The Effect of Cinacalcet on Calcific Uremic Arteriolopathy Events in Patients Receiving Hemodialysis: The EVOLVE Trial

Jürgen Floege,* Yumi Kubo,† Anna Floege,* Glenn M. Chertow,‡ and Patrick S. Parfrey§

Abstract
Background and objectives Uncontrolled secondary hyperparathyroidism (sHPT) in patients with ESRD is a risk factor for calcific uremic arteriolopathy (CUA; calciphylaxis).

Design, setting, participants, & measurements Adverse event reports collected during the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events trial were used to determine the frequency of CUA in patients receiving hemodialysis who had moderate to severe sHPT, as well as the effects of cinacalcet versus placebo. CUA events were collected while patients were receiving the study drug.

Results Among the 3861 trial patients who received at least one dose of the study drug, 18 patients randomly assigned to placebo and six assigned to cinacalcet developed CUA (unadjusted relative hazard, 0.31; 95% confidence interval [95% CI], 0.13 to 0.79; P=0.014). Corresponding cumulative event rates (95% CI) at year 4 were 0.011% (0.006% to 0.018%) and 0.005% (0.002% to 0.010%). By multivariable analysis, other factors associated with CUA included female sex, higher body mass index, higher diastolic BP, and history of dyslipidemia or parathyroidectomy. Median (10%, 90% percentile) plasma parathyroid hormone concentrations proximal to the report of CUA were 796 (225, 2093) pg/ml and 410 (71, 4957) pg/ml in patients randomly assigned to placebo and cinacalcet, respectively. Active use of vitamin K antagonists was recorded in 11 of 24 patients with CUA, nine randomly assigned to placebo, and two to cinacalcet.

Conclusion Cinacalcet appeared to reduce the incidence of CUA in hemodialysis recipients who have moderate to severe sHPT.


Introduction
Calcific uremic arteriolopathy (CUA), often referred to as calciphylaxis, is a relatively rare syndrome, which carries a 1-year survival rate of only 45% (1–5). The central pathologic lesion in CUA is a calcified media of small and medium-sized arterial vessels of the skin and fat tissue, leading to progressive and extremely painful cutaneous ulcerations (1–5). Infections of such skin lesions represent the main reason for the high mortality of CUA (1–5). CUA rarely manifests in patients with normal kidney function (6), and most cases are confined to patients with advanced CKD and in particular ESRD (1). The exact prevalence of CUA in the dialysis population is unknown; estimates range from 1% to 4% of all patients with ESRD (7–9).

The pathogenesis of CUA is incompletely understood. Recent data suggest that CUA involves a cell-mediated, bone morphogenetic protein-2-driven osteogenic process with extensive subcutaneous extra-cellular matrix remodeling and deposition of hydroxypatite (10). A cascade consisting of matrix remodeling, calcification, endothelial damage and thrombus formation, luminal obstruction, and finally development of full-blown CUA has been postulated (10). Risk factors for CUA identified in clinical studies include CKD/ESRD, female sex, diabetes mellitus, obesity, and vitamin K antagonism (3–5,11,12). With respect to mineral bone disorders in CKD/ESRD, CUA prevalence is higher in patients with hyperphosphatemia and those receiving calcium-containing phosphate binders (3–5). Both low-turnover bone disease in ESRD and high-turnover bone disease associated with severe secondary hyperparathyroidism (sHPT) have been associated with CUA (13,14).

At present it is unknown whether specific therapies that decrease excessive parathyroid hormone (PTH) concentrations raise or lower the incidence of CUA. In the current analysis, we aimed to confirm or refute known risk factors for CUA and to test the hypothesis that a reduction in PTH with cinacalcet reduces the frequency of CUA in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial (www.ClinicalTrials.gov registration number: NCT00345839) (15,16).
Materials and Methods

Study Population and Design

In the EVOLVE trial, 3883 patients with sHPT receiving hemodialysis were randomly assigned 1:1 to receive cinacalcet (Sensipar or Mimpara, Amgen, Inc.) or placebo in addition to conventional therapies for CKD–mineral and bone disorder. Eligible participants were undergoing hemodialysis three times per week and had 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). The dose of study drug was titrated 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 (17). The dialysis prescription, type/doses of phosphate binders, vitamin D sterols, calcium supplements and other medications, and other medical procedures were administered at the discretion of treating physicians. The trial assessed the effect of treatment with cinacalcet compared with placebo in addition to other conventional therapies (calcitriol or vitamin D sterols and phosphate binders) on the primary composite endpoint of all-cause mortality and major cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event). The study design, baseline characteristics of the participants, primary results, and effect of cinacalcet on severe unremitting hyperparathyroidism have been previously published (15–18). The intervention lasted up to 64 months. The trial was sponsored by Amgen, Inc. An academic Executive Committee with direct oversight of all final analyses and publications led the trial. The ethics committees at all participating sites approved the study, and all patients provided informed consent.

All adverse events, including CUA, were collected while patients were receiving the study drug. In contrast to the components of the primary composite outcome and selected secondary outcomes (i.e., stroke, parathyroidectomy, and clinical fracture), CUA adverse events were not adjudicated. The estimated incidence of CUA was based on the report of local investigators and was not necessarily confirmed by biopsy or other means. All demographic and laboratory data analyzed were collected as part of the primary study (15,16).

Statistical Analyses

All randomly assigned patients who received at least one dose of the study drug (n=3861; the safety analysis set) were included in these analyses. All CUA cases that occurred during the adverse event reporting period were reviewed and included. The observation period was from the first dose date of the study drug to initial CUA, excluding the time adverse events were not collected as per the protocol. A two-sided Gray test was used to compare the cumulative incidence function estimates of the survival time between the treatment groups. Fine-Gray subdistributional hazards regression models were used to calculate the relative hazard (cinacalcet versus placebo) and 95% confidence intervals (95% CIs). We performed unadjusted and multivariable analyses. The multivariable analysis was adjusted for baseline covariates using a backward selection procedure at a significance level of 0.10. Potential covariates included baseline patient and demographic characteristics, concomitant medication use, cardiovascular history, and laboratory measures. Because findings in the primary analysis of the EVOLVE trial (determining the effect of cinacalcet versus placebo on the primary composite endpoint through use of an unadjusted intention-to-treat analysis) were not statistically significant, analysis results with a P value <0.05 were deemed nominally statistically significant. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

Figure 1. | Cumulative incidence plot of time to calcific uremic arteriolopathy adverse event (safety analysis set).
Table 1. Key baseline demographic and medical history characteristics by occurrence of calcific uremic arteriolopathy adverse event during the study (safety analysis set)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CUA (n=24)</th>
<th>No CUA (n=3837)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=18)</td>
<td>Cinacalcet (N=6)</td>
<td>Total (N=24)</td>
</tr>
<tr>
<td>Median age (10%, 90% percentile) (yr)</td>
<td>54.5 (43.0, 71.0)</td>
<td>59.5 (32.0, 63.0)</td>
<td>56.0 (43.0, 63.0)</td>
</tr>
<tr>
<td>Age category, n (%)</td>
<td>16 (88.9)</td>
<td>6 (100)</td>
<td>22 (91.7)</td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>2 (11.1)</td>
<td>0 (0.0)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>11 (61.1)</td>
<td>4 (66.7)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Race group, n (%)</td>
<td>6 (100)</td>
<td>1 (16.7)</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>White</td>
<td>1 (16.7)</td>
<td>2 (33.3)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Black</td>
<td>9 (33.3)</td>
<td>1 (16.7)</td>
<td>10 (37.0)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (61.1)</td>
<td>4 (66.7)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Median BMI (10%, 90% percentile) (kg/m²)</td>
<td>34.4 (21.7, 43.5)</td>
<td>28.5 (21.3, 37.3)</td>
<td>34.1 (23.1, 41.8)</td>
</tr>
<tr>
<td>BP (10%, 90% percentile) (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>163.0 (120.0, 184.0)</td>
<td>153.5 (137.0, 209.0)</td>
<td>162.5 (137.0, 184.0)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85.0 (67.0, 100.0)</td>
<td>80.0 (72.0, 130.0)</td>
<td>83.0 (70.0, 100.0)</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>6 (33.3)</td>
<td>3 (50.0)</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Current</td>
<td>3 (16.7)</td>
<td>1 (16.7)</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Former</td>
<td>9 (50.0)</td>
<td>2 (33.3)</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Type 2</td>
<td>11 (61.1)</td>
<td>2 (33.3)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>History of cardiovascular disease, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (100)</td>
<td>6 (100)</td>
<td>24 (100)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9 (50.0)</td>
<td>2 (33.3)</td>
<td>11 (45.8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>8 (44.4)</td>
<td>0 (0.0)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>CABG</td>
<td>1 (5.6)</td>
<td>2 (33.3)</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>PCI</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (5.6)</td>
<td>1 (16.7)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1 (5.6)</td>
<td>0 (0.0)</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Amputation</td>
<td>2 (11.1)</td>
<td>0 (0.0)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (22.2)</td>
<td>0 (0.0)</td>
<td>4 (16.7)</td>
</tr>
</tbody>
</table>
Results
CUA Incidence
Among the 3861 trial patients who received at least one dose of study drug, 24 patients developed CUA: 18 patients randomly assigned to placebo and six patients assigned to cinacalcet (unadjusted relative hazard, 0.31; 95% CI, 0.13 to 0.79; \( P = 0.014 \)). The median (10%, 90% percentile) time to CUA was 1.3 (0.2, 4.5) years in patients randomly assigned to placebo and 1.8 (0.9, 3.1) years in patients assigned to cinacalcet. Corresponding cumulative event rates (95% CI) at year 4 were 0.011% (0.006% to 0.018%) and 0.005% (0.002% to 0.010%), respectively (Figure 1).

Baseline Characteristics
Table 1 shows baseline characteristics of patients who were reported to have developed CUA and those of all other trial participants. Compared with the latter, patients who developed CUA were more likely to be younger and female; to have a higher Quételet (body mass) index (BMI); to have hypertension, diabetes mellitus, and/or dyslipidemia; and to have had a history of heart failure, peripheral vascular disease, or prior parathyroidectomy (with severe enough recurrence of sHPT to meet the trial inclusion criteria). In contrast, ethnicity, region of origin, dialysis vintage, dialysis access, dialysate calcium, tobacco use, history of fractures or coronary artery disease, and baseline laboratory values were not associated with CUA (Table 2).

Laboratory Findings Immediately Before CUA Manifestation
Laboratory findings most proximal to the reporting of CUA are shown in Table 3. Median (10%, 90% percentiles) plasma intact PTH at the time of CUA was 796 (225, 2093) pg/ml and 410 (71, 4957) pg/ml in patients randomly assigned to placebo and cinacalcet, respectively. Corresponding total serum calcium concentrations were 9.8 (8.5, 10.6) mg/dl and 9.7 (8.0, 11.6) mg/dl, respectively. Corresponding serum phosphate concentrations were 5.8 (4.5, 8.1) mg/dl and 6.3 (3.4, 10.2) mg/dl, and alkaline phosphatase values were 98 (67, 148) U/L and 190 (65, 648) U/L.

Concomitant Medications Immediately before CUA Manifestation
Table 4 shows the use of concomitant medications in patients reported to have developed CUA. Only one of 18 patients with CUA in the placebo group had received commercial cinacalcet (single 30-mg dose at 5 months before the onset of CUA). Vitamin K antagonists were actively prescribed in 11 of 24 (46%) patients with CUA: nine among those assigned to placebo and two among those assigned to cinacalcet. Four of 24 (17%) patients were receiving vitamin K antagonists at baseline; others started vitamin K antagonists during the trial. In contrast, among patients not developing CUA, vitamin K antagonist prescription ranged from 7.4% (284 of 3837 patients) at study year 1 to 5.1% (196 of 3837 patients) at study year 3. Because we did not collect complete data on concomitant medication use throughout the trial, we cannot be certain which patients were prescribed vitamin K antagonists and, if so, when during the trial. Thus, we could not include this variable in the regression model. Among patients diagnosed with CUA, data on vitamin K antagonist use were obtained from direct review of medical records.

<table>
<thead>
<tr>
<th>Table 1. (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>History of parathyroidectomy, n (%)</td>
</tr>
<tr>
<td>History of dyslipidemia, n (%)</td>
</tr>
</tbody>
</table>

\( N_1 \) refers to number of patients in the safety analysis set; \( \% \) percentages are based on \( N_1 \). CUA, calcific uremic arteriolopathy; BMI, body mass index; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CUA (n=25)</th>
<th>No CUA (n=3858)</th>
<th>( P ) Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N&lt;sub&gt;2&lt;/sub&gt;=19)</td>
<td>Cinacalcet (N&lt;sub&gt;2&lt;/sub&gt;=6)</td>
<td>Total (N&lt;sub&gt;2&lt;/sub&gt;=25)</td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>515 (285, 1339)</td>
<td>857 (344, 2755)</td>
<td>579 (333, 2121)</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl)</td>
<td>9.9 (9.0, 10.6)</td>
<td>10.5 (9.7, 10.8)</td>
<td>10.1 (9.5, 10.6)</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>6.4 (4.6, 9.5)</td>
<td>6.6 (4.8, 8.2)</td>
<td>6.4 (4.8, 8.8)</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>14.5 (6.38)</td>
<td>20.5 (14.26)</td>
<td>15.8 (8.28)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>91 (59, 151)</td>
<td>129 (59, 590)</td>
<td>91 (59, 166)</td>
</tr>
<tr>
<td>Bone alkaline phosphatase (µg/L)</td>
<td>17.53 (9.6, 32.89)</td>
<td>31.51 (10.29, 139.66)</td>
<td>20.96 (10.21, 38.2)</td>
</tr>
<tr>
<td>N-telopeptide (nmol/L)</td>
<td>141.6 (45.6, 280.4)</td>
<td>620.9 (134.4, 1414.1)</td>
<td>196.2 (52.8, 692.8)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.9 (8.4, 13.2)</td>
<td>11.7 (9.1, 12.7)</td>
<td>11.7 (9.1, 12.7)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.6 (3.1, 4.0)</td>
<td>3.5 (3.3, 4.2)</td>
<td>3.6 (3.3, 4.0)</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>7.0 (6.2, 7.7)</td>
<td>6.8 (5.8, 7.1)</td>
<td>6.9 (6.2, 7.5)</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>18.8 (14.4, 26.0)</td>
<td>23.3 (18.9, 24.9)</td>
<td>19.3 (14.7, 24.9)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>9.7 (4.7, 13.6)</td>
<td>10.9 (7.7, 12.8)</td>
<td>10.0 (6.4, 13.2)</td>
</tr>
</tbody>
</table>

Values are expressed as median (10%, 90% percentile). \( N_2 \) refers to number of patients in the safety analysis set; \( n \) percentages are based on \( N_2 \). CUA, calcific uremic arteriolopathy; PTH, parathyroid hormone; 25(OH)D, 1,25-dihydroxyvitamin D.

<sup>a</sup>Wilcoxon rank-sum test was used for continuous variables and chi-square test was used for categorical variables. Comparisons are between patients who experienced a CUA adverse event compared with those who did not.
Risk Factors for CUA
After adjustment for baseline characteristics, the relative hazard (cinacalcet versus placebo) was 0.25 (95% CI, 0.10 to 0.67). Baseline factors independently associated with a higher rate of CUA included random assignment to placebo, female sex, higher BMI, higher diastolic BP, history of dyslipidemia, history of parathyroidectomy, and former tobacco use (Table 5).

Discussion
Within the EVOLVE trial, 24 of 3861 enrolled patients who received at least one dose of the study drug developed CUA. The overall exposure-adjusted rate of 0.3 per 100 patient-years in our total population is relatively low. In the literature, a prevalence of 1%–4% was reported among nonselected patients receiving maintenance dialysis (1,3,19). It is unlikely that CUA was substantially underreported, given the severity of the diagnosis. Rather, our data suggest that the CUA risk in our selected population of relatively young patients with advanced shPT may be lower than that of a nonselected maintenance hemodialysis population.

Our central observation was that a cinacalcet-based therapeutic regimen in hemodialysis patients with advanced shPT reduced CUA incidence by 69%–75%, considering unadjusted or adjusted data, respectively. This observation makes EVOLVE the first randomized controlled trial of this intervention to show a reduced risk of CUA. To date, the therapeutic approach undertaken to prevent or ameliorate CUA has been deduced from case-control studies that identified risk factors for CUA in patients with ESRD, including hyperphosphatemia, peritoneal dialysis (rather than hemodialysis), diabetes mellitus, obesity, and the use of vitamin K antagonists (3–5,11,12).

The role of shPT in the pathogenesis of CUA is not well understood. In some cases with extremely high plasma PTH concentrations, subtotal or total parathyroidectomy was effective in ameliorating CUA (1). In other reports, lower levels of PTH (“oversuppression”) which are associated with low bone turnover, were also associated with CUA (1). In the EVOLVE population, a relatively young group of patients with moderate to severe shPT, cinacalcet therapy appeared to reduce the risk of CUA. Among patients randomly assigned to placebo (in other words, patients

### Table 3. Laboratory values before onset of calcific uremic arteriolopathy adverse event

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=18)</th>
<th>Cinacalcet (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>796 (225, 2093)</td>
<td>410 (71, 4957)</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>9.8 (8.5, 10.6)</td>
<td>9.7 (8.0, 11.6)</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>5.8 (4.5, 8.1)</td>
<td>6.3 (3.4, 10.2)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>98 (67, 148)</td>
<td>190 (65, 648)</td>
</tr>
<tr>
<td>Bone alkaline phosphatase (µg/L)</td>
<td>15.56 (7.97, 33.62)</td>
<td>44.01 (15.97, 188.97)</td>
</tr>
<tr>
<td>N-telopeptide (nmol/L)</td>
<td>205.2 (36.8, 490.5)</td>
<td>491.4 (109.9, 1471.4)</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.4 (8.3, 13.2)</td>
<td>11.6 (6.7, 15.1)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.4 (2.7, 3.8)</td>
<td>3.2 (2.8, 4.1)</td>
</tr>
<tr>
<td>Total protein (g/dl)</td>
<td>6.9 (6.4, 7.9)</td>
<td>6.9 (5.9, 7.3)</td>
</tr>
</tbody>
</table>

Values are expressed as median (10%, 90% percentile). PTH, parathyroid hormone.

### Table 4. Concomitant medication use before onset of calcific uremic arteriolopathy adverse event

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=18)</th>
<th>Cinacalcet (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D sterol use (%)</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>Median IV paricalcitol-equivalent dose (10%, 90% percentile) (µg/wk)</td>
<td>15 (6, 24)</td>
<td>10 (5, 45)</td>
</tr>
<tr>
<td>Phosphate binder use (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Calcium-containing phosphate binder use (%)</td>
<td>67</td>
<td>83</td>
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<tr>
<td><strong>Study drug dose</strong></td>
<td></td>
<td></td>
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<tr>
<td>Patients (n)</td>
<td>N/A</td>
<td>5</td>
</tr>
<tr>
<td>Median dose (10%, 90% percentile) (mg/d)</td>
<td>30 (30, 180)</td>
<td></td>
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<tr>
<td><strong>Commercial cinacalcet dose</strong></td>
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<td></td>
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<tr>
<td>Patients (n)</td>
<td>1</td>
<td>NA</td>
</tr>
<tr>
<td>Median dose (10%, 90% percentile) (mg/d)</td>
<td>30a</td>
<td>NA</td>
</tr>
<tr>
<td>Statin use (%)</td>
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<td>100</td>
</tr>
<tr>
<td>Warfarin or other oral anti-coagulant use (%)</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Erythropoietin agents (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Iron use (%)</td>
<td>78</td>
<td>83</td>
</tr>
</tbody>
</table>

*aSingle dose at 5 months before calcific uremic arteriolopathy onset.

n refers to number of patients in the safety analysis set. Percentages are based on n. IV, intravenous; N/A, not available.
In summary, upon carefully examining safety/adverse event data from the EVOLVE trial, the largest and longest randomized clinical trial conducted in the hemodialysis population, we confirmed important associations among a variety of known risk factors for CUA, including diabetes mellitus, obesity, and the use of vitamin K antagonists. We also found a 69%–75% risk reduction in CUA among patients randomly assigned to cinacalcet, the first suggestion from a prospective trial that any therapeutic strategy could reduce the risk of CUA.

Acknowledgments
This study was supported by Amgen, Inc., Thousand Oaks, CA.
Disclosures

As Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events executive committee members, J.F., G.M.C., and P.S.P. have received consulting fees from Amgen. Y.K. is employed by and owns stock in Amgen. In addition, J.F. has received consulting fees, travel support, or lecture fees from Amgen, Abbott, Fresenius Medical Care, Genzyme, Chugai Pharmaceuticals, and Boehringer Ingelheim and royalties from Elsevier. P.S.P. has received lecture support from Amgen; is a board member of Satellite Healthcare, Inc.; has provided consultation to Reata Pharmaceuticals; and owns stock or stock options in Ardelyx, Home Dialysis Plus, Puracath, and Thrasos.

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Received: October 15, 2014 Accepted: February 2, 2015

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