Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

ABSTRACT

BACKGROUND
Disorders of mineral metabolism, including secondary hyperparathyroidism, are thought to contribute to extraskeletal (including vascular) calcification among patients with chronic kidney disease. It has been hypothesized that treatment with the calcimimetic agent cinacalcet might reduce the risk of death or nonfatal cardiovascular events in such patients.

METHODS
In this clinical trial, we randomly assigned 3883 patients with moderate-to-severe secondary hyperparathyroidism (median level of intact parathyroid hormone, 693 pg per milliliter [10th to 90th percentile, 363 to 1694]) who were undergoing hemodialysis to receive either cinacalcet or placebo. All patients were eligible to receive conventional therapy, including phosphate binders, vitamin D sterols, or both. The patients were followed for up to 64 months. The primary composite end point was the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. The primary analysis was performed on the basis of the intention-to-treat principle.

RESULTS
The median duration of study-drug exposure was 21.2 months in the cinacalcet group, versus 17.5 months in the placebo group. The primary composite end point was reached in 938 of 1948 patients (48.2%) in the cinacalcet group and 952 of 1935 patients (49.2%) in the placebo group (relative hazard in the cinacalcet group vs. the placebo group, 0.93; 95% confidence interval, 0.85 to 1.02; P = 0.11). Hypocalcemia and gastrointestinal adverse events were significantly more frequent in patients receiving cinacalcet.

CONCLUSIONS
In an unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis. (Funded by Amgen; EVOLVE ClinicalTrials.gov number, NCT00345839.)

Members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Glenn M. Chertow at Stanford University School of Medicine, 780 Welch Rd., Suite 106, Palo Alto, CA 93034, or at gchertow@stanford.edu.

*Members of the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on November 3, 2012, at NEJM.org.

DOI: 10.1056/NEJMoas1205624
Copyright © 2012 Massachusetts Medical Society.
**CARDIOVASCULAR DISEASE IS VERY COMMON AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE, INCLUDING THOSE TREATED WITH HEMODIALYSIS, AMONG WHOM THE RISK OF DEATH FROM CARDIOVASCULAR DISEASE IS INCREASED BY A FACTOR OF 10 OR MORE AS COMPARED WITH THE RISK IN THE GENERAL POPULATION.** Cardiovascular risk factors that have been linked to chronic kidney disease include heightened states of inflammation, oxidative stress, activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, endothelial dysfunction, retention of uremic toxins promoting atherosclerosis and arteriosclerosis, abnormalities in platelet aggregation, anemia, and disorders of bone and mineral metabolism, including hyperphosphatemia, hypercalcemia, and secondary hyperparathyroidism. In observational studies of patients undergoing dialysis, elevated serum levels of phosphorus, calcium, parathyroid hormone, alkaline phosphatase, and fibroblast growth factor 23 (FGF23) have been associated with death and cardiovascular events. Disorders of mineral metabolism are thought to contribute to arterial calcification and diminished vascular compliance, contributing to myocardial ischemia, heart failure, and sudden death.

Cinacalcet (Sensipar/Mimpara, Amgen), a calcimimetic agent that acts by allosteric activation of the calcium-sensing receptor on parathyroid tissue, was approved for clinical use after its safety and efficacy in lowering levels of parathyroid hormone were shown in multiple randomized, controlled trials; levels of serum calcium and phosphorus were also consistently reduced. In a study that pooled the results of three such trials of cinacalcet with a duration of 6 or more months, Cunningham et al. reported a reduction in the risk of cardiovascular events and fracture and a marked reduction in the rate of parathyroidectomy. The results of one trial suggested that cinacalcet attenuated the progression of vascular and cardiac-valve calcification. We designed the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial to test the hypothesis that treatment with cinacalcet would reduce the risks of death and nonfatal cardiovascular events among patients with secondary hyperparathyroidism who were undergoing dialysis.

**STUDY DESIGN**
In this multicenter, prospective, randomized, placebo-controlled trial, we compared cinacalcet with placebo in 3883 adults undergoing dialysis. All the patients were eligible to receive conventional therapy, including phosphate binders, vitamin D sterols, or both. The study design and the baseline characteristics of the patients have been reported previously. The study was approved by the institutional review board at each participating study site.

Randomization was stratified according to country and diabetes status with the use of fixed blocks. The sponsor, investigators, and patients were unaware of the treatment assignments.

**STUDY POPULATION**
Specific inclusion and exclusion criteria are listed in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Written informed consent was obtained from all patients.

**STUDY INTERVENTION**
After randomization, patients received either cinacalcet or placebo at a starting dose of 30 mg daily. Patients were eligible for dose escalation once every 4 weeks during a 20-week escalation phase (to 60 mg, 90 mg, 120 mg, or 180 mg daily) or every 8 weeks during follow-up, depending on levels of plasma parathyroid hormone and serum calcium. All patients received safety information regarding known risks and side effects of cinacalcet. Dialysis, phosphate binders, vitamin D sterols, calcium supplements, and other medications were prescribed at the discretion of the treating physician, who were encouraged to adhere to published clinical-practice guidelines. Patients underwent laboratory testing, electrocardiography, and assessment of health-related quality of life according to the study design shown in Figure S1 in the Supplementary Appendix.

**STUDY END POINTS**
The primary composite end point was the time to death or the first nonfatal cardiovascular event (myocardial infarction, hospitalization for unsta-
ble angina, heart failure, or a peripheral vascular event), as defined in detail in Table S2 in the Supplementary Appendix. Secondary end points included the time to the individual components of the primary composite end point, death from cardiovascular causes, stroke, bone fracture, and parathyroidectomy. All primary and secondary end points were adjudicated by an independent clinical-events classification group.

**BIOCHEMICAL MEASUREMENTS**

We measured plasma levels of parathyroid hormone and serum levels of calcium and phosphorus in central laboratories periodically throughout the trial. We performed an immunometric assay that detects the full-length peptide hormone along with various N-terminally truncated parathyroid hormone fragments (as captured on intact parathyroid hormone assay).

**STUDY OVERSIGHT**

The study was sponsored by Amgen. An executive committee that was led by academic investigators supervised the trial design and operation, with representatives of Amgen as nonvoting members. An independent data monitoring committee reviewed safety data and interim analyses for efficacy. The sponsor collected the trial data and analyzed them according to a predefined statistical analysis plan. The analyses were verified by independent statisticians at Frontier Science, contracted by Amgen to support the EVOLVE data monitoring committee. The protocol and its amendments are available at NEJM.org.

The lead author wrote the first draft of the manuscript, and all coauthors provided substantive editing and approval. The executive committee made the decision to submit the manuscript for publication and takes full responsibility for the integrity of the data and interpretation of trial results and for the fidelity of this report to the study protocol.

**STATISTICAL ANALYSIS**

We calculated the proposed sample size on the basis of the following assumptions: an annual rate of the primary composite end point of 23.2% in the placebo group, a 20% treatment effect, a 1.5-year enrollment period, a 4-year total study duration, an annual rate of loss to follow-up of 1%, an annual rate of dropout (withdrawal from active treatment before a primary event) of 10% in the cinacalcet group, and a rate of drop-in (use of commercially available cinacalcet before a primary event) of 10% in the placebo group. On the basis of a two-sided log-rank test for equality of survival functions, accounting for planned interim analyses with an overall alpha level of 0.05, we determined that a primary event would need to occur in 1882 patients in order to ensure a power of approximately 90%. After it became apparent that the overall (blinded) event rate was below 20.8%, we extended the trial by 16 months to allow for accrual of the requisite number of events.

We collected and analyzed all end-point data in accordance with the intention-to-treat principle. For the time to the primary event, we computed Kaplan–Meier product-limit estimates of the event-free survival time and compared groups using a two-sided log-rank test stratified according to country and diabetes status. We calculated relative hazards and 95% confidence intervals from Cox proportional-hazards regression models, stratified according to country and diabetes status. We conducted prespecified multivariable analyses in which we adjusted for baseline characteristics. We used a closed-testing procedure to control the family-wise type I error rate at 0.05 between the primary composite end point and the secondary end points. The Hochberg procedure was prespecified to test significance among secondary end points. Since the primary end point was not significant, reported P values should be considered nominal.

We conducted prespecified companion analyses with lag censoring, in which data were censored 6 months after patients stopped using a study drug. We chose 6 months as the anticipated duration of any effect of altered mineral metabolism on extraskeletal calcification. Reasons for discontinuing a study drug before an end point included kidney transplantation, parathyroidectomy, and initiation of commercially available cinacalcet. We conducted companion analyses in which data were censored after these three events, alone or in combination. Finally, we compared event rates for all components of the primary composite end point using negative binomial
regression and analyzed the time to multiple individual cardiovascular events, using the Andersen–Gill extension of the Cox model.

Data on adverse events were collected while patients were taking a study drug. Three prespecified interim analyses were conducted by Frontier Science with the use of intention-to-treat data, with no censoring or adjustment (at approximately 25%, 50%, and 75% of accrued events), resulting in a significance level of 0.044 for the final analysis. Statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute).
RESULTS

PATIENTS

From August 22, 2006, through January 31, 2008, a total of 3883 patients underwent randomization, including 1430 (36.8%) in the United States, 1188 (30.6%) in Europe, 687 (17.7%) in Latin America, 283 (7.3%) in Russia, 149 (3.8%) in Australia, and 146 (3.8%) in Canada (Fig. 1). The trial population was diverse in terms of age, sex, and race or ethnic group; diabetes mellitus and underlying cardiovascular disease were relatively common (Table 1). A detailed description of baseline characteristics is provided in Table 3 in the Supplementary Appendix.

STUDY TREATMENT

The median duration of study-drug exposure was longer in the cinacalcet group than in the placebo group (21.2 months vs. 17.5 months). The daily median dose was 55 mg (10th to 90th percentile, 28 to 130) for cinacalcet and 125 mg (10th to 90th percentile, 43 to 161) for placebo. A total of 80.0% of patients in the placebo group reached the maximum daily dose, as compared with 38.3% of those in the cinacalcet group. Figure 2 shows the cumulative incidence of discontinuation of the study drug. Using the original assumption of a 20% treatment effect, but with the observed study duration and observed rates of events, dropout, and drop-in, which we assumed to be constant, we reestimated the statistical power to be 54%.

Table S4 in the Supplementary Appendix provides additional details about study-drug discontinuation. In the placebo group, 384 of 1935 patients (19.8%) began receiving commercially available cinacalcet before the occurrence of a primary event (corresponding to an annual rate of 7.4%). In the cinacalcet group, 1207 of 1948 patients (62.0%) discontinued the study drug, corresponding to an annual rate of 27.3%. Although study-drug discontinuation was common, only 2.1% of patients were lost to follow-up during the study period of more than 5 years.

INTENTION-TO-TREAT ANALYSIS

Primary Composite End Point

The primary composite end point was reached in 938 of 1948 patients (48.2%) in the cinacalcet group, as compared with 952 of 1935 patients

Table 1. Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cinacalcet (N = 1948)</th>
<th>Placebo (N = 1935)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>55.0</td>
<td>54.0</td>
</tr>
<tr>
<td>10th to 90th percentile</td>
<td>35.0–74.0</td>
<td>35.0–73.0</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>41.5</td>
<td>39.7</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57.7</td>
<td>57.7</td>
</tr>
<tr>
<td>Black</td>
<td>21.0</td>
<td>22.1</td>
</tr>
<tr>
<td>Other</td>
<td>21.3</td>
<td>20.2</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>26.3</td>
<td>26.4</td>
</tr>
<tr>
<td>10th to 90th percentile</td>
<td>20.4–36.4</td>
<td>20.6–36.7</td>
</tr>
<tr>
<td>Duration of dialysis (mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>45.4</td>
<td>45.1</td>
</tr>
<tr>
<td>10th to 90th percentile</td>
<td>8.5–142.0</td>
<td>9.9–149.6</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>140</td>
<td>141</td>
</tr>
<tr>
<td>10th to 90th percentile</td>
<td>110–176</td>
<td>111–177</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>10th to 90th percentile</td>
<td>60–100</td>
<td>60–100</td>
</tr>
<tr>
<td>Medical history (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>33.6</td>
<td>33.5</td>
</tr>
<tr>
<td>Type 1</td>
<td>3.7</td>
<td>4.2</td>
</tr>
<tr>
<td>Type 2</td>
<td>29.8</td>
<td>29.4</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>92.5</td>
<td>91.7</td>
</tr>
<tr>
<td>Heart failure</td>
<td>23.1</td>
<td>23.6</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>16.1</td>
<td>16.6</td>
</tr>
<tr>
<td>Coronary-artery bypass grafting</td>
<td>6.9</td>
<td>8.0</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>6.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12.3</td>
<td>12.6</td>
</tr>
<tr>
<td>Stroke</td>
<td>8.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>5.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Amputation</td>
<td>6.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10.4</td>
<td>11.6</td>
</tr>
</tbody>
</table>

* There were no significant differences between the two groups except for mean diastolic blood pressure (P=0.02) and transient ischemic attack (P<0.05).
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
(49.2%) in the placebo group (relative hazard in the cinacalcet group vs. the placebo group, stratified according to country and diabetes status, 0.93; 95% confidence interval [CI], 0.85 to 1.02; \( P = 0.11 \)) (Fig. 3A). After adjustment for baseline characteristics, the relative hazard for the primary composite end point was 0.88 (95% CI, 0.79 to 0.97; \( P = 0.008 \)) (Table S5 in the Supplementary Appendix), and the relative hazard for death was 0.86 (95% CI, 0.78 to 0.96; \( P = 0.006 \)).
Cinacalcet and Cardiovascular Disease

A Primary Composite End Point

Hazard ratio, 0.93 (95% CI, 0.85 – 1.02)
P = 0.11 by log-rank test

No. at Risk
Placebo 1935 1804 1693 1579 1476 1384 1312 1224 1160 1109 1053 996 940 650 404 114
Cinacalcet 1948 1842 1739 1638 1556 1472 1384 1303 1230 1177 1115 1051 989 679 399 113

B Death

Hazard ratio, 0.94 (95% CI, 0.85 – 1.04)
P = 0.25 by log-rank test

No. at Risk
Placebo 1935 1882 1828 1754 1694 1622 1559 1486 1426 1388 1334 1283 1232 886 537 162
Cinacalcet 1948 1903 1845 1779 1736 1680 1621 1565 1507 1462 1412 1354 1292 899 546 167

C Myocardial Infarction

Hazard ratio, 0.97 (95% CI, 0.79 – 1.19)
P = 0.80 by log-rank test

No. at Risk
Placebo 1935 1857 1780 1684 1603 1521 1443 1366 1298 1254 1193 1136 1089 754 463 133
Cinacalcet 1948 1877 1799 1715 1648 1579 1512 1439 1377 1326 1268 1204 1139 785 466 137

D Unstable Angina

Hazard ratio, 0.82 (95% CI, 0.58 – 1.18)
P = 0.28 by log-rank test

No. at Risk
Placebo 1935 1858 1792 1703 1621 1548 1476 1400 1335 1293 1233 1181 1129 787 485 138
Cinacalcet 1948 1891 1822 1742 1686 1624 1556 1484 1423 1371 1317 1252 1187 812 482 140

E Heart Failure

Hazard ratio, 0.82 (95% CI, 0.68 – 0.99)
P = 0.08 by log-rank test

No. at Risk
Placebo 1935 1842 1753 1652 1565 1478 1404 1335 1264 1216 1159 1110 1054 737 464 129
Cinacalcet 1948 1873 1798 1712 1649 1579 1499 1422 1357 1301 1242 1176 1115 769 452 128

F Peripheral Vascular Event

Hazard ratio, 0.87 (95% CI, 0.72 – 1.07)
P = 0.19 by log-rank test

No. at Risk
Placebo 1935 1843 1766 1667 1575 1491 1433 1358 1279 1286 1184 1129 1077 750 470 137
Cinacalcet 1948 1882 1802 1711 1647 1586 1513 1438 1376 1326 1266 1196 1137 776 465 137
The numbers of events for the components of the composite end point in the cinacalcet group were 703 deaths, 187 myocardial infarctions, 56 hospitalizations for unstable angina, 206 episodes of heart failure, and 184 peripheral vascular events. In the placebo group, the numbers were 718 deaths, 183 myocardial infarctions, 66 hospitalizations for unstable angina, 236 episodes of heart failure, and 200 peripheral vascular events. Relative hazards for the components of the composite end point minimally favored the cinacalcet group (Fig. 3B through 3F). Figure S2 in the Supplementary Appendix shows relative hazards for the primary composite end point stratified according to prespecified baseline clinical characteristics. The effect of cinacalcet was more pronounced among older patients (P=0.03 for interaction).

Secondary End Points
Stroke was adjudicated in 115 patients in the cinacalcet group as compared with 102 patients in the placebo group (relative hazard, 1.07; 95% CI, 0.82 to 1.40; P=0.61). Death from cardiovascular causes was reported in 377 patients in the cinacalcet group and 391 in the placebo group (relative hazard, 0.92; 95% CI, 0.80 to 1.07; P=0.28). Parathyroidectomy and fracture results are shown in Text A in the Supplementary Appendix.

Multiple Cardiovascular Events
Myocardial infarction, hospitalization for unstable angina, heart failure, and peripheral vascular and stroke events per patient are shown in Figure S3 in the Supplementary Appendix. Cumulative event rates for the primary composite end point were 25.3 (95% CI, 24.1 to 26.5) per 100 patient-years in the cinacalcet group and 27.3 (95% CI, 26.0 to 28.5) per 100 patient-years in the placebo group, a nominally significant result (P=0.02). There were no significant effects of cinacalcet on the risk of multiple cardiovascular events (Table S6 in the Supplementary Appendix).

Biochemical Measures
Median plasma levels of parathyroid hormone and serum levels of calcium, phosphorus, and the calcium–phosphorus product over time are shown in Figure S4 in the Supplementary Appendix. As expected, there was substantial group separation in levels of parathyroid hormone and calcium, which was maximal at approximately 4 months and narrowed over time.

Concomitant Interventions
The provision of antiplatelet agents, statins, beta-blockers, and inhibitors of the renin–angiotensin–aldosterone system did not materially change over time in either group (Fig. S5 in the Supplementary Appendix).

Lag-Censoring Analysis
Censoring of data at 6 months after study-drug discontinuation yielded 638 primary composite end points in the cinacalcet group as compared with 658 in the placebo group (relative hazard, 0.85; 95% CI, 0.76 to 0.95; P=0.003) (Fig. 4A). Figure 4, panels B through F, shows the components of the primary composite end point with the use of lag censoring; mortality was significantly reduced in the cinacalcet group (relative hazard, 0.83; 95% CI, 0.73 to 0.96; P=0.009). Table S7 in the Supplementary Appendix shows the results of an exploratory analysis comparing a range of lag durations used in calculating the relative hazard for the primary composite end point. Figure S6 in the Supplementary Appendix shows corresponding values for median levels of parathyroid hormone, calcium, phosphorus, and the calcium–phosphorus product; larger relative differences were sustained over time.

Other Sensitivity Analyses
When we censored data for patients after kidney transplantation, parathyroidectomy, or use of commercially available cinacalcet, relative hazards for the primary composite end point were 0.90 (95% CI, 0.82 to 0.99; P=0.03) for all three prespecified analyses. Censoring at the time of any of these three events yielded a relative hazard of 0.84 (95% CI, 0.76 to 0.93; P<0.001). An inverse probability of censoring–weighted analysis is presented in Text B in the Supplementary Appendix.

Adverse Events
Hypocalcemia developed in seven times as many patients in the cinacalcet group as in the placebo...
A Primary Composite End Point

Hazard ratio, 0.85 (95% CI, 0.76–0.95)
P=0.003 by log-rank test

Study Month

No. at Risk
Placebo 1935 1789 1615 1299 1080 875 739 625 525 474 419 353 303 263 180 93 26
Cinacalcet 1948 1835 1627 1376 1179 1002 847 731 632 551 491 425 362 239 130 28

B Death

Hazard ratio, 0.83 (95% CI, 0.73–0.96)
P=0.009 by log-rank test

Study Month

No. at Risk
Placebo 1935 1861 1729 1422 1211 1004 867 743 628 567 499 429 380 324 234 119 33
Cinacalcet 1948 1890 1717 1474 1282 1113 967 857 757 663 597 518 452 293 167 42

C Myocardial Infarction

Hazard ratio, 0.91 (95% CI, 0.71–1.17)
P=0.47 by log-rank test

Study Month

No. at Risk
Placebo 1935 1849 1704 1394 1186 974 829 707 598 542 479 408 358 216 109 29
Cinacalcet 1948 1871 1686 1442 1252 1082 937 823 723 630 565 488 424 279 158 39

D Unstable Angina

Hazard ratio, 0.70 (95% CI, 0.47–1.06)
P=0.09 by log-rank test

Study Month

No. at Risk
Placebo 1935 1850 1717 1410 1191 986 847 725 617 557 489 420 371 227 116 32
Cinacalcet 1948 1885 1706 1462 1271 1099 952 840 737 642 579 505 438 283 160 41

E Heart Failure

Hazard ratio, 0.72 (95% CI, 0.58–0.89)
P=0.003 by log-rank test

Study Month

No. at Risk
Placebo 1935 1834 1681 1371 1158 949 810 690 581 521 459 397 345 208 109 31
Cinacalcet 1948 1867 1686 1438 1246 1069 913 800 700 609 545 474 408 270 148 35

F Peripheral Vascular Event

Hazard ratio, 0.80 (95% CI, 0.63–1.02)
P=0.07 by log-rank test

Study Month

No. at Risk
Placebo 1935 1835 1691 1376 1159 950 824 705 593 537 474 404 354 217 111 30
Cinacalcet 1948 1876 1687 1440 1244 1077 926 815 717 629 560 484 422 275 156 38
group, and nausea and vomiting were twice as common with cinacalcet (Table 2). Adverse effects led to discontinuation of the study drug in 18.1% of patients in the cinacalcet group and 13.0% of those in the placebo group. Rates of serious adverse events were similar in the two groups. Neoplastic events occurred in 115 patients in the cinacalcet group and 90 patients in the placebo group, corresponding to exposure-adjusted rates of 2.9 and 2.5 events per 100 patient-years, respectively. Of the neoplastic events, 25 in the cinacalcet group and 23 in the placebo

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Event Name</th>
<th>No. of Patients</th>
<th>Exposure-Adjusted Rate†</th>
<th>Crude Incidence‡</th>
<th>No. of Patients</th>
<th>Exposure-Adjusted Rate†</th>
<th>Crude Incidence‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse events§</td>
<td></td>
<td>1806</td>
<td>273.2</td>
<td>93.2</td>
<td>1748</td>
<td>217.8</td>
<td>90.9</td>
</tr>
<tr>
<td>Nausea§</td>
<td></td>
<td>563</td>
<td>18.3</td>
<td>29.1</td>
<td>299</td>
<td>9.1</td>
<td>15.5</td>
</tr>
<tr>
<td>Vomiting§</td>
<td></td>
<td>497</td>
<td>15.4</td>
<td>25.6</td>
<td>264</td>
<td>8.0</td>
<td>13.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>397</td>
<td>12.0</td>
<td>20.5</td>
<td>360</td>
<td>11.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td>1338</td>
<td>53.3</td>
<td>69.0</td>
<td>1351</td>
<td>56.9</td>
<td>70.3</td>
</tr>
<tr>
<td>Treatment-related events</td>
<td>Adverse events§</td>
<td>890</td>
<td>35.3</td>
<td>45.9</td>
<td>363</td>
<td>11.3</td>
<td>18.9</td>
</tr>
<tr>
<td>Serious adverse events¶</td>
<td></td>
<td>69</td>
<td>1.8</td>
<td>3.6</td>
<td>44</td>
<td>1.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Events associated with important identified risk</td>
<td>Convulsions</td>
<td>48</td>
<td>1.2</td>
<td>2.5</td>
<td>30</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Hypocalcemia§</td>
<td></td>
<td>240</td>
<td>6.7</td>
<td>12.4</td>
<td>33</td>
<td>0.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td></td>
<td>183</td>
<td>4.9</td>
<td>9.4</td>
<td>160</td>
<td>4.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Additional adverse events of interest</td>
<td>Acute pancreatitis</td>
<td>20</td>
<td>0.5</td>
<td>1.0</td>
<td>20</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Possibly drug-related hepatic disorder</td>
<td></td>
<td>45</td>
<td>1.1</td>
<td>2.3</td>
<td>30</td>
<td>1.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Nervous system disorder∥</td>
<td></td>
<td>711</td>
<td>24.3</td>
<td>36.7</td>
<td>586</td>
<td>20.5</td>
<td>30.5</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td></td>
<td>18</td>
<td>0.4</td>
<td>0.9</td>
<td>23</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Neoplastic event††</td>
<td>Any</td>
<td>115</td>
<td>2.9</td>
<td>5.9</td>
<td>90</td>
<td>2.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Fatal</td>
<td></td>
<td>25</td>
<td>0.6</td>
<td>1.3</td>
<td>23</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Calciphylaxis</td>
<td></td>
<td>6</td>
<td>0.1</td>
<td>0.3</td>
<td>18</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td></td>
<td>32</td>
<td>0.8</td>
<td>1.7</td>
<td>36</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td></td>
<td>28</td>
<td>0.7</td>
<td>1.4</td>
<td>30</td>
<td>0.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Listed are data for patients who received at least one dose of a study drug. P values were calculated for the exposure-adjusted incidence rate with the use of a two-sided normal approximation.
† The exposure-adjusted rate was calculated as 100 times the total number of patients who had a first event divided by the total number of patient-years of exposure. Exposure excludes gaps of more than 7 days between stopping and restarting of a study drug.
‡ The crude incidence was calculated as 100 times the total number of patients who had an event divided by the number of patients who received at least one dose of a study drug.
§ P<0.001.
¶ P=0.049.
∥ P<0.01.
** This category includes all patients with events reported in the system organ class of the Medical Dictionary for Regulatory Activities. Headache, dizziness, and paresthesia were the most commonly reported adverse events in this category.
†† Organ-specific neoplastic events are described in Table S7 in the Supplementary Appendix.
group were fatal (exposure-adjusted event rate, 0.6 per 100 patient-years in each group). Organ-specific neoplastic events are listed in Table S8 in the Supplementary Appendix.

### Discussion

A limited number of interventions that are designed to enhance overall and cardiovascular health have been tested in patients undergoing dialysis. Normalization of the hematocrit with erythropoiesis-stimulating agents resulted in nominally higher rates of death, cardiovascular events, and vascular-access thrombosis. Higher-dose dialysis and high-flux dialysis membranes did not reduce the rates of death or cardiovascular events or improve nutritional status or health-related quality of life. Several trials of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors showed no significant benefits, despite consistently positive effects in the general population and in patients with chronic kidney disease not requiring dialysis.

Secondary hyperparathyroidism has emerged as one of several complications associated with chronic kidney disease that might explain the exceptionally high rates of cardiovascular events and death among patients with end-stage renal disease. Several observational studies have shown significantly increased risks of death and cardiovascular events associated with levels of parathyroid hormone in excess of 600 pg per milliliter. Other studies have shown mixed results, with U-shaped, null, or inverse associations between the parathyroid hormone level and mortality, possibly confounded by nutritional status or inflammatory disease. No randomized, controlled trial has determined whether lowering the parathyroid hormone level reduces rates of death, cardiovascular events, or other major complications of mineral and bone disorders associated with chronic kidney disease.

In our study, there was a nonsignificant 7% reduction in the risk of the primary composite end point with cinacalcet in the intention-to-treat analysis. Given this result, the trial should be interpreted as nondefinitive. After adjustment for baseline characteristics, there was a nominally significant 12% reduction in risk. Other large randomized, controlled trials have shown more pronounced effect estimates after adjustment for unexpected differences in baseline determinants of risk. Although analyses accounting for study-drug exposure are subject to chance, bias, and confounding, we observed consistent and nominally significant effects, including a 15% reduction in the primary composite end point and a 17% reduction in mortality. Since parathyroidectomy or the initiation of treatment with commercially available cinacalcet would be expected to sharply reduce parathyroid hormone levels, differential application of these interventions after randomization would be expected to reduce the separation between groups and bias the estimate of the treatment effect toward the null.

The trial results must be interpreted in context. Patients undergoing dialysis are frequently frail and chronically ill. In the United States, mortality (20.7% per year) and morbidity (median, 2 hospitalizations and 12 hospital days per year) are extraordinarily high for such patients, who commonly have cardiopulmonary, gastrointestinal, musculoskeletal, and neurocognitive symptoms, along with a median pill burden of 19 per day. Thus, recruitment for and retention in clinical trials is particularly challenging.

Cinacalcet reduced the rate of parathyroidectomy by more than half. The use of parathyroidectomy varied widely according to age, sex, and geographic region, with the lowest use in the United States and among the elderly. In an attempt to account for variation in the use of a surgical procedure for which there are no definitive indications, we used a conservative definition of severe, unremitting hyperparathyroidism that was based on available clinical-practice guidelines (Text A in the Supplementary Appendix). Combining data from patients who met biochemical criteria for severe, unremitting hyperparathyroidism with those from patients who actually underwent parathyroidectomy may provide a more accurate measure of secondary hyperparathyroidism that is refractory to conventional medical therapy.

Our study has several strengths. We enrolled patients from many geographic regions, who were diverse in terms of age, race or ethnic group, and underlying kidney and cardiovascular disease. Patients who were assigned to receive either cinacalcet or placebo were all eligible to receive active therapy for mineral and bone disorders associated with chronic kidney disease, including phosphate binders and vitamin D sterols, along with frequent prescription of antihypertensive,
antiplatelet, and lipid-lowering agents. All cardiovascular end points were independently adjudicated, and relatively few patients were lost to follow-up.

However, the study has several important limitations. The statistical power was hampered by a lower-than-anticipated event rate, which required a prolongation of follow-up time, a particularly problematic issue given the high rate of dropout related to trial fatigue, gastrointestinal side effects, and other factors. Although dropout was common in both groups, more patients in the cinacalcet group dropped out because of adverse effects. Although less frequent than dropout, the use of commercially available cinacalcet by near-eligible patients influenced the relative hazard and level of significance.

Analyses adjusted for baseline characteristics or taking into account the effects of parathyroidectomy, kidney transplantation, and ongoing study-drug use suggest that cinacalcet may result in nominally significant reductions in the risk of death or first myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event (relative reduction, 10 to 15%; absolute reduction, 2 to 3 percentage points). However, in the unadjusted intention-to-treat analysis, as prespecified in the protocol, cinacalcet did not significantly reduce the risk of death or major cardiovascular events.

Supported by Amgen.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

Members of the writing committee — Glenn M. Chertow, M.D., M.P.H., Stanford University School of Medicine, Palo Alto, CA; Geoffrey A. Block, M.D., Denver Nephrology, Denver; Ricardo Correa-Rotter, M.D., Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City; Tilman B. Drüeke, M.D., Picardie University School of Medicine and Pharmacy, Amiens, France; Jürgen Fleoje, M.D., Rheinisch-Westfälische Technische Hochschule Aachen University Hospital, Aachen, Germany; William G. Goodman, M.D., Amgen, Thousand Oaks, CA; Gerard M. London, M.D., Hôpital Manhès, Paris; Kenneth W. Mahaffey, M.D., Duke Clinical Research Institute, Durham, NC; T. Christian H. Mix, M.D., Amgen, Thousand Oaks, CA; Sharon M. Moe, M.D., Indiana University School of Medicine, Roudebush Veterans Affairs Medical Center, Indianapolis; Marie-Louise Trotman, M.S., Amgen, Thousand Oaks, CA; David C. Wheeler, M.D., University College London, London; and Patrick S. Parfrey, M.D., Health Sciences Center, St. John’s, NF, Canada — assume responsibility for the content and integrity of this article.

REFERENCES


Copyright © 2012 Massachusetts Medical Society.