Comparative Effects of Etelcalcetide and Maxacalcitol on Serum Calcification Propensity in Secondary Hyperparathyroidism

A Randomized Clinical Trial

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Abstract

Background and objectives Vitamin D receptor activators and calcimimetics (calcium-sensing receptor agonists) are two major options for medical treatment of secondary hyperparathyroidism. A higher serum calcification propensity (a shorter T_{50} value) is a novel surrogate marker of calcification stress and mortality in patients with CKD. We tested a hypothesis that a calcimimetic agent etelcalcetide is more effective in increasing T_{50} value than a vitamin D receptor activator maxacalcitol.

Design, setting, participants, & measurements A randomized, multicenter, open-label, blinded end point trial with active control was conducted in patients with secondary hyperparathyroidism undergoing hemodialysis in Japan. Patients were randomly assigned to receive intravenous etelcalcetide 5 mg thrice weekly (etelcalcetide group) or intravenous maxacalcitol 5 or 10 μg thrice weekly (maxacalcitol group). The primary, secondary, and tertiary outcomes were changes in T_{50} value, handgrip strength, and score of the Dementia Assessment Sheet for Community-Based Integrated Care System from baseline to 12 months, respectively.

Results In total, 425 patients from 23 dialysis centers were screened for eligibility, 326 patients were randomized (etelcalcetide, $n=167$; control, $n=159$), and 321 were included in the intention-to-treat analysis (median age, 66 years; 113 women [35%]). The median (interquartile range) of T_{50} value was changed from 116 minutes (interquartile range, 90–151) to 131 minutes (interquartile range, 102–176) in the maxacalcitol group, whereas it was changed from 123 minutes (interquartile range, 98–174) to 166 minutes (interquartile range, 127–218) in the etelcalcetide group. The increase in T_{50} value was significantly greater in the etelcalcetide group (difference in change, 20 minutes; 95% confidence interval, 7 to 34 minutes; $P=0.004$). No significant between-group difference was found in the change in handgrip strength or in the Dementia Assessment Sheet for Community-Based Integrated Care System score.

Conclusions Etelcalcetide was more effective in increasing T_{50} value than maxacalcitol among patients on hemodialysis with secondary hyperparathyroidism. There was no difference in handgrip strength or cognition between the two drugs.

Clinical Trial registry name and registration number: VICTORY; UMIN000030636 and jRCTs051180156

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Introduction

Mineral bone disorder in CKD is considered as one of the important factors explaining the high mortality rate in patients with CKD, including those receiving hemodialysis (1–4). Secondary hyperparathyroidism results in high turnover bone, bone mineral loss, calcification of soft tissues including arteries, and a higher risk of cardiovascular disease and mortality. There are two major options for medical treatment for secondary hyperparathyroidism, namely, vitamin D receptor activators (VDRAs) and calcimimetics (calcium-sensing receptor agonists). The Kidney Disease Improving Global Outcomes (KDIGO) 2017 clinical practice guideline (5) suggests the use of calcimimetics, calcitriol, vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs in

patients with CKD undergoing dialysis requiring parathyroid hormone (PTH)–lowering therapy. The guideline does not recommend calcimimetics or VDRAs as a preferred choice of treatment. Choice may depend on other outcomes than PTH levels that are important for individual patients, such as mortality, calcification stress, sarcopenia, and cognition. So far, however, no such comparison was made between the two classes of drugs (6).

Phosphate plays important roles in vascular calcification (7) and mortality (3,4). The toxicity of phosphate is thought to be exerted by calciprotein particles, nanosized colloidal particles consisted of calcium phosphate crystals stabilized by a glycoprotein fetuin-A (8,9). The primary calciprotein particles <100 nm are considered as physiologic carriers of calcium and phosphate. However, after they undergo spontaneous transformation to the secondary calciprotein particles >100 nm, these larger calciprotein particles have highly cytotoxic and proinflammatory properties (10). The propensity of transformation to the secondary calciprotein particles can be assessed by measuring time required to transform into the secondary calciprotein particles *in vitro*, called serum calcification propensity (T_{50}) (11). A shorter T_{50}, which means a higher calcification propensity, was associated with arterial calcification (12), arterial stiffness (13), and a higher risk of all-cause death in cohorts of dialysis-independent (14) and -dependent patients with CKD (15), and also in kidney transplant recipients (16). Thus, T_{50} could be a surrogate marker of poor clinical outcomes attributable to calcification stress.

Sarcopenia and cognitive impairment have emerged as important health concerns in aging societies (17), and vitamin D may play some roles (18). Vitamin D receptor knockout mice show abnormal development of skeletal muscles (19). Observational human studies reported associations of vitamin D status with physical performance (20) and cognitive decline (21) in the elderly and in patients with CKD (22,23) as well.

We hypothesized that treatment with a calcimimetic agent is more effective in suppressing T_{50} compared with treatment with a VDRA, whereas a VDRA may be better in preventing decline in muscle strength and/or cognition in patients with secondary hyperparathyroidism undergoing hemodialysis.

Materials and Methods

Study Oversight

This trial named "VDRA vs. Intravenous Calcimimetics in the Treatment Of Renal patients with secondary hYperparathyroidism" (VICTORY) was designed and overseen by the representative principal investigator and the steering committee at Osaka City University, and it was conducted in accordance with the principles of the Declaration of Helsinki; the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labor and Welfare, Japan (December 22, 2014; revised on February 28, 2017); and the Clinical Trial Act (act no. 16 of April 14, 2017). The protocol was reviewed and approved by the Ethical Committee of Osaka City University Graduate School of Medicine (approval no. 3879) and the Osaka City University Hospital Certified Review Board (approval no. OCU0011). All participants gave written informed consent before the study. To address the Clinical Trial Act, which came into force on April 1, 2019, this trial was registered in the Japan Registry of Clinical Trials after enrollment of patients, in addition to the registration in the University Hospital Medical Information Network Clinical Trials Registry, which was made before the patient enrollment.

Study Design

This clinical trial with a randomized, open-label, blinded end point design compared the effects of a calcimimetic agent etelcalcetide (intervention group) versus a VDRA maxacalcitol (control group) on the change in T_{50} from baseline to 12 months in patients with secondary hyperparathyroidism receiving maintenance hemodialysis. The protocol and statistical analysis plan are available in Supplemental Material. Supplemental Figure 1 shows the synopsis of this trial.

Study Population

The participants were patients with secondary hyperparathyroidism aged 20–80 years who were receiving hemodialysis thrice weekly, whose serum intact PTH was ≥241 pg/ml and serum corrected calcium was ≥8.4 mg/dl, and who were not taking any calcimimetics or VDRAs at randomization. These laboratory values were derived from the 2012 version of the clinical practice guideline by the Japanese Society for Dialysis Therapy (24). Detailed inclusion and exclusion criteria are listed in Supplemental Table 1. Eligible patients were screened at 23 dialysis facilities in Osaka, Japan.

Randomization

Randomization (1:1) using computer-generated random numbers with a permuted block scheme was performed. Randomization was stratified by sex (men or women), age (<65 or ≥65 years old), and serum phosphate level (<6.0 or ≥6.0 mg/dl). Allocation was distributed through the web-based system called Research Electronic Data Capture (https://projectredcap.org/about/) (25,26) at Osaka City University (http://www.hosp.med.osaka-cu.ac.jp/self/hyokac/redcap/index.shtml).

Intervention and Follow-Up in the Etelcalcetide Group

The patients allocated to the etelcalcetide (intervention) group were assigned to receive intravenous etelcalcetide thrice weekly administered *via* blood access at the end of each dialysis session. The initial dose was set at 5 mg following directions on the package insert of etelcalcetide hydrochloride (PARSABIV; Ono Pharmaceuticals, Co. Ltd., Osaka, Japan). Dose adjustment was permitted to achieve the target range of intact PTH (between 60 and 240 pg/ml) and to avoid hypocalcemia in the dose range between 2.5 and 15 mg per shot. Oral VDRAs were allowed only to avoid hypocalcemia even after the dose of etelcalcetide was reduced to 2.5 mg per shot. Intravenous VDRA preparations were prohibited, but they could be used if hypocalcemia could not be relieved by dose reduction of etelcalcetide and use of an oral VDRA. Temporal cessation of etelcalcetide was made if corrected calcium was <7.5 mg/dl, and etelcalcetide was restarted when corrected

calcium returned to ≥8.4 mg/dL. In this group, "discontinuation of study drug" was defined when etelcalcetide was not administered continuously for 42 days or longer regardless of the reason.

Intervention and Follow-Up in the Maxacalcitol Group

The patients allocated to the maxacalcitol (control) group were assigned to receive intravenous maxacalcitol thrice weekly administered *via* blood access at the end of each dialysis session. The initial dose was set at 5 μg thrice weekly in patients with serum intact PTH <500 pg/ml and 10 μg thrice weekly in patients with intact PTH ≥500 pg/ml following directions on the package insert of maxacalcitol (OXAROL; Chugai Pharmaceuticals, Co. Ltd., Tokyo, Japan). Dose adjustment was permitted to achieve the target range of intact PTH (between 60 and 240 pg/ml) and to avoid hypercalcemia in the dose range between 2.5 and 10 μg per shot. Oral calcimimetics (cinacalcet and evocalcet) were allowed only to avoid hypercalcemia even after the dose of maxacalcitol was reduced to 2.5 μg per shot. Intravenous calcimimetic agent (etelcalcetide) was prohibited, but it could be used if hypercalcemia could not be relieved by dose reduction of maxacalcitol and use of an oral calcimimetic agent. Temporal cessation of maxacalcitol was made if corrected calcium was >11.5 mg/dl, and maxacalcitol was restarted when corrected calcium returned to <11.0 mg/dl. In this group, "discontinuation of study drug" was defined when maxacalcitol was not administered continuously for 42 days or longer regardless of the reason.

Study Outcomes and Adverse Events

The primary, secondary, and tertiary efficacy outcomes were the changes from study visit at 0–12 months in T_{50} (11), handgrip strength (27), and cognition (28), respectively. T_{50} was measured using the method by Pasch *et al.* (11) in our laboratory (29). Cognition was assessed by the Dementia Assessment Sheet for Community-Based Integrated Care System (DASC-21) (28). Details of these methods are available in Supplemental Tables 2 and 3.

Supplemental Table 4 shows other subsidiary outcomes, including (*1*) changes in T_{50} at visits from 0 to 3 months and from 0 to 6 months; (*2*) presence or absence of achieving the target ranges of serum corrected calcium, phosphate, and intact PTH (24) at 3, 6, and 12 months; and (*3*) >30% reduction in intact PTH from baseline at 3, 6, and 12 months.

The safety assessment included all serious adverse events (SAEs), hypocalcemia and hypercalcemia requiring cessation of study drug, symptoms (nausea, vomiting, dysgeusia, diarrhea, itching, irritability, and others), and falls.

Other Measurements

Serum levels of albumin, calcium, phosphate, intact PTH, intact fibroblast growth factor-23 (FGF23), fetuin-A, and magnesium were centrally measured at SRL, Inc. (Tokyo, Japan). Other clinical data, including laboratory measurements at each site, were collected from the medical records.

Interim Analysis and Stopping Guideline

The independent monitoring committee conducted interim data viewing to review the status of recruitment and interim safety profile and gave a recommendation to continue the trial as planned. However, no interim analysis of the primary outcome was done for possible early stopping of recruitment. We recruited participants as much as possible within the scheduled recruitment period.

Sample Size Determination

Sample size was computed comparing mean T_{50} at 12 months between the two groups. Because there are few published data available on T_{50}, we estimated T_{50} value on the basis of the reported association between T_{50} and phosphate level by Pasch *et al.* (15). The mean (SD) T_{50} value at 12 months among the control group was assumed to be 215 (84) minutes on the basis of the mean T_{50} level among patients on hemodialysis with elevated PTH levels in the work by Pasch *et al.* (15). The mean T_{50} at 12 months in the intervention group was assumed to be 240 minutes according to the average change of phosphate level among the patients using etelcalcetide in the work by Block *et al.* (30) and that for the patients using maxacalcitol in the work by Hayashi *et al.* (31). At two-tailed significance level of 5%, 178 patients are required to achieve 80% statistical power. On the basis of the above calculations, assuming that the frequency of dropout is approximately 10%, it would be necessary to enroll 200 participants per group for a total of 400 participants.

Statistical Analyses

We defined three populations for analysis: a full analysis set, a per-protocol set, and a safety analysis set. The detailed definitions are available in the protocol and statistical analysis plan (Supplemental Material). The primary efficacy analysis was done with full analysis set according to the principle of intention to treat. Missing data were imputed by the last observation carried forward method. In the per-protocol set, last observation carried forward was done up to the time of discontinuation of treatment or withdrawal from the study. To describe results, continuous data were summarized as medians and interquartile ranges, and categorical variables were summarized as numbers and percentages. For comparisons of the outcomes between the allocation groups, we performed multivariable-adjusted linear regression analyses with adjustment for the stratification variables used for randomization, including age, sex, and phosphate level at the visit at 0 months. Least square means and 95% confidence intervals (95% CIs) were calculated for each group, and the estimated absolute differences between the groups were reported with 95% CIs. Although we planned to transform the residuals when normality assumption was not met, no transformation was done (excluding intact FGF23) because the residuals were deemed to follow normal distribution. All of these statistical inferences were made at two-sided significance level of 5%. All calculations were conducted using R version 4.0.2 (https://cran.r-project.org/).

Results

Flow and Baseline Characteristics of Participants

Figure 1 shows the flow of participants. The participant recruitment was open on February 1, 2018; the first patient was enrolled on February 28, 2018; and the last patient was enrolled on January 9, 2019. The last day of follow-up was December 27, 2019. Eligibility was assessed in 425 pre-enrolled patients. Following a washout period for up to 8 weeks, 99 patients were found not to meet the eligibility criteria (serum corrected calcium and intact PTH levels in most cases). Finally, because of the scheduled period for enrollment, we ended the enrollment and randomization with 326 patients. Of the 326 patients who were randomized, two patients were excluded from the safety analysis set because they did not receive the study drug. Additionally, three patients were excluded from the full analysis set because of protocol violation. Further, two patients were excluded from the per-protocol set because they were found ineligible during intervention. Thus, the safety analysis set, the full analysis set, and the per-protocol set included 324, 321, and 319 participants, respectively. Table 1 gives the baseline characteristics of the two groups in the full analysis set.

Changes in Laboratory Data and Medications

Figure 2 shows the changes in select laboratory data. Intact PTH levels were decreased following the interventions in both groups. Phosphate level showed a modest decrease in the etelcalcetide group, whereas it stayed almost unchanged in the maxacalcitol group. Corrected calcium and calcium × phosphate product decreased in the etelcalcetide group, whereas they increased in the maxacalcitol group. FGF23 showed a decrease in the etelcalcetide

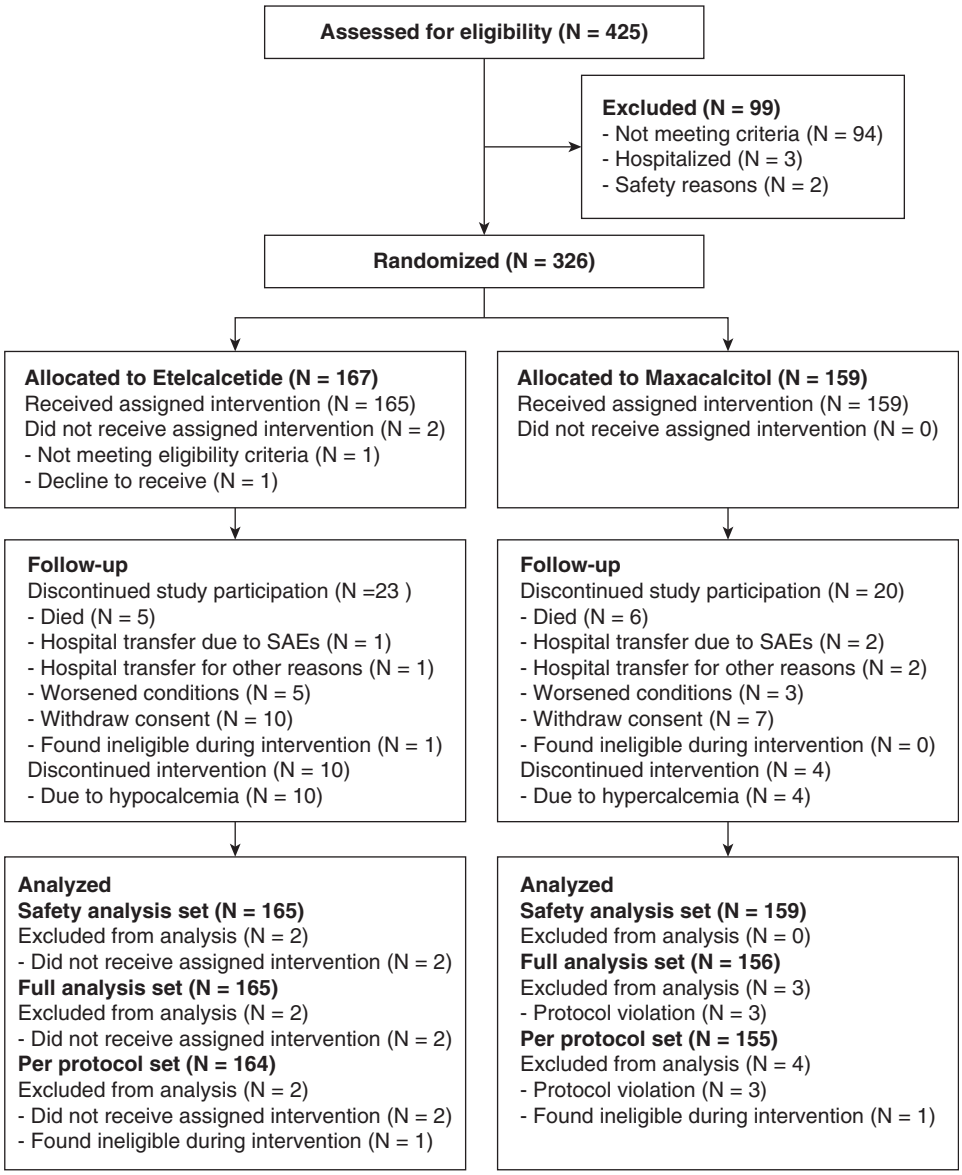

Figure 1. | **This chart indicates the flow of participants.** SAE, serious adverse event.

Table 1. Baseline characteristics of participants in a randomized clinical trial comparing the effects of etelcalcitide and maxacalcitol on serum calcification propensity

Characteristics	Etelcalcetide Group, n=165	Maxacalcitol Group, n=156
Age, yr	66 (55–71)	66 (57–71)
Men, *N* (%)	110 (67)	98 (63)
Women, *N* (%)	55 (33)	58 (37)
Duration of hemodialysis, yr	6.2 (3.1–14.8)	7.1 (3.7–14.3)
Diabetic kidney disease, *N* (%)	69 (42)	56 (36)
Medical history, *N* (%)		
Cerebral infarction	12 (7)	10 (6)
Cerebral hemorrhage	5 (3)	1 (1)
Subarachnoidal hemorrhage	0 (0)	1 (1)
Myocardial infarction	8 (5)	11 (7)
Coronary revascularization	15 (9)	21 (13)
Amputation of ischemic limb	5 (3)	4 (3)
Leg artery intervention/bypass	3 (2)	12 (8)
Atrial fibrillation	13 (8)	8 (5)
Bone fracture	13 (8)	23 (15)
Falls in the preceding year	19 (12)	19 (12)
Systolic BP, mm Hg	145 (132–163)	151 (136–163)
Diastolic BP, mm Hg	78 (69–88)	80 (71–87)
Height, cm	162 (157–169)	162 (154–168)
Weight, kg	60 (52–69)	59 (50–68)
Body mass index, kg/m^2	22.5 (20.4–25.2)	22.2 (20.0–25.5)
Serum biochemistry		
Albumin, g/dl	3.7 (3.5–3.9)	3.7 (3.5–3.9)
Intact PTH, pg/ml	418 (313–563)	436 (338–600)
Corrected calcium, mg/dl	9.2 (8.8–9.6)	9.2 (8.9–9.5)
Phosphate, mg/dl	5.5 (4.6–6.2)	5.6 (4.9–6.6)
Magnesium, mg/dl	2.6 (2.4–2.8)	2.6 (2.4–2.8)
Intact FGF23, pg/ml	3500 (1290–8300)	4100 (1140–10,625)
Fetuin-A, μg/ml	253 (216–310)	254 (222–299)
Phosphate binder use, *N* (%)		
Calcium carbonate	85 (52)	81 (52)
Lanthanum carbonate	83 (50)	82 (53)
Ferric citrate hydrate	32 (19)	30 (19)
Sucroferric oxyhydroxide	17 (10)	10 (6)
Sevelamer hydrochloride	35 (21)	28 (18)
Bixalomer	12 (7)	13 (8)
Magnesium oxide use, *N* (%)	2 (1)	5 (3)
Hemodialysis conditions		
Time of dialysis per week, h	12.0 (12.0–12.3)	12.0 (12.0–12.0)
Surface area of dialyzer membrane, m^2	2.1 (1.8–2.1)	2.1 (1.5–2.1)
Kt/V	1.50 (1.33–1.71)	1.50 (1.33–1.70)
Blood flow rate, ml/h	230 (200–250)	220 (200–250)
Dialysate flow rate, ml/h	500 (500–500)	500 (500–500)
Dialysate calcium concentration, mEq/L, *N* (%)		
2.5	25 (15)	25 (16)
2.75	87 (53)	85 (54)
3.0	53 (32)	46 (29)

Continuous variables were summarized as medians (interquartile ranges), and categorical variables were summarized as numbers (percentages). PTH, parathyroid hormone; FGF23, fibroblast growth factor-23.

group, whereas an increase was observed in the maxacalcitol group. Fetuin-A and magnesium stayed unchanged in both groups.

Figure 3 summarizes changes in medications related to CKD mineral bone disorder. In the etelcalcetide group, discontinuation of the study drug occurred in ten patients. Use of calcium carbonate was increased, whereas use of lanthanum carbonate was decreased. Oral alfacalcidol was used in 44 of 144 patients (31%) at the visit at 12 months to treat hypocalcemia, but intravenous VDRAs were not used in this group. In the maxacalcitol group, four patients discontinued the study drug, and 17 patients received oral calcimimetics (cinacalcet or evocalcet). Use of calcium carbonate was decreased, whereas use of lanthanum carbonate and use of sucroferric oxyhydroxide were increased. Cinacalcet and evocalcet were used in some patients, but etelcalcetide was not used in this group. Dialysate calcium concentration was not changed during the trial in either group.

Primary, Secondary, and Tertiary Outcomes

Table 2 gives the results on T_{50}, handgrip strength, and DASC-21 at the visits at 0 and 12 months and the changes in these measurements during 12 months in each group. Figure 4 graphically depicts these data. The change in T_{50} was significantly greater by 20 minutes in the etelcalcetide group versus the maxacalcitol group. There was no significant between-group difference in the change in

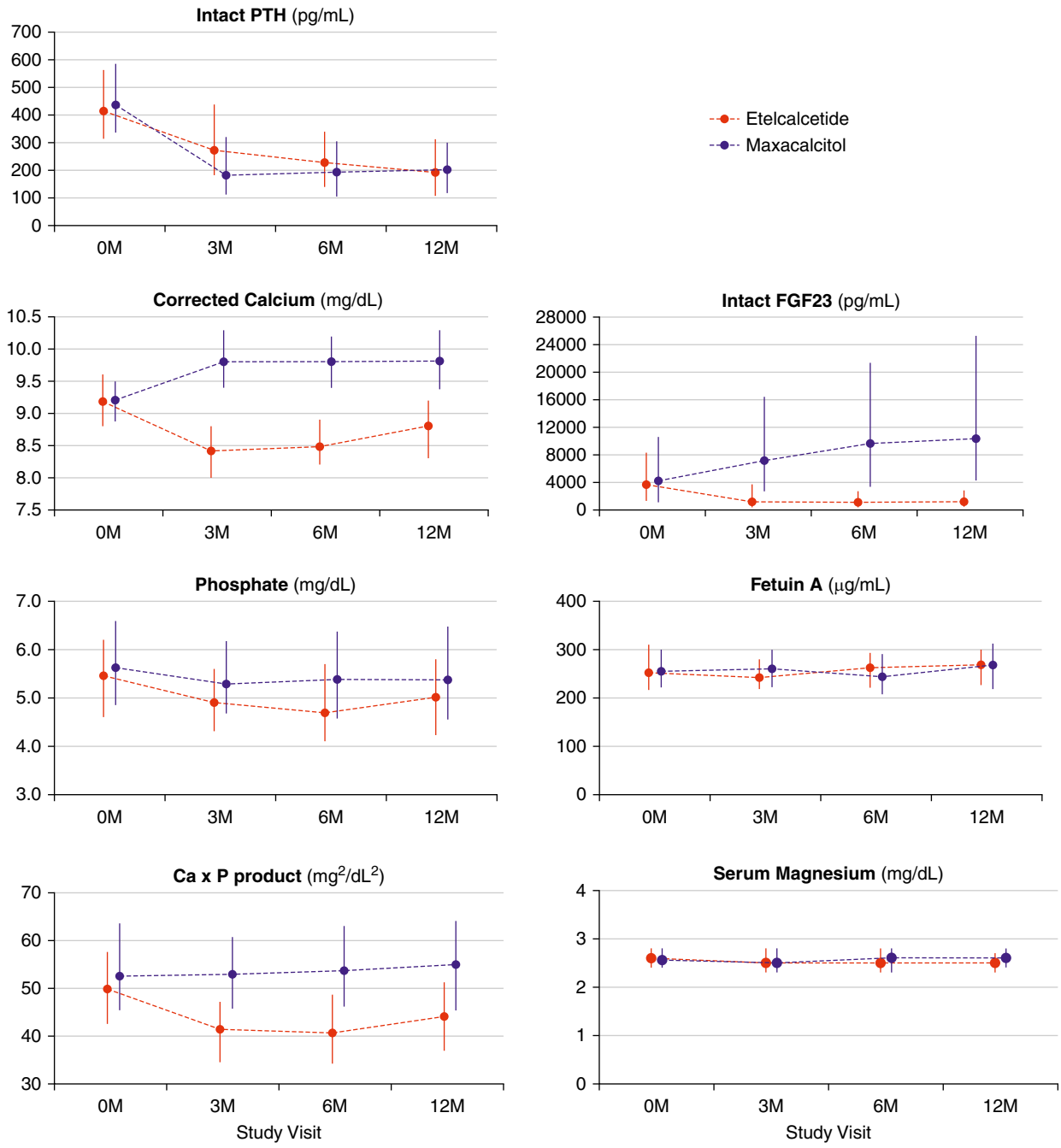

Figure 2. | **The graphs depict the changes in laboratory data during the trial.** Circles and vertical bars represent medians and interquartile ranges. Differences in calcium (Ca) × phosphate (P) product and intact fibroblast growth factor-23 (FGF23) levels are significant at visits at 3, 6, and 12 months (M; $P<0.001$ for all). *Post hoc* between-group comparison showed significant differences in serum P and corrected Ca levels at visits at 3, 6, and 12 M ($P<0.001$ for all). These comparisons were done after adjustment for age, sex, and serum P at baseline. PTH, parathyroid hormone.

handgrip strength or in the change in DASC-21. A *post hoc* sensitivity analysis using a mixed effect model also showed a significant difference in the primary outcome between the groups at the visits at 3, 6, and 12 months ($P<0.001$ for all).

Other Subsidiary Efficacy Outcomes

Other subsidiary efficacy outcomes are summarized in Table 3.

Additional Efficacy Analyses with the Per-Protocol Set

Supplemental Table 5 shows analyses of the primary, secondary, and tertiary efficacy outcomes using the per-protocol set. These results were essentially the same with the results using the full analysis set.

Adverse Events

Table 4 summarizes adverse events. The total numbers of reports of SAEs were 41 (32 cases; 19.4%) in the

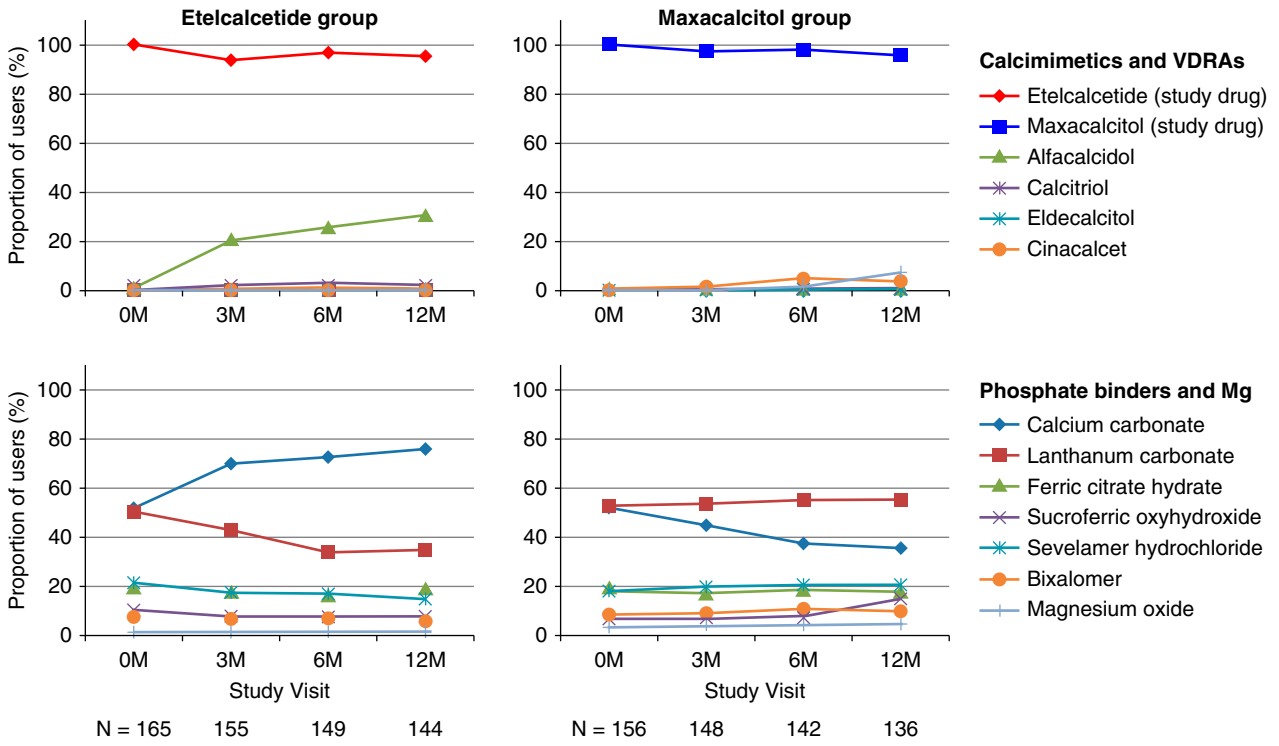

Figure 3. | **These graphs show the changes in medications during the trial.** The study drug (etelcalcetide or maxacalcitol) was continued in most of the participants in each group. In the etelcalcetide group, the use of alfacalcidol, the increased use of calcium carbonate, and the decreased use of lanthanum carbonate were noted. Mg, magnesium; VDRA, vitamin D receptor activator.

etelcalcetide group and 70 (44 cases; 27.7%) in the maxacalcitol group. The most frequent symptom was itching, and it was comparable between the two groups. The numbers of falls were comparable between the two groups. Temporal cessation of study drug occurred in 33 occasions in 30 participants (18.2%) in the etelcalcetide group and in ten occasions in ten participants (6.3%) in the maxacalcitol group. These dose interruptions were all due to hypocalcemia and hypercalcemia in the etelcalcetide group and the maxacalcitol group, respectively.

Discussion

This study compared the effects of etelcalcetide and maxacalcitol on T_{50}, handgrip strength, and DASC-21 as the primary, secondary, and tertiary outcomes, respectively, in

Table 2. Primary, secondary, and tertiary outcomes in full analysis set

Outcomes	Etelcalcetide Group	Maxacalcitol Group	Between-Group Difference
T_{50}, min			
0 mo	123 (98–174) n=165	116 (90–151) n=156	
3 mo	141 (117–175) n=149	108 (84–145) n=148	
6 mo	153 (117–190) n=148	105 (79–134) n=141	
12 mo	166 (127–218) n=143	131 (102–176) n=133	
Change from 0 to 12 mo	29 (16 to 43) n=165	9 (–4 to 22) n=156	20 (7 to 34) P=0.004
Handgrip strength, kg			
0 mo	23.5 (17.4–28.4) n=164	22.7 (16.4–29.0) n=155	
12 mo	22.9 (17.8–28.4) n=142	21.6 (16.1–27.8) n=135	
Change from 0 to 12 mo	0.0 (–1.0 to 1.1) n=164	−0.1 (–1.1 to 0.9) n=155	0.2 (–0.9 to 1.2) P=0.76
DASC-21, points			
0 mo	22.0 (21.0–23.0) n=162	21.0 (21.0–23.0) n=150	
12 mo	21.5 (21.0–23.0) n=140	21.0 (21.0–23.0) n=133	
Change from 0 to 12 mo	−0.0 (–1.0 to 1.0) n=162	0.6 (–0.5 to 1.6) n=150	−0.6 (–1.6 to 0.5) P=0.29

Measurements at each visit were summarized as medians (interquartile ranges) with number of patients. Changes from 0 to 12 months and between-group differences were least square means (95% confidence intervals), which were estimated with imputation of missing data by the last observation carried forward method. T_{50}, serum calcification propensity; 0 mo, visit at baseline; 3 mo, visit at 3 months; 6 mo, visit at 6 months; 12 mo, visit at 12 months; DASC-21, Dementia Assessment Sheet for Community-Based Integrated Care System.

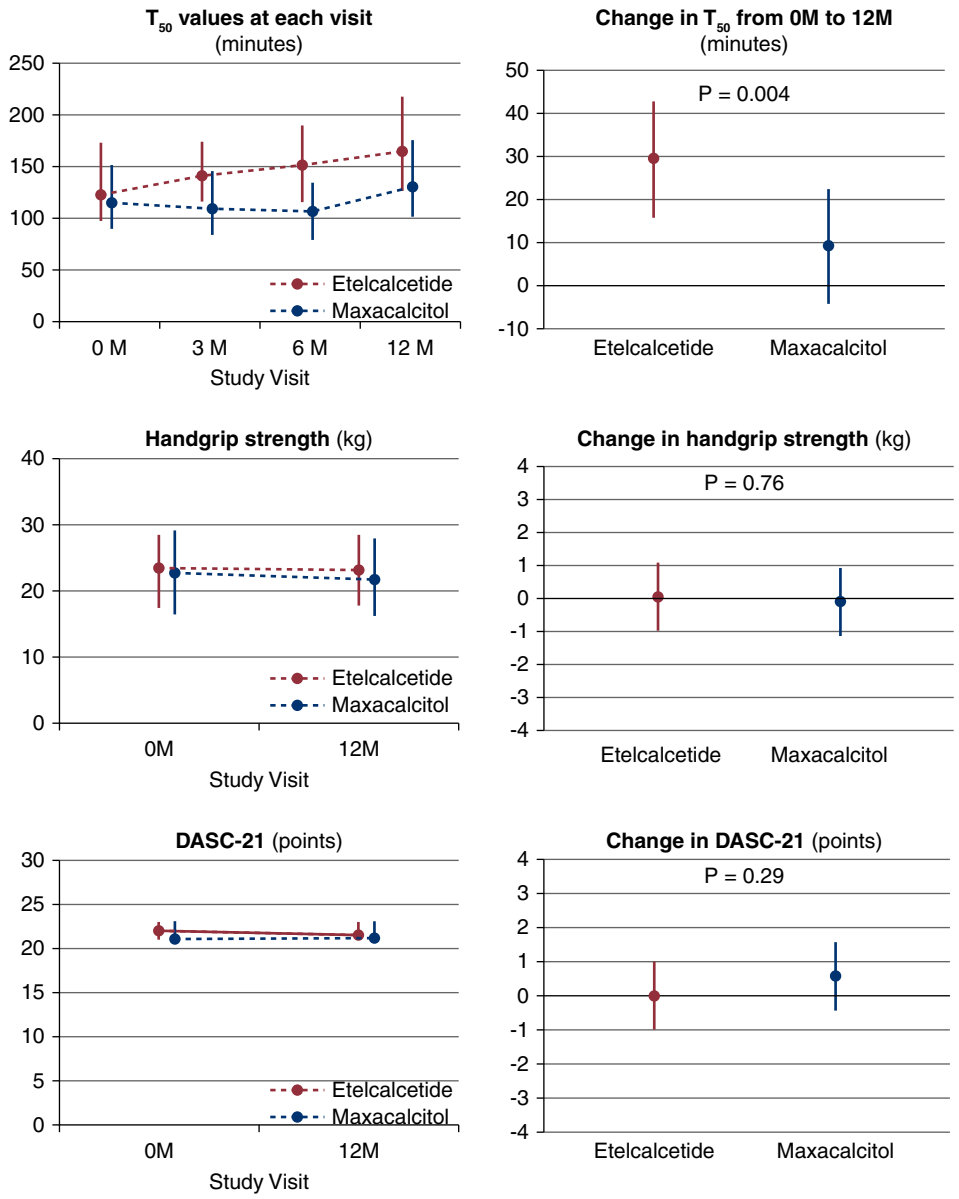

Figure 4. | **The increase in T_{50} (primary outcome) was greater in the etelcalcetide group than the maxacalcitol group.** No difference was significant in the change in handgrip strength (secondary outcome) or DASC-21 score (tertiary outcome) between the groups. The left panels show medians (interquartile ranges), and the right panels show least square means (95% confidence intervals) of the changes from 0 to 12 M in serum calcification propensity (T_{50}), handgrip strength, and Dementia Assessment Sheet for Community-Based Integrated Care System (DASC-21). *P* values are for between-group comparison. The individual values are given in Table 2.

patients with secondary hyperparathyroidism undergoing hemodialysis. The change in T_{50} following the intervention for 12 months was significantly greater in the etelcalcetide group than in the maxacalcitol group, whereas there was no difference in the change in handgrip strength or DASC-21 between the two groups.

The observed between-group difference in the change in T_{50} can be explained mainly by the different effects of the two drugs on phosphate and calcium levels, because T_{50} was reported to correlate inversely with serum phosphate and calcium levels (15). In this trial, *post hoc* analyses showed significant between-group differences in serum phosphate and corrected calcium levels at the visits at 3 months ($P=0.005$), 6 months ($P<0.001$), and 12 months ($P<0.001$). Serum magnesium, another factor that increases T_{50} (32,33), remained unchanged in both groups. There is a report that serum fetuin-A concentration was increased in patients with secondary hyperparathyroidism after treatment with a VDRA paricalcitol (34). Because fetuin-A is a potent inhibitor of calcification (8) and the key glycoprotein component of calciprotein particles (35), an increase in serum fetuin-A could result in an increase in T_{50} (14). However, there was no change in serum fetuin-A level in either the maxacalcitol group or the etelcalcetide group.

Potential roles of vitamin D in muscular health have been suggested by experimental studies (19) and observational

Table 3. Other subsidiary efficacy outcomes

Outcomes	Etelcalcetide Group	Maxacalcitol Group	*P* Value
Change in T_{50} from 0 to 3 mo, min	16 (6 to 26)	−11 (–21 to –0)	<0.001
Change in T_{50} from 0 to 6 mo, min	18 (6 to 31)	−16 (–28 to –3)	<0.001
Corrected Ca in target range, mo, *n*/*N* (%)			
3	75/149 (50)	92/148 (62)	0.06
6	91/148 (62)	90/141 (64)	0.94
12	95/142 (67)	83/132 (63)	0.49
P in target range, mo, *n*/*N* (%)			
3	110/149 (74)	104/148 (70)	0.66
6	117/148 (79)	90/141 (64)	0.002
12	101/142 (71)	81/132 (61)	0.08
Intact PTH in target range, mo, *n*/*N* (%)			
3	53/149 (36)	80/148 (54)	<0.001
6	71/148 (48)	76/141 (54)	0.17
12	74/142 (52)	74/132 (56)	0.39
Ca, P, and intact PTH all in target range, mo, *n*/*N* (%)			
3	18/149 (12)	41/148 (28)	<0.001
6	38/148 (26)	30/141 (21)	0.36
12	37/142 (26)	33/132 (25)	0.87
>30% reduction in intact PTH, mo, *n*/*N* (%)			
3	73/149 (49)	121/148 (82)	<0.001
6	101/148 (68)	109/141 (77)	0.04
12	102/142 (72)	107/132 (81)	0.04
Ca × P product, mo, mg^2/dl^2			
3	43 (40 to 45)	54 (51 to 56)	<0.001
6	41 (39 to 44)	54 (51 to 56)	<0.001
12	45 (42 to 47)	54 (51 to 56)	<0.001
Fetuin-A, mo, μg/ml			
3	243 (230 to 256)	260 (247 to 273)	0.01
6	246 (233 to 258)	241 (229 to 254)	0.50
12	259 (247 to 270)	261 (250 to 273)	0.63
Intact FGF23, mo, pg/ml			
3	850 (661–11,093)	3312 (2578–4256)	<0.001
6	721 (556–934)	4729 (3652–6125)	<0.001
12	836 (629–1109)	4853 (3660–6434)	<0.001

Changes in T_{50} and other laboratory data excluding intact FGF23 are shown as least square means (95% confidence intervals). For intact FGF23, these values were calculated after logarithmic transformation, and the table gives the values by exponential retransformation. Laboratory data in target ranges are given in number of patients in target range (*n*), number of patients at each visit (*N*), and percentage in parentheses. Statistical analysis was done by adjusting for age, sex, and P level at baseline. The target ranges recommended by the clinical practice guideline by the Japanese Society for Dialysis Therapy (2012) were corrected C between 8.4 and 10.0 mg/dl, P between 3.5 and 6.0 mg/dl, and intact PTH between 60 and 240 pg/ml (24). The changes in T_{50} from 0 to 3 months and from 0 to 6 months were calculated with missing values being imputed by the last observation carried forward method. The numbers of patients in the target ranges are shown by the numbers of patients at each visit without imputation. All tests for between-group comparison were adjusted for age and serum P at baseline. T_{50}, serum calcification propensity; Ca, calcium; 3, visit at 3 months; 6, visit at 6 months; 12, visit at 12 months; P, phosphate; PTH, parathyroid hormone; FGF23, fibroblast growth factor-23.

human studies (20,36). However, this trial showed no effect of maxacalcitol or etelcalcetide on handgrip strength. This is consistent with the study by Westerberg *et al.* (37) that showed no effect of high-dose cholecalciferol on handgrip strength in patients with secondary hyperparathyroidism and CKD stages 3 and 4. A longer study period might be needed. Previous observational studies might have been confounded by some factors, such as higher sunshine exposure in individuals with higher physical activity. Vitamin D action may be more important in muscle development in early stages than the maintenance of muscular function in later stages of life.

There was no change in DASC-21 score in either group, and there was no intergroup difference in the changes in DASC-21. However, the apparently neutral effects on DASC-21 should be interpreted carefully. The very low baseline scores of DASC-21 indicate almost full performance of cognition and activity of daily living levels, which made it difficult to detect improvement in these outcomes, if any, by the so-called ceiling effect. Thus, the results of this study regarding cognition and activity of daily living are inconclusive.

How can we translate our finding on T_{50} into hard clinical end points? According to the *post hoc* analysis of the EVOLVE trial (15) in patients with secondary hyperparathyroidism undergoing hemodialysis, a shorter T_{50} value was associated with higher risks of all-cause mortality and myocardial infarction, with hazard ratios of 1.10 (95% CI, 1.02 to 1.17) and 1.38 (95% CI, 1.19 to 1.60) per one SD of T_{50}, respectively. According to another study in patients with CKD predialysis (14), a longitudinal increase of aortic pulse wave velocity was inversely associated with serum T_{50} at baseline, with an odds ratio of 0.52 (95% CI, 0.31 to 0.85) per one SD of T_{50}. In this trial, the observed between-group difference of the change in T_{50} during 12 months of treatment (20 minutes) corresponds to 0.36 SD of T_{50} at

Table 4. Adverse events in safety analysis set

Adverse Events	Etelcalcetide Group, $n=165$	Maxacalcitol Group, $n=159$
Serious adverse events		
Any serious adverse events	41 (32; 19%)	70 (44; 28%)
All-cause death	5 (5; 3%)	6 (6; 4%)
Any hospitalization	38 (30; 18%)	65 (40; 25%)
Cardiac events	8 (5; 3%)	4 (4; 3%)
Cerebrovascular events	1 (1; 1%)	6 (6; 4%)
Peripheral vascular event	9 (9; 5%)	14 (10; 6%)
Infectious disease	3 (3; 2%)	20 (14; 9%)
Malignancy	3 (3; 2%)	10 (6; 4%)
Other serious adverse events	17 (15; 9%)	16 (13; 8%)
Symptoms		
Nausea	11 (9; 5%)	24 (17; 11%)
Vomiting	10 (8; 5%)	16 (12; 8%)
Dysgeusia/cacogeusia	7 (4; 2%)	5 (3; 2%)
Diarrhea	22 (16; 10%)	10 (7; 4%)
Itching	58 (30; 18%)	72 (38; 24%)
Irritability/jitteriness	20 (15; 9%)	24 (16; 10%)
Falls	47 (28; 17%)	38 (27; 17%)
Hypercalcemia requiring temporal cessation of study drug	0 (0; 0%)	10 (10; 6%)
Hypocalcemia requiring temporal cessation of study drug	33 (30; 18%)	0 (0; 0%)

The table gives numbers of event (number of patients; percentage of participants) by group. Some patients had repeated adverse events in the same category.

baseline. Thus, it may be translated into modest effects on hard clinical end points and aortic stiffness. Although we had collected data on SAEs, including mortality and hospitalization, for safety assessment, the follow-up period for 12 months may not be long enough. Clearly, we need further studies to directly address this issue.

The KDIGO clinical practice guideline does not prioritize calcimimetics or VDRAs in the treatment for secondary hyperparathyroidism (5). In choosing a treatment, considerations may be important regarding not only the effect on PTH but also influence on outcomes such as cardiovascular disease, calcification stress, sarcopenia, and cognition. Previous randomized trials in CKD failed to show the beneficial effects of VDRA on left ventricular mass (38,39) or cardiovascular events (40) as compared with placebo or standard care. This study provides novel evidence that treatment with etelcalcetide had a greater effect of calcification propensity reduction than treatment with maxacalcitol, whereas no difference was found on strength or cognition. Numerically fewer patients in the etelcalcetide group experienced SAEs, which may affect the choice to some extent.

There are several limitations in this study. First, this study did not compare the effects of the two study drugs on clinical hard end points as the primary outcome as discussed above. Second, this randomized trial was not a double-blinded one. However, this hardly affected the result on the primary efficacy outcome of T_{50} because T_{50} was measured by persons who were masked to the information on assigned treatment. Third, the results of this study in Japan may not be applicable to patients in other countries where background characteristics of patients and the target ranges of intact PTH are different. Fourth, there was temporal cessation of etelcalcetide in 30 patients and use of oral alfacalcidol in 44 patients in the etelcalcetide group due to hypocalcemia, whereas ten patients skipped maxacalcitol and 17 patients received oral cinacalcet or evocalcet in the maxacalcitol group due to hypercalcemia. This "contamination" of treatments may underestimate the true effects of these drugs. Fifth, this study was underpowered because only 326 patients were enrolled as compared with the target number of 400. Sixth, the T_{50} values in this trial were much lower than those reported for dialysis-dependent and -independent patients with CKD from Western countries. Although the reason was unknown, it hardly affects the conclusion. On the other hand, the strengths of this study include the randomized design, the 12 months of follow-up, and the use of intravenously administered drugs as study drugs that prohibited the issue of nonadherence.

In conclusion, this study showed that treatment with etelcalcetide was more effective in increasing T_{50}, namely in suppressing calcification propensity, than treatment with maxacalcitol in patients with secondary hyperparathyroidism undergoing hemodialysis. No difference was found on the effects on handgrip strength or DASC-21 between the two groups. These results provide novel evidence in the treatment of secondary hyperparathyroidism. Further studies are needed to confirm these results in other settings and to examine the potential effects on hard clinical outcomes.

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Data Sharing Statement

Individual participant data that underline the results reported in this article (text, tables, figures, and appendices) after de-identification, study protocol, and statistical analysis plan will be shared with researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. Data sharing will be available in a period beginning 3 months and ending 5 years following article publication. Proposals should be directed to t-shoji@med.osaka-cu.ac.jp.

Supplemental Material

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Supplemental Material. Study protocol of the VICTORY trial and statistical analysis plan.

Supplemental Table 1. Inclusion and exclusion criteria.

Supplemental Table 2. Assay method of serum calcification propensity (T_{50}).

Supplemental Table 3. Methods for handgrip strength and DASC-21 measurements.

Supplemental Table 4. List of primary, secondary, tertiary, and other subsidiary outcomes.

Supplemental Table 5. Additional efficacy analysis with per-protocol set.

Supplemental Figure 1. Synopsis of this trial plan.

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