


Received for publication: 28.1.2012; Accepted in revised form: 10.7.2012

doi: 10.1093/ndt/gfs356
Advance Access publication 30 September 2012

Protocol adherence and the progression of cardiovascular calcification in the ADVANCE study

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Abstract

Background. The ADVANCE study assessed the progression of vascular and cardiac valve calcification in 360 hemodialysis patients with secondary hyperparathyroidism (sHPT) assigned randomly to treatment either with cinacalcet plus low-dose vitamin D (<6 µg/week of intravenous paricalcitol equivalent) or with varying doses of vitamin D alone for 52 weeks. The primary efficacy endpoint was progression of coronary artery calcification (CAC).

Methods. In this post-hoc analysis, we compared CAC progression among 70 protocol-adherent subjects given cinacalcet and low doses of vitamin D (CPA) as specified in the study protocol and 120 control subjects given...
vitamin D sterols.

**Results.** Baseline patient characteristics did not differ between CPA and control subjects. The mean (standard error of the mean, SEM) doses of vitamin D at week 2 were 4.7 (0.3) and 12.8 (1.0) µg/week in CPA and control subjects, respectively, and the corresponding mean cumulative doses of vitamin D over 52 weeks in each group were 225 (22) and 671 (47) µg. The median change in Agatston CAC score after 52 weeks was less in CPA subjects than in controls (17.8% versus 31.3%, P = 0.02). The median increase in calcification scores in the aortic valve also was less in CPA subjects than in controls (6.0% versus 51.5% P = 0.02). Reductions in serum parathyroid hormone, calcium, and phosphorus levels were significantly greater in CPA subjects than in controls (P < 0.05).

**Conclusions.** The progression of cardiovascular calcification was attenuated among cinacalcet-treated subjects with shHPT given low doses of vitamin D per protocol compared with control subjects in whom shHPT was treated with higher doses of vitamin D sterols alone.

**Keywords:** cardiovascular calcification; cinacalcet; post-hoc analysis; vitamin D

**Introduction**

Patients with chronic kidney disease who are managed with hemodialysis often have evidence of cardiovascular calcification including coronary artery calcification (CAC) [1, 2], findings associated previously with high mortality rates [3, 4]. The factors associated with CAC in such patients include increasing age, smoking, older dialysis vintage, diabetes, and elevated circulating concentrations of calcium, phosphorus, and parathyroid hormone (PTH), biochemical disturbances commonly associated with secondary hyperparathyroidism (shHPT) [1, 2, 5]. Treatment with the calcimimetic agent cinacalcet or with any of several vitamin D analogs has been shown to lower calcium, phosphorus, and parathyroid hormone levels. The impact of treatment with cinacalcet or vitamin D analogs on cardiovascular calcification has been evaluated only recently.

The ADVANCE study (NCT00379899) assessed interval changes in CAC scores over 52 weeks of follow-up as measured by multi-detector helical computed tomography (MDCT) among hemodialysis patients with shHPT. All subjects had CAC at baseline, and changes in CAC scores were compared among those treated either with cinacalcet and low doses of vitamin D analogs or with larger, varying doses of vitamin D sterols (see the Methods section for details) [6]. As reported elsewhere [6], increases in CAC scores over 12 months were generally less among subjects given cinacalcet together with low doses of vitamin D than among those given larger doses of vitamin D sterols. Nevertheless, a substantial number of subjects assigned to treatment with cinacalcet received weekly doses of vitamin D sterols that exceeded the amount specified in the study protocol, diminishing inter-group differences.

The current report summarizes interval changes in CAC scores and changes in calcium scores at other cardiovascular sites among 70 subjects treated for 52 weeks with cinacalcet and low doses of vitamin D sterols, defined as ≤6 µg/week of intravenous paricalcitol equivalent, as specified originally in the ADVANCE study protocol. The findings among these 70 cinacalcet, protocol-adherent subjects (CPA) are compared with the results from control subjects with shHPT treated conventionally with larger, varying doses of vitamin D analogs. For descriptive purposes, calcium scores from cinacalcet-treated, protocol non-adherent subjects (NCPA) who received doses of vitamin D sterols which exceeded those recommended in the study protocol also are provided.

**Subjects and methods**

**Study design and participants**

The design of ADVANCE and the methods therein have been described in detail elsewhere [5, 6]. Briefly, this was a prospective, randomized, controlled trial that evaluated the progression of vascular and cardiac valve calcification in 360 subjects with shHPT and baseline Agatston CAC scores of ≥30 as measured by MDCT. All participants had been treated with hemodialysis for ≥3 months.

The study participants were randomly assigned to treatment for 52 weeks either with cinacalcet and low doses of vitamin D sterols or with flexible doses of vitamin D sterols alone as deemed appropriate by the treating physician. Among subjects assigned to treatment with cinacalcet, doses were adjusted between 30 and 180 mg/day during the first 20 weeks of the study to achieve PTH levels between 150 and 300 pg/mL. Low doses of vitamin D sterols equivalent to a weekly dose of ≤6 µg of intravenous paricalcitol also were given in divided doses either intravenously during thrice-weekly hemodialysis sessions or orally each day. The study protocol stated specifically that the dose of vitamin D was not to exceed an amount equivalent to 6 µg of intravenous paricalcitol per week among those receiving cinacalcet. Subjects assigned to the control group were treated with larger, varying doses of vitamin D sterols given intravenously during thrice-weekly hemodialysis procedures or orally every day.

All subjects used calcium-based phosphate-binding agents exclusively. Doses of vitamin D sterols and/or phosphate-binding agents were adjusted for safety reasons according to the existing treatment guidelines based upon periodic measurements of serum calcium and phosphorus levels.

CAC scores and calcium scores at the thoracic aorta, aortic valve, and mitral valve were determined by both the Agatston and volume methods at baseline and at 52 weeks as described previously [5, 6]. The percentage change in CAC from baseline to week 52 was calculated, and the proportion of subjects with >15% progression of CAC at week 52 was determined. Changes from baseline to the end of the study in plasma PTH levels and in the concentrations of calcium, phosphorus, and Ca × P in serum were assessed using the average of values measured at 44 and 52 weeks of treatment.

**Post-hoc analysis**

As reported previously, the primary endpoint in the ADVANCE study was the percentage change in Agatston CAC score from baseline to week 52 [6]. Because only a portion of those assigned to treatment with cinacalcet actually received low doses of vitamin D sterols as specified in the study protocol, the current post-hoc analysis was done using the results from the 70 cinacalcet-treated subjects managed per protocol (CPA) as defined previously. These subjects received doses of vitamin D equivalent to ≤2 µg of intravenous paricalcitol three times per week as documented at the week 2 study visit. The results from CPA subjects were compared with those obtained from 120 control subjects [6].
Statistical comparisons between the groups were done for interval changes in calcium scores, for serum biochemical parameters, for the cumulative doses of vitamin D steroids and for the cumulative doses of elemental calcium contained in phosphate-binding agents over the 52-week study. The results from 45 NCPA subjects given doses of vitamin D that exceeded the equivalent of 2 µg of paricalcitol thrice-weekly at variance with the study protocol are also summarized. These data are provided solely for descriptive purposes and were not included in statistical assessments.

Adverse events and serious adverse events were recorded for all study participants by treatment category.

Statistical methods

The results are presented as mean values with standard deviation (SD) or standard error of the mean (SEM) where appropriate. The differences between CPA and control subjects were evaluated using a generalized Cochran–Mantel–Haenszel (CMH) test on ranks, stratified by the CAC score at baseline. The stratum-adjusted median differences and the corresponding 95% confidence intervals (CI) were determined by inverting the CMH test and conducting a numerical search. The P-values < 0.05 were considered to be statistically significant without adjustment for multiple comparisons among groups.

Two sensitivity analyses were done to assess possible biases introduced by sub-grouping cinacalcet-treated subjects by vitamin D sterol dose. One analysis compared data from the 70 CPA subjects with the results from a sample of 70 control subjects after matching for baseline vitamin D sterol dose. A second analysis compared the results from CPA subjects with those from all control subjects after adjusting for baseline vitamin D sterol dose.

Results

Study subjects

Demographic and clinical characteristics at baseline did not differ between CPA and control subjects (Table 1). The baseline values for plasma PTH and serum calcium concentrations also did not differ between the groups. The mean (SD) serum phosphorus concentrations at baseline were higher, however, in CPA subjects than in controls, 6.2 (1.9) versus 5.4 (1.7) mg/dL (Table 1), a finding consistent with that reported originally among all subjects assigned to treatment with cinacalcet [6].

The prevalence of major comorbidities such as diabetes and hypertension was generally similar among CPA and control subjects as well as in the NCPA comparator group (Table 1). Peripheral vascular disease and congestive heart failure affected fewer individuals in the CPA and NCPA groups compared with controls (Table 1). The proportion of study participants receiving treatment with a vitamin D sterol at baseline was lower in CPA subjects than in controls, and the mean dose of vitamin D at baseline was also lower (Table 2). The proportion of patients who used a calcium-containing, phosphate-binding agent at baseline did not differ, however, between CPA and control subjects.

Medication use

The use of vitamin D sterols during the study differed substantially among the groups (Figure 1). The mean weekly dose of vitamin D at week 2 was 4.7 (0.3) µg in CPA subjects and 12.8 (1.0) µg in controls. Although the weekly dose of vitamin D remained relatively constant throughout the study in these two groups, the weekly dose of vitamin D at each interval of follow-up was lower among CPA subjects compared with controls.

Despite protocol guidance, the mean weekly dose of vitamin D among NCPA subjects at week 2 was 16.7 (1.6) µg (Figure 1). Weekly doses decreased gradually thereafter, reached a nadir at week 36 and then increased. The mean weekly vitamin D dose at each study visit exceeded the amount recommended in the study protocol.

As expected, the mean cumulative dose of vitamin D during the 52-week study was lower among CPA subjects than among controls (Table 2). The mean cumulative dose of vitamin D among NCPA subjects was modestly lower

<table>
<thead>
<tr>
<th>Table 1. Demographics, clinical, and biochemical characteristics at baseline</th>
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<tbody>
<tr>
<td><strong>Cinacalcet + vitamin D sterols</strong></td>
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<td>-----------------------------------</td>
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<tr>
<td><strong>Women/men (n, %)</strong></td>
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<td><strong>Age, years (mean, SD)</strong></td>
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<tr>
<td><strong>Time on hemodialysis, months (median, Q1 and Q3)</strong></td>
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<tr>
<td><strong>Body mass index, kg/m² (mean, SD)</strong></td>
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<tr>
<td><strong>CAC score (Agatston; median, Q1 and Q3)</strong></td>
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<tr>
<td><strong>Comorbidities:</strong></td>
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<tr>
<td>Diabetes mellitus</td>
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<td>Hypertension</td>
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<td>Peripheral vascular disease</td>
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<td>Cerebrovascular accident</td>
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<td>Myocardial infarction</td>
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<td>Coronary artery disease</td>
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<td>Congestive heart failure</td>
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<tr>
<td><strong>Biochemical measurements:</strong></td>
</tr>
<tr>
<td>iPTH, pg/mL (median, Q1 and Q3)</td>
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<tr>
<td>Serum calcium, mg/dL (mean, SD)</td>
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<tr>
<td>Serum phosphorus, mg/dL (mean, SD)</td>
</tr>
</tbody>
</table>

CAC, coronary artery calcification; CPA, cinacalcet, protocol adherent; NCPA, cinacalcet, protocol non-adherent; iPTH, intact parathyroid hormone; Q1 and Q3, 1st and 3rd quartiles; SD, standard deviation.

*P < 0.01 between the CPA and the control groups from a chi-square test for proportions and an unpaired t-test for means.
than among controls, but it exceeded by far the mean cumulative dose among CPA subjects (Table 2).

The median daily cinacalcet dose at week 52 was 29 mg both in CPA (Q1, Q3: 18, 54) and in NCPA (Q1, Q3: 16, 60) subjects, whereas the median daily dose was 30 mg at all other time points. The interquartile dosage range at each study visit was also quite similar.

The median cumulative dose of a calcium-based phosphate binder at the end of study did not differ between CPA and control subjects (Table 2). The median cumulative dose did not differ materially among NCPA subjects, CPA subjects and controls.

Cardiovascular calcification

Increases in calcium scores, as measured by Agatston and volume scoring methods, were less among CPA subjects compared with controls at all sites evaluated (Figure 2, Table 3). For CAC and aortic valve scores, the differences between the groups were statistically significant by both scoring methods (Table 3). The results from two sensitivity analyses to assess the potential for bias attributable to sub-grouping of cinacalcet-treated subjects by vitamin D sterol dose confirmed these findings. Increases in calcium scores among NCPA subjects also were generally less than in controls (Table 3).

The proportion of study participants who had >15% progression of CAC was lower among CPA subjects (29%) than among control subjects (58%) for those with baseline Agatston CAC scores ≥1000. For individuals with baseline CAC scores of <1000, the proportion of subjects with an increase in CAC >15% did not differ between the groups (Figure 3). Nevertheless, the proportion of subjects with an increase in CAC >15% differed significantly between CPA subjects and controls when all participants were considered without regard to baseline CAC scores (P = 0.04, CMH test). Among NCPA

![Mean dose of vitamin D sterols, in µg/week of intravenous paricalcitol equivalents. Error bars show SEM. Subjects not taking any vitamin D sterols were not included in this calculation. Numbers of subjects at each time point are shown below the graph. CPA, cinacalcet, protocol adherent; NCPA, cinacalcet, protocol non-adherent.](https://academic.oup.com/ndt/article-abstract/28/1/146/1827817)

![Median differences (and 95% CI) between the CPA subgroup and the control group in the percentage change in calcium scores from baseline to week 52 at four anatomical sites, measured by Agatston and volume scoring methods.](https://academic.oup.com/ndt/article-abstract/28/1/146/1827817)
subjects, the proportion who had >15% progression of CAC was quite similar to that for controls.

Biochemical outcomes

The reductions in plasma PTH levels from baseline to the end of study (mean of weeks 44 and 52) were greater in CPA subjects than in controls (P < 0.05) (Figure 4). Similarly, the decreases in serum calcium and Ca × P values during the same interval again were greater in CPA subjects compared with controls (data not shown). Plasma PTH levels also decreased substantially among NCPA subjects, and the values at each interval of follow-up did not differ materially from those observed in CPA subjects. Plasma PTH levels both in CPA and in NCPA subjects were substantially lower throughout the study than in controls (Figure 4).

Among CPA subjects, PTH levels fell substantially from baseline values during the first two weeks of study, declined further until week 14 and rose somewhat thereafter (Figure 4). Similar changes occurred among NCPA subjects. In contrast, PTH levels decreased only modestly during the study among control subjects. Serum calcium and phosphorus concentrations and Ca × P values were consistently lower throughout the study among CPA and NCPA subjects compared with controls (data not shown).

Tolerability and safety

Adverse events among patients in the ADVANCE study have been reported elsewhere [6]. The biochemical responses to treatment either with cinacalcet and low doses of vitamin D or with larger doses of vitamin D alone were assessed further by calculating the proportion

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Table 3. Progression of calcification (Agatston and volume scores) from baseline to week 52; values are median (first and third quartile) for percentage change in score

<table>
<thead>
<tr>
<th></th>
<th>CPA</th>
<th>NCPA</th>
<th>Control</th>
<th>P-value a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>70</td>
<td>45</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>Agatston</td>
<td>17.8 (−1.8, 54.7)</td>
<td>39.5 (4.4, 65.5)</td>
<td>31.3 (7.6, 81.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume</td>
<td>21.3 (0.9, 47.1)</td>
<td>22.3 (3.4, 65.3)</td>
<td>30.1 (10.3, 78.0)</td>
<td>0.004</td>
</tr>
<tr>
<td>Thoracic aorta</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>54</td>
<td>35</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Agatston</td>
<td>23.7 (2.2, 39.8)</td>
<td>12.1 (0.0, 57.5)</td>
<td>33.1 (3.8, 69.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Volume</td>
<td>16.5 (1.5, 43.2)</td>
<td>16.1 (3.1, 59.4)</td>
<td>29.3 (6.4, 71.6)</td>
<td>0.09</td>
</tr>
<tr>
<td>Aortic valve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>37</td>
<td>19</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Agatston</td>
<td>6.0 (−16.8, 34.4)</td>
<td>6.7 (−15.8, 73.5)</td>
<td>51.5 (−9.9, 123.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume</td>
<td>2.8 (−20.1, 28.2)</td>
<td>14.8 (−10.7, 63.4)</td>
<td>35.3 (−13.3, 78.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mitral valve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>33</td>
<td>19</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Agatston</td>
<td>6.7 (−22.0, 117.5)</td>
<td>21.5 (−8.3, 54.9)</td>
<td>54.4 (−3.9, 177.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Volume</td>
<td>8.5 (−17.5, 100.3)</td>
<td>25.6 (−8.4, 37.7)</td>
<td>42.0 (−10.6, 125.1)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

CPA, cinacalcet, protocol adherent; NCPA, cinacalcet, protocol non-adherent.

P-value for difference between the CPA subgroup and the control group.
of patients with serum calcium or phosphorus concentrations above or below the specified limits at each study visit. As expected, the proportion of cinacalcet-treated subjects with a serum calcium concentration <8.0 or <7.5 mg/dL during the study was greater than among control subjects whether or not they were managed per protocol. In contrast, the proportion of patients with a serum calcium concentration >10.2 mg/dL was higher among control subjects treated with vitamin D sterols alone (20/119) than among those given cinacalcet (5/68). The proportion of patients with a serum calcium concentration <8 mg/dL was higher among CPA subjects than in controls across the study; however, the proportion of patients with a serum calcium concentration <7.5 mg/dL was higher among CPA subjects than in controls only from week 6 to week 28. The proportion of patients with a serum phosphorus concentration >5.5 mg/dL during the study did not differ between CPA subjects and controls.

Discussion

The current post-hoc analyses of data from the ADVANCE study provide additional evidence that different strategies for treating sHPT have divergent effects on the progression of cardiovascular calcification among patients receiving hemodialysis treatment. As reported originally [6], the use of cinacalcet together with low doses of vitamin D analogs lowered plasma PTH levels more effectively among hemodialysis patients with sHPT and attenuated increases in CAC and cardiac valve calcium scores over 52 weeks compared with treatment using larger, varying doses of vitamin D sterols alone. However, 45 of 115 cinacalcet-treated subjects, or nearly 40% of those assigned to treatment with cinacalcet and low doses of vitamin D sterols, unexpectedly received weekly doses of vitamin D throughout the study that exceeded amounts specified in the protocol, that is, doses greater than the equivalent of 6 μg of paricalcitol per week. Most protocol deviations were attributable to the activities of investigators and study personnel, not to the failure of study participants to comply with, or adhere to, study procedures. Because vitamin D analogs can raise serum calcium and phosphorus concentrations and because inappropriate continued use of these compounds can aggravate cardiovascular calcification among patients undergoing dialysis, we sought to determine whether compliance with the therapeutic strategy set forth originally in the ADVANCE study protocol conferred additional benefit with respect to the progression of cardiovascular calcification.

We found that the percentage increase from baseline to 52 weeks in CAC scores and in aortic valve calcium scores measured by either the Agatston or the volume method was statistically significantly smaller in CPA subjects than in controls. Qualitatively similar differences between the groups were seen for interval changes in calcium scores at the thoracic aorta and mitral valve over 52 weeks, but these differences did not reach statistical significance. The proportion of CPA subjects that experienced an increase in CAC >15% from baseline to week 52 was also smaller than that of controls. This favorable effect was most pronounced among patients with baseline Agatston CAC scores ≥1000. Although patients with sHPT and advanced CAC may benefit most from treatment with cinacalcet with respect to the progression of CAC, the progression of CAC in each of the three strata as defined by baseline CAC scores was consistently less in CPA subjects than in controls. The results thus suggest that treatment with cinacalcet combined with low doses of vitamin D sterols attenuates the progression of CAC without regard to the extent of CAC at baseline among hemodialysis patients with sHPT.

The biochemical response to treatment with cinacalcet differed substantially from that observed among subjects treated with larger, varying doses of vitamin D analogs alone. Such findings are consistent with results reported previously. Plasma PTH levels decreased substantially during the study both in CPA and in NCPA subjects. Serum calcium and phosphorus concentrations also decreased during treatment with cinacalcet without regard to protocol adherence, even among NCPA subjects who continued to receive weekly doses of vitamin D analogs that far exceeded doses recommended in the study protocol. In contrast, decreases in plasma PTH levels among control subjects during 52 weeks of treatment with varying doses of vitamin D analogs were smaller than in those observed among cinacalcet-treated subjects, and serum calcium and phosphorus concentrations were largely unchanged from baseline. Such findings confirm the favorable effect of cinacalcet therapy to reduce plasma PTH levels while lowering serum phosphorus concentrations despite ongoing treatment with vitamin D among hemodialysis patients with sHPT.

The mechanisms responsible for the progression of cardiovascular calcification among patients with sHPT who require treatment with hemodialysis are incompletely understood. Elevated serum calcium and phosphorus concentrations, high plasma PTH levels, alterations in the circulating levels of certain proteins such as uncarboxylated matrix Gla-protein (MGP), fetuin A, osteocalcin, osteoprotegerin, and pyrophosphate and changes in the levels of expression in cardiovascular tissues of key modifiers of extra-osseous calcification such as MGP and osteopontin have all been implicated [7]. Logistical and analytical issues precluded a systematic assessment of variations in the serum levels of MGP, fetuin A and osteocalcin among subjects in the ADVANCE study. In addition, differences between the treatment groups in the expression of potentially important mediators of calcification in vascular and other soft tissues could not be evaluated. Nevertheless, the current results suggest that decreases in plasma PTH levels together with reductions in serum calcium and phosphorus concentrations during treatment with cinacalcet are associated with lower rates of progression of cardiovascular calcification among hemodialysis patients with sHPT. A beneficial effect of cinacalcet therapy on cardiovascular calcification is supported by evidence of a statistically significant difference in the progression of cardiovascular calcification between CPA subjects and controls. Additional studies are required, however, to determine whether treatment with
cinacalcet alone without concurrent vitamin D administration can further attenuate the progression of cardiovascular calcification among dialysis patients with sHPT.

Strengths of the current study include the relatively large number of subjects evaluated using advanced imaging methods to assess cardiovascular calcification and the prospective nature of data collection within a randomized clinical trial. Calcium scores were determined at four cardiovascular sites including the cardiac valves. Robust statistical methods were used for all analyses, including sensitivity analyses.

Study limitations include the post-hoc nature of the analyses presented herein and their attendant vulnerability to error. Specifically, the CPA and NCPA subgroups were defined using a post-baseline criterion, so any comparison between CPA and controls is subject to confounding related to the treatment itself. Such an approach became necessary, however, to examine the hypothesis tested originally in ADVANCE because of the large number of protocol deviations, a result that highlights the importance of closely supervising and carefully monitoring all aspects of a clinical trial. The potential for bias and additional confounding is thus readily acknowledged. Neither the original study nor the current analyses were designed to determine the most suitable dose of vitamin D analogs to be used in conjunction with cinacalcet or to assess the effect of treatment with vitamin D sterols on the evolution of vascular calcification during the treatment of sHPT among patients receiving hemodialysis. Prospective clinical trials are required to address these issues.

In summary, post-hoc analyses of data from the ADVANCE study provide additional evidence that different strategies for treating sHPT have important effects on the progression of cardiovascular calcification among patients with sHPT who require hemodialysis. Treatment with cinacalcet together with low doses of vitamin D sterols is associated with less progression of cardiovascular calcification compared with conventional treatment using large, varying doses of vitamin D analogs alone. Lower plasma PTH levels and lower serum calcium and phosphorus concentrations during treatment with cinacalcet and low doses of vitamin D sterols may account for these findings, but direct, favorable effects on the process of vascular calcification cannot be excluded completely.

Acknowledgements. These data have not been published previously, except in abstract form at the American Society of Nephrology Kidney Week 2010 and the Australia and New Zealand Society of Nephrology Annual Scientific Meeting 2011. The ADVANCE study was sponsored by Amgen, Inc. Medical writing assistance was provided by Roger Nutter of Bioscript Stirling, with funding from Amgen (Europe) GmbH, and editorial assistance by Caterina Hatzifoti and Lucy Hyatt, both of Amgen (Europe) GmbH.

Conflict of interest statement. P.U.T. has received fees for clinical research, speaking and expert consultancy from Amgen, Shire, Novartis, Roche, Fresenius and Hemotech. J.F. has received consultancy and lecture fees from Amgen and lecture fees from Abbott, Genzyme, Shire and Fresenius. C.H. has received travel and research grants from Amgen. E.P. has nothing to declare. W.G.G. and M.R. are employees and stockholders in Amgen. F.P. has worked on behalf of Amgen. P.R. has received research grants from Amgen and Genzyme.

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Received for publication: 2.2.2012; Accepted in revised form: 27.6.2012