patients with ESRD (17,18). Using mammograms to assess breast arterial calcification (a marker of generalized medial artery calcification) in patients with CKD, age and eGFR were independent predictors of the presence and severity of medial arterial calcification (19). In patients on hemodialysis with high calcification scores compared with those with

little or no calcification, age and diabetes were two of three independent predictors of severe calcification (20). It seems reasonable to suggest that younger patients in EVOLVE, in whom diabetes mellitus was present less frequently, had less baseline atherosclerotic disease and less arteriosclerosis than older patients, and were thus less susceptible to the beneficial effect of cinacalcet. In addition, there is a link between demineralization of bone and the presence of vascular calcification (21). Because both of these processes are associated with older age, this link

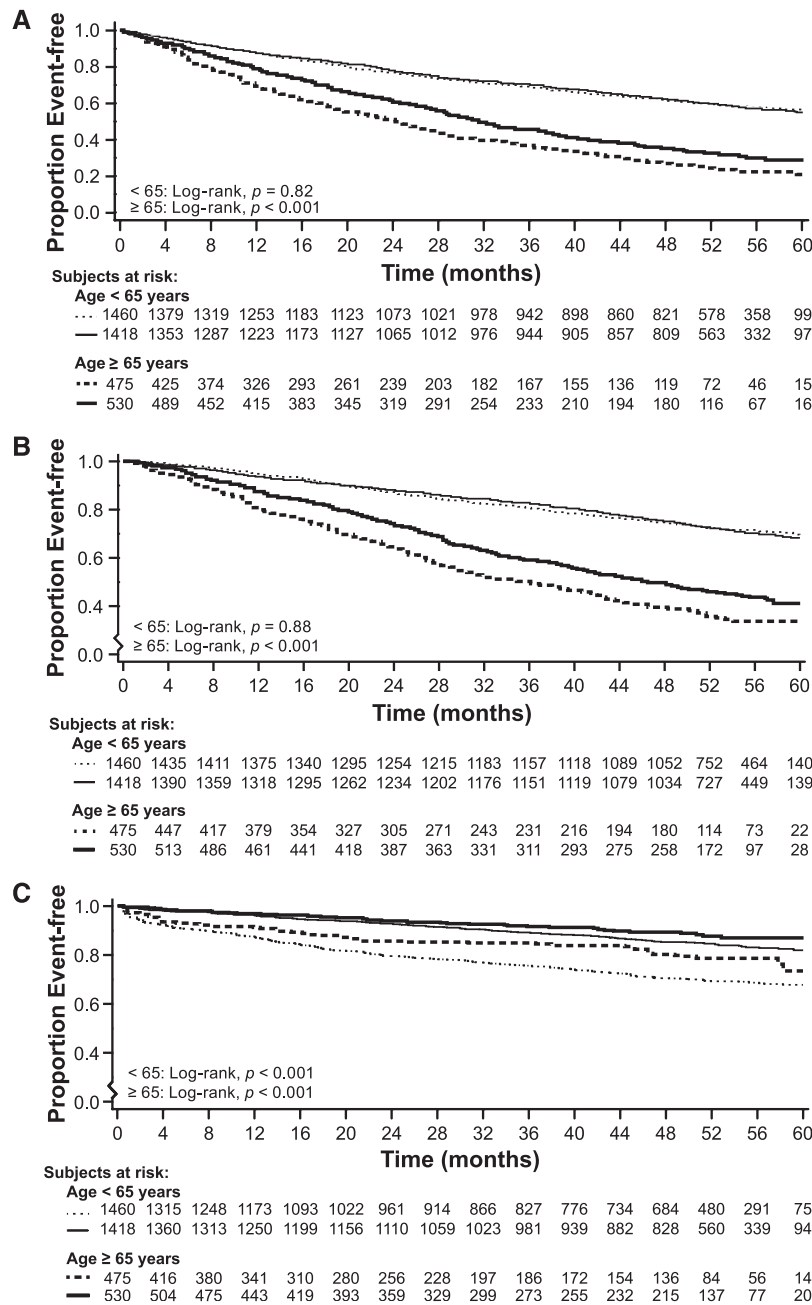


Figure 2. | Kaplan-Meier time-to-event curves for clinical end points. Time to the primary composite cardiovascular end point (A), to death (B), and to severe unremitting hyperparathyroidism (C) in the groups randomized to placebo (dotted line, <65 years; dashed line, ≥ 65 years) and to cinacalct (solid line, <65 years; bold line, ≥ 65 years) by age group.

may explain the more pronounced effect of cinacalct in older patients.

There are several strengths to the analyses presented here. Our results are derived from a relatively large global RCT, with end points adjudicated by a blinded clinical events committee, with low drop-out rates and very little missing outcome data. Although we focused on a subgroup analysis, older versus younger age was one of only seven prespecified subgroups. The analyses presented consider only an intention-to-treat approach, the most conservative of all analytic approaches, because it assesses the effect of randomization to treatment and takes no account of nonadherence to study

drug. Using methods to account for nonadherence, the estimated effects of cinacalct were more pronounced (12). In subgroup analyses, differences in baseline characteristics between the intervention and control groups are more likely to vary by chance but we focused on treatment effects adjusted for baseline covariates. Clearly, the statistical power of the EVOLVE trial to detect treatment differences in the younger patients was low due to the small number of events.

Ten criteria associated with design, analysis, and context have been proposed to assess the credibility of a subgroup effect in RCTs (22). The age treatment effect in the EVOLVE trial met most of these criteria: (1) age ≥ 65 and <65 years

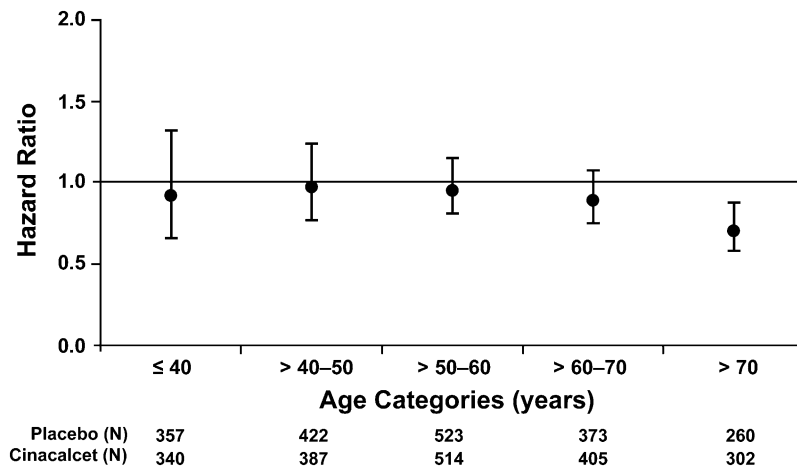


Figure 3. | Unadjusted relative hazards (± 95% confidence intervals) by decade for the primary composite end point (cinacalcet versus placebo) using intention-to-treat analysis.

was a baseline characteristic, although (2) the subgroup was not a stratification factor at randomization; (3) the age subgroup analysis was prespecified before the start of the trial, and (4) was one of a small number ($n=7$) of prespecified subgroup hypotheses tested; (5) the test of treatment×age interaction was significant; (6) the age×interaction effect was significant and independent of other significant interactions; (7) the direction of the age subgroup effect was not prespecified; (8) the age subgroup effect is consistent with that reported for the phosphate binder sevelamer, compared with calcium-based phosphate binders on mortality in 2103 patients receiving hemodialysis (23); (9) the age subgroup effect was consistent across related outcomes (all-cause mortality, myocardial infarction, and peripheral vascular disease, but not unstable angina); and (10) the

biologic rationale for the age subgroup effect (lower baseline CV risk and higher use of cointerventions that lower PTH in younger patients) is logical. We suggest that the cinacalcet effect modification by age is credible, but another trial of calcimimetics would be beneficial for informing clinical practice.

Cinacalcet decreased the risk of death and of major CV events in older, but not younger, patients with moderate to severe sHPT who were receiving hemodialysis. Cinacalcet reduced the risk of severe unremitting HPT in all patients. CV effect modification by age may be partly explained by differences in baseline CV risk and by differential application of cointerventions that reduce PTH. Clinicians will need to balance the potential benefits of cinacalcet on the CKD-associated CVD and MBD with its known adverse

Table 2. Annualized event rates and hazard ratios for cardiovascular end points and mortality by age group

| End Point | Age <65 yr ($n=2878$) | | | Age ≥65 yr ($n=1005$) | | |
|-----------------------------|-------------------------|---------------------------|------------------------|-------------------------|--------------------------|------------------------|
| | Annual Event Rate | | Relative Hazard | Annual Event Rate | | Relative Hazard |
| | Placebo ($N_1=1460$) | Cinacalcet ($N_1=1418$) | | Placebo ($N_1=475$) | Cinacalcet ($N_1=530$) | |
| Primary composite CVD | 11.4 (10.6 to 12.3) | 11.3 (10.5 to 12.2) | 0.99 (0.88 to 1.11) | 28.3 (25.9 to 30.9) | 22.6 (20.5 to 24.7) | 0.74 (0.63 to 0.86) |
| All-cause mortality | 7.0 (6.4 to 7.7) | 7.1 (6.5 to 7.8) | 1.01 (0.88 to 1.16) | 20.4 (18.4 to 22.5) | 15.9 (14.3 to 17.7) | 0.73 (0.62 to 0.86) |
| Myocardial infarction | 1.9 (1.6 to 2.3) | 2.4 (2.0 to 2.8) | 1.2 (0.92 to 1.57) | 6.3 (5.0 to 7.8) | 4.0 (3.1 to 5.0) | 0.60 (0.43 to 0.85) |
| Unstable angina | 0.9 (0.7 to 1.2) | 0.6 (0.4 to 0.9) | 0.66 (0.43 to 1.03) | 1.2 (0.7 to 2.0) | 1.4 (0.9 to 2.1) | 1.19 (0.62 to 2.29) |
| Heart failure | 2.9 (2.5 to 3.4) | 2.5 (2.1 to 2.9) | 0.82 (0.64 to 1.03) | 6.6 (5.3 to 8.1) | 4.8 (3.8 to 6.0) | 0.76 (0.56 to 1.05) |
| Peripheral vascular disease | 2.3 (1.9 to 2.7) | 2.2 (1.8 to 2.7) | 0.99 (0.76 to 1.28) | 6.3 (5.0 to 7.8) | 4.2 (4.2 to 5.3) | 0.69 (0.49 to 0.96) |

Data are presented with 95% confidence intervals. CVD, cardiovascular disease.

effects, including nausea, vomiting, and hypocalcemia, when determining the optimal approach to the treatment of sHPT in all patients on dialysis.

Acknowledgments

The Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial was funded by Amgen.

The EVOLVE investigators are as follows: *Argentina*: J. Santos, C. Najun Zarazaga, I. Marin, N. Garrote, A. Cusumano, N. Peñalba, E. Del Valle, L. Juncos, J. Martinez Saye, L. Lef, V. Altobelli, G. Petraglia, G. Rosa Diez, W. Douthat, J. Lobo, C. Gallart, A. Lafalla, G. Diez, B. Linares, N. Lopez, N. Ramirez, R. Gonzalez, R. Valtuille, H. Beresan, O. Hermida, G. Rudolf, N. Marchetta, M. Rano, M. Ramirez, and N. García; *Australia*: A. Gillies, B. Jones, E. Pedagogos, R. Walker, G. Talaulikar, K. Bannister, M. Suranyi, A. Kark, S. Roger, P. Kerr, A. Disney, P. Mount, M. Fraenkel, M. Mathew, R. Fassett, M. Jose, C. Hawley, M. Lonergan, J. Mackie, P. Ferrari, S. Menahem, J. Sabto, B. Hutchison, R. Langham, and C. Pollock; *Austria*: H. Holzer, R. Oberbauer, I. Arias, H. Graf, G. Mayer, K. Lhotta, U. Neyer, R. Klausner, W. Hoerl, S. Horn, J. Kovarik, R. Kramar, and M. Eigner; *Belgium*: M. Dhaene, J. Billiouw, J. De Meester, X. Warling, P. Cambier-Dwelschauwers, P. Evenepoel, R. Daelemans, M. Dratwa, B. Maes, J. Stolear, T. Dejagere, J. Vanwallegem, K. Bouman, M. Jadoul, J. Peeters, R. Vanholder, C. Tielemans, and J. Donck; *Brazil*: F. Almeida, J. Picollo de Oliveira, E. Burdmann, V. Garcia, F. Saldanha Thome, L. Deboni, R. Bregman, J. Lugon, S. Araújo, S. Ferreira Filho, E. de Francesco Daher, M. Sperto Baptista, A. Carvalho, D. d'Avila, M. Moyses Neto, L. Yu, M. Bastos, P. Sampaio Lacativa, V. Jorgetti, E. de Almeida Romão, J. Cardeal da Costa, R. Pecoits Filho, P. Gordan, N. Salgado, M. Teixeira Araújo, S. Neiva Coelho, I. Oliveira, R. Moyses, L. Vasconcellos, P. Batista, J. Luiz Gross, and A. Pedrosa; *Canada*: S. Cournoyer, M. LeBlanc, S. Chow, S. Karunakaran, G. Wong, S. Tobe, S. Desmeules, D. Zimmerman, S. Murphy, P. Montambault, S. Donnelly, J. MacRae, B. Culleton, S. Soroka, C. Rabbat, K. Jindal, M. Vasilevsky, M. Michaud, E. Wijeyesinghe, J. Zacharias, C. Lok, N. Muirhead, M. Verrelli, G. Da Roza, and D. Sapir; *Denmark*: K. Olgaard, H. Daugaard, L. Brandt, and P. Jensen; *France*: H. Boulechfar, K. Ang, P. Simon, P. Rieu, P. Brunet, G. Touchard, G. London, P. Urena Torres, C. Combe, A. Durrbach, J. Ortiz, T. Hannedouche, C. Vela, A. Lionet, P. Ryckelynck, P. Zaoui, G. Choukroun, H. Fessi, P. Lang, P. Stroumza, D. Joly, C. Mousson, and M. Laville; *Germany*: F. Dellanna, C. Erley, J. Braun, M. Rambausek, W. Riegel, M. Klingberg, E. Schwertfeger, V. Wizemann, K. Eckardt, H. Reichel, J. Floege, J. Passauer, E. Hübel, N. Frischmuth, R. Liebl, R. Fiedler, V. Schwenger, A. Voßkübler, U. Kunzendorf, L. Renders, D. Rattensberger, L. Rump, M. Ketteler, H. Neumayer, F. Zantvoort, and R. Stahl; *Hungary*: E. Ladanyi, I. Kulcsar, I. Mezei, B. Csiky, C. Rikker, O. Arkossy, K. Berta, J. Szegedi, L. Major, S. Ferenczi, A. Fekete, T. Szabo, G. Zakar, G. Wagner, S. Kazup Erdelyine, and B. Borbas; *Ireland*: J. Eustace and D. Reddan; *Italy*: G. Capasso, F. Locatelli, G. Villa, M. Cozzolino, D. Brancaccio, P. Messa, P. Bolasco, B. Ricciardi, F. Malberti, E. Moriero, G. Cannella, V. Ortalda, S. Stefoni, G. Frascà, G. Cappelli, A. Albertazzi, C. Zoccali, M. Farina, A. Elli, F. Avella, P. Ondeï, G. Mingardi, R. Errico, A. Losito, S. Di Giulio, G. Pertosa, F. Schena, G. Grandaliano, L. Gesualdo, and M. Auricchio; *Mexico*: T. Bochicchio-Ricardelli, R. Correa-Rotter, F. Aranda Verástegui, J. Peña, A. Chew Wong, J. Cruz-Valdez, M. Torres Zamora, M. Solis, M. Sebastian Diaz, M. Vital Flores, and E. Alvarez Sandoval; *The Netherlands*: M. van den Dorpel, H. Brink, W. Van Kuijk, C. Vermeij, P. Smak Gregoor, E. Hagen, and F. van der Sande; *Poland*: M. Klinger, M. Nowicki, M. Muszytowski, K. Bidas, W. Bentkowski, A. Wiecek, A. Ksiazek, K. Marczywski, M. Ostrowski, M. Switalski, W. Sulowicz, J. Matuszkiewicz-Rowinska, M. Mysliwiec, M. Durlik, and B. Rutkowski; *Portugal*: F. Macario, B.

Carvalho, J. Frazao, D. Machado, and A. Weigert; *Russia*: A. Andrushev, O. Khurstalev, A. Zemtchenkov, K. Gurevich, K. Staroselsky, N. Khadikova, L. Rozhinskaya, G. Timokhovskaya, A. Stokov, O. Balkarova, V. Ermolenko, E. Kolmakova, M. Komandenko, M. Timofeev, V. Shilo, G. Shostka, A. Smirnov, V. Anashkin, G. Volgina, O. Domashenko, A. Gurevich, and D. Perlin; *Spain*: J. Martínez García, E. Andrés Ribes, E. Coll Piera, M. Fernandez Lucas, M. Galicia, M. Prados, M. González, R. Romero, Á. Martín de Francisco, J. Montenegro, C. Santiago, F. García, J. Alcázar de La Ossa, J. Arrieta, J. Pons, A. Martín-Malo, J. Soler Amigó, and A. Cases; *Sweden*: G. Sterner, G. Jensen, B. Wikström, S. Jacobson, U. Lund, L. Weiss, and A. Ståhl; *Switzerland*: B. von Albertini, M. Burnier, P. Meier, P. Martin, D. Uehlinger, and M. Dickenmann; *United Kingdom*: M. Yaqoob, D. Zehnder, P. Kalra, D. Wheeler, N. Padmanabhan, S. Roe, D. Eadington, N. Pritchard, A. Hutchison, S. Davies, M. Wilkie, M. Davies, P. Pai, P. Swift, J. Kwan, D. Goldsmith, C. Tomson, J. Stratton, and I. Dasgupta; and *United States*: S. Sarkar, M. Moustafa, K. Gandhi, A. Jamal, E. Galindo-Ramos, J. Tuazon, D. Battle, K. Tucker, B. Schiller-Moran, A. Assefi, C. Martinez, L. Samuels, J. Goldman, J. Cangiano-Rivera, R. Darwish, M. Lee, J. Topf, K. Kapatkin, H. Baer, R. Kopelman, M. Acharya, D. Tharpe, M. Bernardo, P. Nader, J. Guzman-Rivera, P. Pergola, M. Sekkarie, E. Alas, P. Zager, K. Liss, J. Navarro, M. Roppolo, C. Denu-Ciocca, A. Kshirsagar, M. El Khatib, K. Kant, D. Scott, B. Murthy, F. Finkelstein, G. Keightley, R. McCrary, J. Pitone, T. Cavalieri, A. Tsang, B. Pellegrino, R. Schmidt, S. Ahmad, C. Brown, E. Friedman, N. Mittman, S. Fadem, W. Shapiro, M. Reddy, S. Goldberger, Y. Woredekal, A. Agarwal, M. Anger, M. Haque, P. Chidester, R. Kohli, S. Rubinstein, G. Newman, R. Gladish, O. Ayodeji, S. Soman, S. Sprague, N. Hunt, T. Gehr, D. Rizk, D. Warnock, D. Polack, M. Pahl, D. Fischer, P. Dreyer, G. James, F. Husserl, T. Rogers, A. Raff, J. Sedor, M. Silver, M. Smith, S. Steinberg, T. DelGiorno, E. Jones, P. D Cunha, J. Cheng, V. Pogue, G. Block, S. Blumenthal, E. Brown, C. Charytan, J. Buerkert, M. Cook, A. Felsenfeld, N. Tareen, A. Gupta, T. Herman, S. Diamond, C. Hura, M. Laski, J. MacLaurin, T. Plumb, G. Brosnahan, J. Kumar, M. Henriquez, C. Poole, E. Osanloo, A. Matalon, C. Sholer, S. Arfeen, M. Azer, M. Belledonne, M. Gross, E. Dunnigan, K. McConnell, B. Becker, F. Skinner, R. Rigolosi, D. Spiegel, M. Stegman, R. Patak, D. Streja, U. Ranjit, T. Youell, T. Wooldridge, C. Stafford, R. Cottiero, M. Weinberg, M. Schonefeld, E. Shahmir, A. Hazzan, A. Ashfaq, K. Bhandari, W. Cleveland, M. Culpepper, J. Golden, L. Lai, Y. Lien, V. Lorica, J. Robertson, K. Malireddi, S. Morse, V. Thakur, A. Israelit, P. Raguram, H. Alfred, W. Weise, F. Al-Saghir, M. El Shahawy, A. Rastogi, A. Nissenson, N. Kopyt, R. Lynn, J. Lea, W. McClellan, P. Teredesai, S. Ong, S. Tolkan, J. Sugihara, T. Minga, R. Mehrotra, R. Minasian, D. Bhatia, R. Specter, J. Capelli, P. Sidhu, S. Dalal, P. Dykes, M. Khan, F. Rahim, M. Saklayen, A. Thomas, B. Michael, M. Torres, H. Al-Bander, B. Murray, A. Abukurah, B. Gupta, S. Nosrati, R. Raja, S. Zeig, M. Braun, A. Amatyia, J. Endsley, Z. Sharon, A. Gupta, G. Dolson, F. Dumler, K. Ntoso, S. Rosansky, N. Kumar, V. Gura, N. Thompson, D. Goldfarb, R. Halligan, J. Middleton, A. Widerhorn, L. Arbeit, J. Arruda, T. Crouch, L. Friedman, S. Khokhar, J. Mittleman, P. Light, B. Taparia, C. West, J. Cotton, R. Dhingra, L. Kleinman, F. Arif, S. Lew, T. Nammour, J. Sterrett, M. Williams, J. Ramirez, J. Rubin, J. McCarthy, S. Noble, M. Chaffin, and A. Rekhi.

Disclosures

All authors have completed and submitted the International Committee of Medical Journal Editors Form for Disclosure of Potential Conflicts of Interest. The members of the Writing Committee affiliated with academic institutions received a stipend from Amgen while serving on the Executive Committee of EVOLVE. B.D. and Y.K. are employees of Amgen; W.G.G. was previously an employee of Amgen.

References

- Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, Collins AJ: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 16: 489–495, 2005
- Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32 [Suppl 3]: S112–S119, 1998
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 76: S1–S130, 2009
- London GM, Guérin AP, Marchais SJ, Métivier F, Pannier B, Adda H: Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 18: 1731–1740, 2003
- London GM: Mechanisms of arterial calcifications and consequences for cardiovascular function. *Kidney Int Suppl* (2011) 3: 442–445, 2013
- Torres PA, De Broe M: Calcium-sensing receptor, calcimimetics, and cardiovascular calcifications in chronic kidney disease. *Kidney Int* 82: 19–25, 2012
- Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Hercz G, Cunningham J, Abu-Alfa AK, Messa P, Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCary LC, Zani VJ, Olson KA, Drüeke TB, Goodman WG: Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 350: 1516–1525, 2004
- Ivanovski O, Nikolov IG, Joki N, Caudrillier A, Phan O, Mentaverri R, Maizel J, Hamada Y, Nguyen-Khoa T, Fukagawa M, Kamel S, Lacour B, Drüeke TB, Massy ZA: The calcimimetic R-568 retards uremia-enhanced vascular calcification and atherosclerosis in apolipoprotein E deficient (apoE^{-/-}) mice. *Atherosclerosis* 205: 55–62, 2009
- Koleganova N, Piecha G, Ritz E, Schmitt CP, Gross ML: A calcimimetic (R-568), but not calcitriol, prevents vascular remodeling in uremia. *Kidney Int* 75: 60–71, 2009
- Hénaut L, Boudot C, Massy ZA, Lopez-Fernandez I, Dupont S, Mary A, Drüeke TB, Kamel S, Brazier M, Mentaverri R: Calcimimetics increase CaSR expression and reduce mineralization in vascular smooth muscle cells: Mechanisms of action. *Cardiovasc Res* 101: 256–265, 2014
- Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, Moustafa M, Goodman WG, Lopez N, Downey G, Dehmel B, Floege J; ADVANCE Study Group: The ADVANCE study: A randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant* 26: 1327–1339, 2011
- Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Trotman ML, Wheeler DC, Parfrey PS; EVOLVE Trial Investigators: Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 367: 2482–2494, 2012
- Parfrey PS, Chertow GM, Block GA, Correa-Rotter R, Drüeke TB, Floege J, Herzog CA, London GM, Mahaffey KW, Moe SM, Wheeler DC, Dehmel B, Trotman ML, Modafferi DM, Goodman WG: The clinical course of treated hyperparathyroidism among patients receiving hemodialysis and the effect of cinacalcet: The EVOLVE trial. *J Clin Endocrinol Metab* 98: 4834–4844, 2013
- Chertow GM, Pupim LB, Block GA, Correa-Rotter R, Drueke TB, Floege J, Goodman WG, London GM, Mahaffey KW, Moe SM, Wheeler DC, Albizem M, Olson K, Klassen P, Parfrey P: Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): rationale and design overview. *Clin J Am Soc Nephrol* 2: 898–905, 2007
- Chertow GM, Correa-Rotter R, Block GA, Drueke TB, Floege J, Goodman WG, Herzog CA, Kubo Y, London GM, Mahaffey KW, Mix TC, Moe SM, Wheeler DC, Parfrey PS: Baseline characteristics of subjects enrolled in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial. *Nephrol Dial Transplant* 27: 2872–2879, 2012
- Chen NX, Moe SM: Vascular calcification: Pathophysiology and risk factors. *Curr Hypertens Rep* 14: 228–237, 2012
- Schwarz U, Buzello M, Ritz E, Stein G, Raabe G, Wiest G, Mall G, Amann K: Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. *Nephrol Dial Transplant* 15: 218–223, 2000
- Gross ML, Meyer HP, Ziebart H, Rieger P, Wenzel U, Amann K, Berger I, Adamczak M, Schirmacher P, Ritz E: Calcification of coronary intima and media: Immunohistochemistry, backscatter imaging, and x-ray analysis in renal and nonrenal patients. *Clin J Am Soc Nephrol* 2: 121–134, 2007
- Hassan NA, D'Orsi ET, D'Orsi CJ, O'Neill WC: The risk for medial arterial calcification in CKD. *Clin J Am Soc Nephrol* 7: 275–279, 2012
- Jean G, Bresson E, Terrat JC, Vanel T, Hurot JM, Lorriaux C, Mayor B, Chazot C: Peripheral vascular calcification in long-haemodialysis patients: Associated factors and survival consequences. *Nephrol Dial Transplant* 24: 948–955, 2009
- London GM, Marchais SJ, Guérin AP, Boutouyrie P, Métivier F, de Vernejoul M-C: Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. *J Am Soc Nephrol* 19: 1827–1835, 2008
- Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F, Bala MM, Bassler D, Mertz D, Diaz-Granados N, Vandvik PO, Malaga G, Srinathan SK, Dahm P, Johnston BC, Alonso-Coello P, Hassouneh B, Walter SD, Heels-Ansdell D, Bhatnagar N, Altman DG, Guyatt GH: Credibility of claims of subgroup effects in randomised controlled trials: systematic review. *BMJ* 344: e1553, 2012
- Suki WN, Zabaneh R, Cangiano JL, Reed J, Fischer D, Garrett L, Ling BN, Chasan-Taber S, Dillon MA, Blair AT, Burke SK: Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 72: 1130–1137, 2007

Received: August 2, 2014 Accepted: January 20, 2015

Published online ahead of print. Publication date available at www.cjasn.org.

This article contains supplemental material online at <http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.07730814/-/DCSupplemental>.