Etelcalcetide Utilization, Dosing Titration, and Chronic Kidney Disease–Mineral and Bone Disease (CKD-MBD) Marker Responses in US Hemodialysis Patients

Angelo Karaboyas, Daniel Muenz, Douglas S. Fuller, Pooja Desai, Tzu-Chieh Lin, Bruce M. Robinson, Sandro Rossetti, and Ronald L. Pisoni

Rationale & Objective: Clinical trial data have demonstrated the efficacy of etelcalcetide for reducing parathyroid hormone (PTH) levels in hemodialysis (HD) patients. We provide a real-world summary of etelcalcetide utilization, dosing, effectiveness, and discontinuation since its US introduction in April 2017.

Study Design: New-user design within prospective cohort.

Setting & Participants: 2,596 new users of etelcalcetide from April 2017 through August 2019 in a national sample of adult maintenance HD patients in the US Dialysis Outcomes and Practice Patterns Study (DOPPS).

Predictors: Baseline PTH, prior cinacalcet use, initial etelcalcetide dose.

Outcome: Trajectories of etelcalcetide dose, chronic kidney disease–mineral and bone disease (CKD-MBD) medications, and levels of PTH, serum calcium, and phosphorus in the 12 months after etelcalcetide initiation.

Analytical Approach: Cumulative incidence methods for etelcalcetide discontinuation and linear generalized estimating equations for trajectory analyses.

Results: By August 2019, etelcalcetide prescriptions increased to 6% of HD patients from their first use in April 2017. Starting etelcalcetide dose was 15 mg/wk in 70% of patients and 7.5 mg/wk in 27% of patients; 49% of new users were prescribed cinacalcet in the prior 3 months. Etelcalcetide discontinuation was 9%, 17%, and 27% by 3, 6, and 12 months after initiation. One year after etelcalcetide initiation, mean PTH levels declined by 40%, from 948 to 566 pg/mL, and the proportion of patients with PTH within target (150-599 pg/mL) increased from 33% to 64% overall, from 0 to 60% among patients with baseline PTH ≥ 600 pg/mL, and from 30% to 63% among patients with prior cinacalcet use. The proportion of patients with serum phosphorus > 5.5 mg/dL decreased from 55% to 45%, while the prevalence of albumin-corrected serum calcium < 7.5 mg/dL remained at 1%-2%. There were increases in use of active vitamin D (from 77% to 87%) and calcium-based phosphate binders (from 41% to 50%) in the 12 months after etelcalcetide initiation.

Limitations: Data are unavailable for provider dosing protocols, dose holds, or reasons for discontinuation.

Conclusions: In the 12 months after etelcalcetide initiation, patients had large and sustained reductions in PTH levels. These results support the utility of etelcalcetide as an effective therapy to achieve the KDIGO-recommended guidelines for CKD-MBD markers in HD patients.

Chronic kidney disease–mineral and bone disorder (CKD-MBD) and secondary hyperparathyroidism (SHPT) are common complications among individuals with kidney failure requiring dialysis.[1,2] Chiefly characterized by markedly elevated serum levels of parathyroid hormone (PTH) and abnormal regulation of serum calcium and phosphorus levels,[3,4] CKD-MBD is associated with a variety of adverse cardiovascular, skeletal, and clinical outcomes.[5-7] The 2003 KDOQI guideline suggested maintaining PTH levels in the 150-300 pg/mL range.[8] In 2009, international KDIGO clinical practice guidelines recommended a higher PTH target of 2 to 9 times the upper normal limit (~130-585 pg/mL) based on low-level evidence,[9] leading to a sudden and dramatic shift in the upper level of PTH target range, from 300 to 600 pg/mL, in many US hemodialysis (HD) facilities.[10] Concomitant with PTH target increases, the Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice

Monitor indicates that the proportion of US HD patients with serum PTH levels above 600 pg/mL has increased from 11% to 23% over the past decade—and from 17% to 31% among US Black patients—as of August 2019.[1] Several large observational studies have consistently shown higher mortality risks for HD patients with high PTH (≥600 pg/mL).[7,11-13]

Calcimimetics act upon the calcium-sensing receptor, causing increased sensitivity to extracellular calcium and reduced mobilization of bone calcium due to reduced PTH levels.[3,14-16] The first-generation calcimimetic, cinacalcet, was approved for US commercial use in 2004 and has been prescribed to >25% of US HD patients.[1] However, several studies have noted nonadherence to daily oral cinacalcet, thereby potentially diminishing the benefit of the therapy.[17-20] Etelcalcetide, a calcimimetic approved for US commercial use in 2017, is in contrast administered intravenously, 3 times weekly at the end of a HD session,

PLAIN-LANGUAGE SUMMARY

Randomized trials have demonstrated the efficacy of etelcalcetide, a calcimimetic approved for US commercial use in 2017, to reduce parathyroid hormone (PTH) levels in hemodialysis patients, but we speculated that its real-world effectiveness outside a controlled trial setting may differ. Studying 2,596 dialysis patients across the United States, we found that the majority of patients starting etelcalcetide had PTH levels well beyond the KDIGO-recommended upper limit, and they experienced large reductions in PTH levels over the subsequent year into the target range. Serum calcium levels also declined, but the use of active vitamin D and calcium-based phosphate binders increased, and the risk of severe hypocalcemia remained low. Intravenously administered etelcalcetide is an effective therapy for PTH reduction and has the potential to improve adherence and decrease pill burden for patients receiving in-center hemodialysis.

and thus has the potential to improve adherence and decrease pill burden for HD patients.

Clinical trial data have demonstrated the efficacy of etelcalcetide for reducing PTH levels (vs placebo and cinacalcet) in HD patients,[21-23] with a favorable benefit-risk profile.[24,25] Observational studies with a small sample size (N < 200) have shown reductions in PTH levels in patients switching from cinacalcet to etelcalcetide,[26-28] which were even greater in a subgroup of patients who were nonadherent to cinacalcet.[27] However, real-world data regarding etelcalcetide utilization practices, effectiveness, and clinical characteristics of HD patients prescribed etelcalcetide are not yet available in a large national sample of US HD patients. In this study, we provide a comprehensive overview of etelcalcetide uptake and dosing among US HD patients, trajectories of CKD-MBD parameters after initiation of etelcalcetide, and estimates of time on therapy.

Methods

Data Source

DOPPS is a longitudinal cohort study of adult maintenance HD patients ongoing since 1996 that is based on a stratified national sample of randomly selected HD facilities. Study approval and patient consent were obtained as required by national and local ethics committee regulations. Detailed information on the DOPPS study design was included in prior publications.[29-32] In this analysis, the study population included HD patients treated in US DOPPS facilities between April 2017 and August 2019 (involving a range of 146-183 facilities per month).

Statistical Analysis

For each study month from April 2017 through August 2019, we estimated the cross-sectional proportion of sample patients who were prescribed at least 1 dose of etelcalcetide. Proportions were estimated using inverse probability weighting to reduce bias from missing data on etelcalcetide usage (missingness: 2% to 20% of patients per month).[33] Weights were derived from a logistic model of having etelcalcetide data, based on age, sex, Black race, dialysis vintage, and diabetes. Subsequent analyses of etelcalcetide initiators were based on a target population of etelcalcetide initiators rather than all HD patients and were thus not weighted to be representative of the US HD sample.

A new-user cohort was identified as patients who were prescribed etelcalcetide after a period of at least 1 month during which the patient was not prescribed etelcalcetide. For patients with multiple initiations defined in this manner, only the first initiation was included. Demographic variables (age, sex, race, and dialysis vintage), baseline CKD-MBD laboratory measurements (serum PTH, albumin-corrected calcium, phosphorus, and total alkaline phosphatase [ALP]), CKD-MBD medication history (active vitamin D, cinacalcet, phosphate binders, dialysate calcium, and dialysate bicarbonate), and other dialysis parameters (single-pool Kt/V and treatment time) were obtained at or within 3 months before etelcalcetide initiation. Comorbid conditions were abstracted from medical records at DOPPS enrollment and included gastrointestinal bleed, coronary artery disease, congestive heart failure, other cardiovascular disease, and diabetes. Patients with baseline PTH < 150 pg/mL were excluded from the new-user cohort (2% of new users).

In the new-user cohort, we examined trajectories of etelcalcetide dose, CKD-MBD laboratory values, and medication use after initiation of etelcalcetide therapy. Last-observation-carry-forward imputation (up to 3 months) was used for dose and all laboratory values. Mean etelcalcetide dose, percentage of patients on MBD medications, mean MBD marker values, and percentage of patients in MBD marker target ranges (PTH, 150-599 pg/mL; albumin-corrected serum calcium, 8.4-10.2 mg/dL; serum phosphorus, 3.5-5.5 mg/dL) while on therapy were estimated separately using generalized estimating equations models, with discrete time since etelcalcetide initiation as the exposure variable and a first-order autoregressive covariance structure to control for within-patient correlation. Dose, laboratory, and medication data were also summarized descriptively in categories using stacked bar charts.

If a patient was not prescribed etelcalcetide in any given month, their data were excluded for that month, though their subsequent data would be included if they restarted therapy. Patient-months for trajectories started at the month of first reported etelcalcetide prescription

and ended at the earliest of study departure (due to death, withdrawal from dialysis, kidney transplantation, switch to peritoneal dialysis, transfer to another facility, recovery of kidney function), 12 months from initiation, or August 2019. Month 0 (baseline) laboratory values were before etelcalcetide initiation. Fitted mean values for each month from the generalized estimating equations models, with robust sandwich-based confidence intervals, were plotted and overlaid with local regression (LOESS) smoothed trend lines to aid visualization.[34]

Discontinuation of etelcalcetide therapy was defined as having no etelcalcetide administrations reported during a study month. Time to first discontinuation was described using cumulative incidence functions in a competing-risks analysis. Patient time at risk for etelcalcetide discontinuation started at the month of first reported etelcalcetide prescription and ended at the earliest of discontinuation, study departure, 12 months from initiation, or August 2019. Death or study departure for any reason was treated as a competing event. We performed a sensitivity analysis ignoring competing risks using Kaplan-Meier methods.

Prespecified analysis subgroups included dialysis organization size, cinacalcet use in the 3 months before etelcalcetide initiation, baseline serum PTH, initial etelcalcetide dose, age (<65 vs ≥65 years old), dialysis vintage (<3 vs ≥3 years), Black versus non-Black race, and diabetic status, with sample sizes described in Table S1. Dialysis organization size subgroups consisted of small/independent dialysis organizations owning fewer than 10 facilities (SDO/IND) and large/medium dialysis organizations owning 10 or more facilities (LDO/MDO).

Results

Etelcalcetide Prescription Prevalence

Etelcalcetide prescriptions were first observed in US DOPPS in April 2017, first increased to over 1% of US HD patients in early 2018, and steadily increased to a plateau of 6% in April-August 2019 (Fig 1). By August 2019, prescription prevalence was 20.0% in SDO/IND facilities and only 4.3% in LDO/MDOs.

New-User Cohort Characteristics

The general characteristics of the 2,596 etelcalcetide new users identified in US DOPPS are summarized in Table 1. The mean age was 67.3 years, and median dialysis vintage was 4.4 years; 51% of the new users were Black. Most patients had been prescribed active vitamin D (83%) or a phosphate binder (85%) in the 3 months before etelcalcetide initiation, and the majority of patients (67%) were prescribed a dialysate calcium of 2.5 mEq/L. About half (49%) of the etelcalcetide initiators had been prescribed cinacalcet in the prior 3 months. At the time of initiation, the mean serum albumin-corrected calcium was 9.2 mg/dL, mean serum phosphorus was 5.9 mg/dL, and median total ALP was 106 U/L. The mean PTH at etelcalcetide initiation was 948 pg/mL overall, 840 pg/mL in SDO/IND facilities, and 1,245 pg/mL in LDO/MDOs. The mean PTH at etelcalcetide initiation was particularly high among patients with prior cinacalcet use who were treated in LDO/MDOs (1,444 pg/mL). The patient characteristics are summarized by dialysis organization size, prior cinacalcet use, and starting dose in Table 1.

Etelcalcetide Discontinuation

The proportions of new users who discontinued etelcalcetide were 9%, 17%, and 27% within 3, 6, and 12
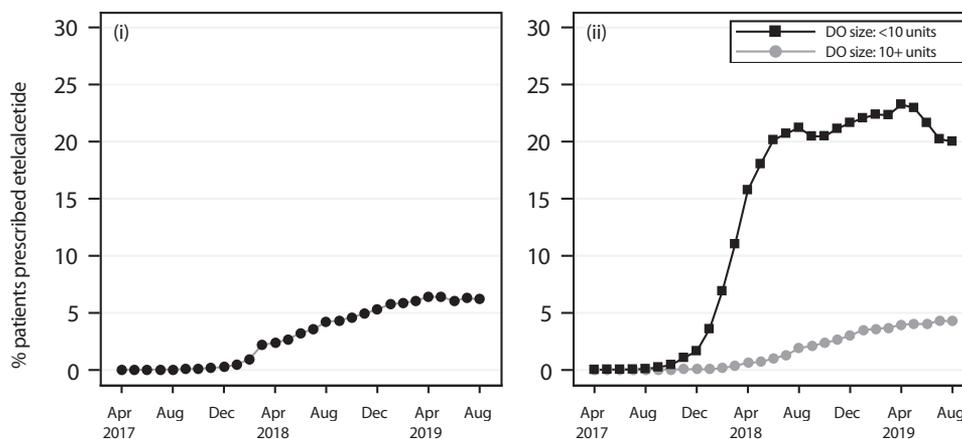

Figure 1. Percent of US hemodialysis patients prescribed etelcalcetide, by month. The sample size varied by month, from 8,799 to 10,737 with a mean of 10,209 patients. The cohort of new users, which is used in the remainder of the analyses, was identified from this sample. DO size subgroups consisted of small/independent DOs owning fewer than 10 facilities and large/medium DOs owning 10 or more facilities. Abbreviation: DO, dialysis organization.

Table 1. New User Cohort Characteristics at Time of Etelcalcetide Initiation

| | Overall (N = 2,596) | Dialysis Organization Size[a] | | Prior Cinacalcet Use[a] | | Initial Etelcalcetide Dose | |
		≥10 Units (n = 606)	<10 Units (n = 1,850)	No (n = 1,329)	Yes (n = 1,267)	7.5 mg/wk (n = 678)	15 mg/wk (n = 1,765)
Age, y	67.3 (13.0)	64.9 (13.8)	68.4 (12.6)	68.3 (12.7)	66.2 (13.3)	68.1 (13.4)	67.2 (12.8)
Dialysis vintage, y	4.4 [2.2-7.7]	5.6 [2.7-8.7]	4.0 [2.0-7.3]	3.2 [1.5-6.0]	5.9 [3.2-9.1]	4.3 [2.1-7.6]	4.4 [2.2-7.7]
Male sex	54%	54%	54%	53%	55%	52%	55%
Black race	51%	69%	45%	46%	55%	54%	50%
GI bleeding at study entry	2%	5%	2%	2%	3%	4%	2%
Coronary artery disease	16%	20%	16%	18%	15%	18%	16%
Congestive heart failure	22%	27%	21%	24%	20%	25%	22%
Other cardiovascular disease	16%	14%	17%	16%	15%	16%	15%
Diabetes	54%	52%	55%	59%	49%	58%	53%
Active vitamin D use[a]	83%	84%	83%	80%	86%	85%	82%
Prior cinacalcet use[a]	49%	57%	45%	0	100%	40%	53%
Phosphate binder use[a]	85%	95%	82%	79%	93%	80%	88%
Calcium based	43%	39%	44%	42%	44%	39%	45%
Non–calcium based	65%	87%	59%	56%	75%	61%	67%
Initial etelcalcetide dose							
7.5 mg/wk	27%	25%	28%	32%	22%	100%	0
15 mg/wk	70%	73%	69%	66%	76%	0	100%
22.5-45 mg/wk	2%	2%	2%	2%	3%	0	0
Mean serum PTH, pg/mL	948 (651)	1,245 (746)	840 (579)	834 (540)	1,068 (732)	844 (581)	983 (667)
Median serum PTH	762 [510-1,158]	1,048 [703-1,578]	698 [467-1,018]	705 [493-1,004]	853 [536-1,376]	686 [465-1,019]	804 [534-1,206]
150-299 pg/mL	6%	2%	8%	5%	7%	7%	6%
300-449 pg/mL	13%	5%	15%	16%	10%	17%	11%
450-599 pg/mL	14%	9%	15%	15%	13%	17%	13%
600-999 pg/mL	33%	29%	35%	39%	27%	33%	33%
1,000+ pg/mL	34%	54%	26%	25%	43%	26%	36%
Albumin-corrected serum calcium	9.2 (0.7)	9.3 (0.7)	9.2 (0.7)	9.2 (0.7)	9.3 (0.7)	9.3 (0.7)	9.2 (0.7)
<7.5 mg/dL	1%	1%	1%	1%	1%	1%	1%
7.5-8.3 mg/dL	8%	6%	8%	10%	6%	7%	8%
8.4-9.4 mg/dL	53%	48%	54%	57%	49%	51%	54%
9.5-10.2 mg/dL	32%	37%	31%	29%	35%	36%	31%
10.3+ mg/dL	6%	7%	6%	4%	9%	5%	7%
Serum phosphorus	5.9 (1.6)	6.2 (1.6)	5.8 (1.6)	5.8 (1.6)	6.0 (1.7)	5.7 (1.6)	6.0 (1.6)
<3.5 mg/dL	5%	3%	5%	4%	5%	6%	4%
3.5-5.5 mg/dL	41%	35%	43%	42%	40%	45%	39%
5.6-6.5 mg/dL	25%	28%	23%	26%	24%	23%	25%
6.6+ mg/dL	30%	34%	28%	28%	32%	26%	32%
Serum total ALP, U/L	106 [78-147]	117 [81-167]	102 [77-142]	103 [77-139]	110 [80-160]	107 [75-155]	105 [79-146]
Single-pool Kt/V	1.6 (0.3)	1.6 (0.3)	1.5 (0.2)	1.5 (0.3)	1.6 (0.2)	1.6 (0.3)	1.5 (0.2)
Treatment time, min	221 (32)	234 (37)	217 (29)	219 (31)	222 (32)	219 (30)	222 (32)
Dialysate calcium							
2-2.25 mEq/L	10%	15%	9%	11%	10%	9%	11%
2.5 mEq/L	67%	22%	81%	69%	66%	70%	66%
2.75-3 mEq/L	16%	42%	8%	15%	18%	16%	16%
3.25-3.5 mEq/L	6%	21%	2%	6%	7%	5%	7%
Dialysate bicarbonate, mEq/L	35 [34-37]	34 [34-35]	35 [35-38]	35 [34-37]	35 [34-37]	35 [34-37]	35 [34-37]

All characteristics reported as %, mean (SD), or median [interquartile range]. Demographic variables were obtained during the month of etelcalcetide initiation. Comorbidities were obtained at DOPPS study entry. Laboratory variables were obtained in the month before etelcalcetide initiation. Initial etelcalcetide dose was unknown for 4% of patients and was >15 mg/wk for 2% of patients. Dialysis organization size was unknown for 5% of patients. Dialysis organization size subgroups consisted of small/independent dialysis organizations owning <10 facilities and large/medium dialysis organizations owning ≥10 facilities. Abbreviations: ALP, alkaline phosphatase; GI, gastrointestinal; PTH, parathyroid hormone.
[a]Active vitamin D, prior cinacalcet, and phosphate binder use defined as any use during the 3 months before etelcalcetide initiation. Calcium-based and non–calcium-based phosphate binder use sum up to greater than overall phosphate binder use because some patients were prescribed both types.

months, respectively. Higher rates of etelcalcetide discontinuation were observed for patients without versus with cinacalcet use in the 3 months before initiation, with PTH < 600 versus ≥ 600 pg/mL at initiation, and with starting etelcalcetide dose of 7.5 versus 15 mg/wk (Fig 2). Higher rates of etelcalcetide discontinuation were also observed for patients <65 versus ≥65 years old and with dialysis vintage <3 versus ≥3 years; minimal differences were observed by race or diabetes status (Fig S1). The proportion of new users who discontinued etelcalcetide was similar when calculated using Kaplan-Meier methods.

Etelcalcetide Dosing Patterns

The starting dose of etelcalcetide for new users was 15 mg/wk (5 mg, 3 times per week) in 70% of patients, 7.5 mg/wk (2.5 mg, 3 times per week) in 27% of patients, and >15 mg/wk in 2% of patients; 92 (4%) patients had an unknown initial dose. Dosing over the subsequent 12 months is illustrated in Figure 3A, both overall and by starting dose. About 40% of the patients starting at 7.5 mg/wk switched to higher doses within 2 months, usually to 15 mg/wk. Among patients starting at 15 mg/wk, 41% remained on 15 mg/wk after 12 months, 34% switched to a higher dose, and 25% switched to 7.5 mg/wk. The overall mean etelcalcetide dose started at 13.3 mg/wk and increased to about 17 mg/wk after several months (Fig 3B). Mean etelcalcetide doses were > 15 mg/wk during the 12-month follow-up period for patients with PTH ≥ 600 pg/mL at initiation and patients prescribed cinacalcet in the 3 months before initiation (Fig 3B). Dose trajectories by patient demographics are illustrated in Figure S2.

PTH Trajectory After Etelcalcetide Initiation

One year after etelcalcetide initiation, the mean PTH levels declined by 40% for patients still on therapy, from 948 to 566 pg/mL (Fig 4A), and the proportion of patients with PTH 150-599 pg/mL increased from 33% to 64% (Fig 4B). Two-thirds of patients initiated etelcalcetide with PTH ≥ 600 pg/mL; in this subgroup (mean PTH of 1,198 pg/mL at initiation), 60% of patients had PTH in the target range (150-599 pg/mL) after 12 months (Fig 4B). Patients prescribed (vs not prescribed) cinacalcet in the 3 months before etelcalcetide initiation had a mean PTH at initiation of 1,046 (vs 838 pg/mL); PTH levels declined in both subgroups after etelcalcetide initiation, and the proportion of patients with PTH 150-599 pg/mL after 12 months was in the range of 60% to 70%. Parallel reductions in PTH levels were observed by starting dose (Fig 4A) and patient
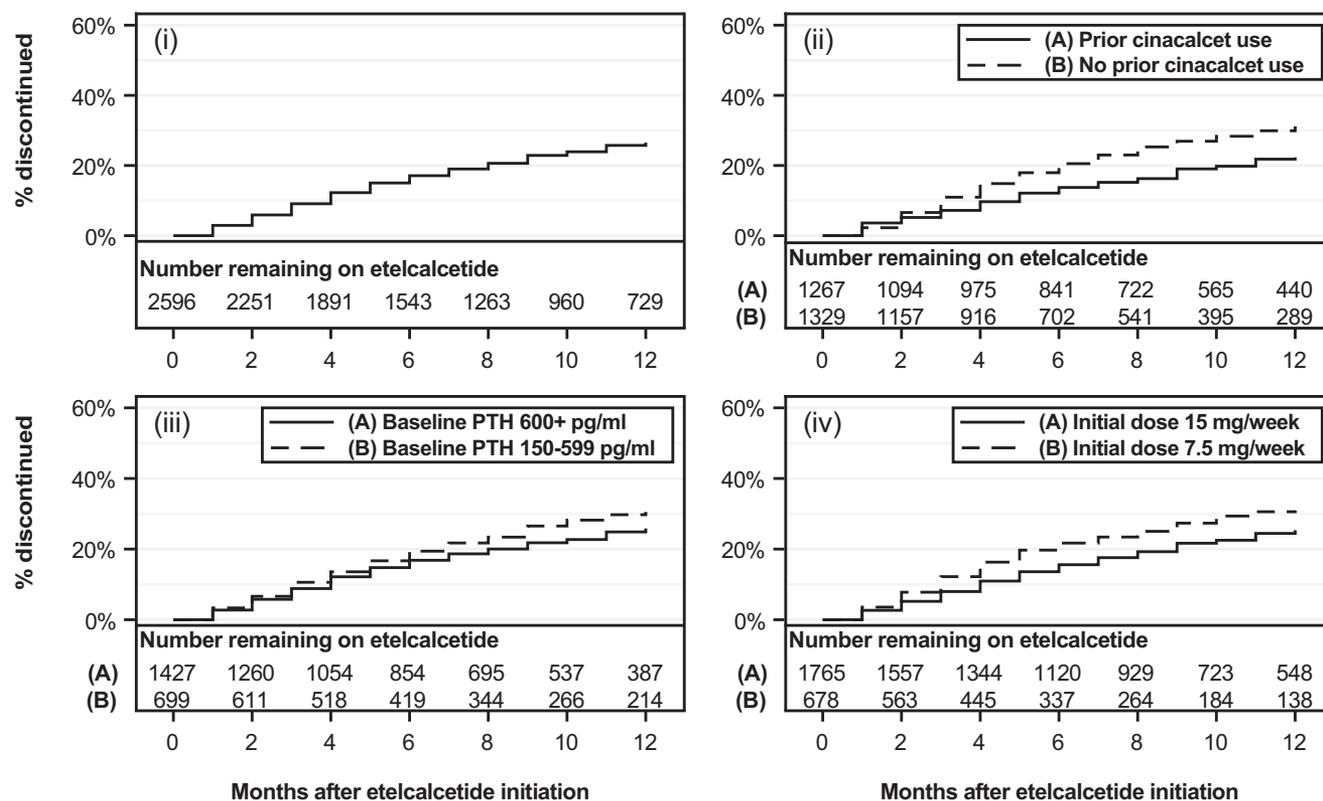

Figure 2. Cumulative incidence of first etelcalcetide discontinuation. Time at risk for etelcalcetide discontinuation ended at the earliest of discontinuation, study departure, 12 months from initiation, or August 2019; study departure was considered a competing event. Patients may have subsequently restarted etelcalcetide. Abbreviation: PTH, parathyroid hormone.
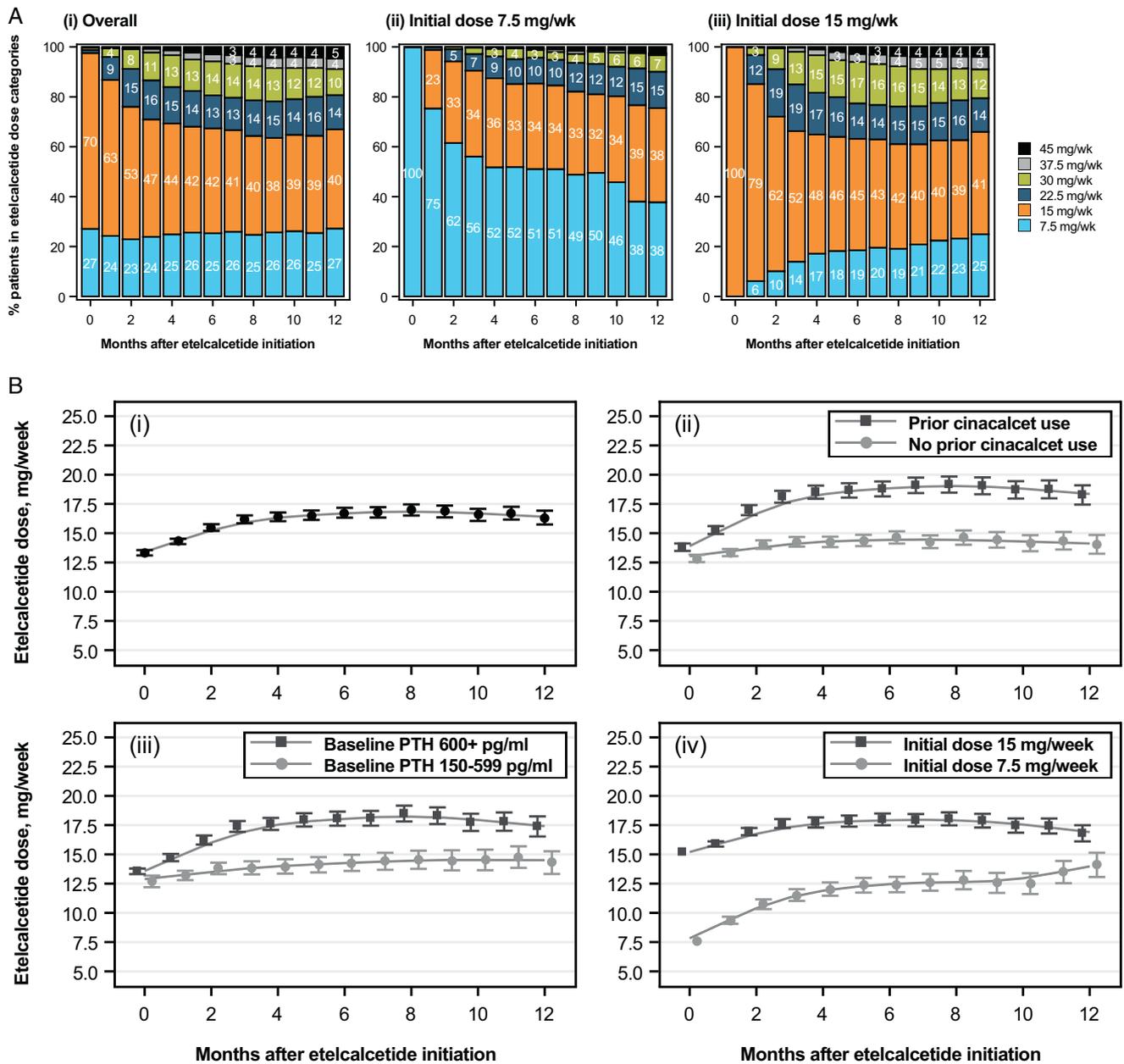
Figure 3. (A) Trajectories of etelcalcetide dose, in categories, after initiation of etelcalcetide. The dose distribution is shown only among patients with an active etelcalcetide prescription in a given month. Sample sizes at 0 and 12 months in each panel were (i) 2,503 and 757, (ii) 678 and 151, and (iii) 1,764 and 570. (B) Trajectories of mean etelcalcetide dose after initiation of etelcalcetide. The mean dose is shown only among patients with an active etelcalcetide prescription in a given month. Error bars indicate 95% CI. Abbreviation: PTH, parathyroid hormone.

demographics (Fig S3) including age, dialysis vintage, race, and diabetes status.

Serum Calcium Trajectory After Etelcalcetide Initiation

Mean serum albumin-corrected calcium levels declined from 9.2 to 8.8 mg/dL in the first 2 months after initiating etelcalcetide and ranged from 8.7 to 8.9 mg/dL (Fig S4) in the subsequent 10 months. The proportion of patients with serum albumin-corrected calcium of 8.4-9.4 mg/dL 12 months after etelcalcetide initiation was 58% overall, 52% among those with baseline PTH ≥ 600 pg/mL, and 67% among those with baseline PTH 150-599 pg/mL (Fig S5). Prevalence of high serum albumin-corrected calcium (≥9.5 mg/dL) was 38% at etelcalcetide initiation, and declined to 15% to 20% during the 12 months after initiation (Fig S5). The proportion of patients with serum albumin-corrected calcium of 7.5-8.3 mg/dL increased from 8% to 27% in
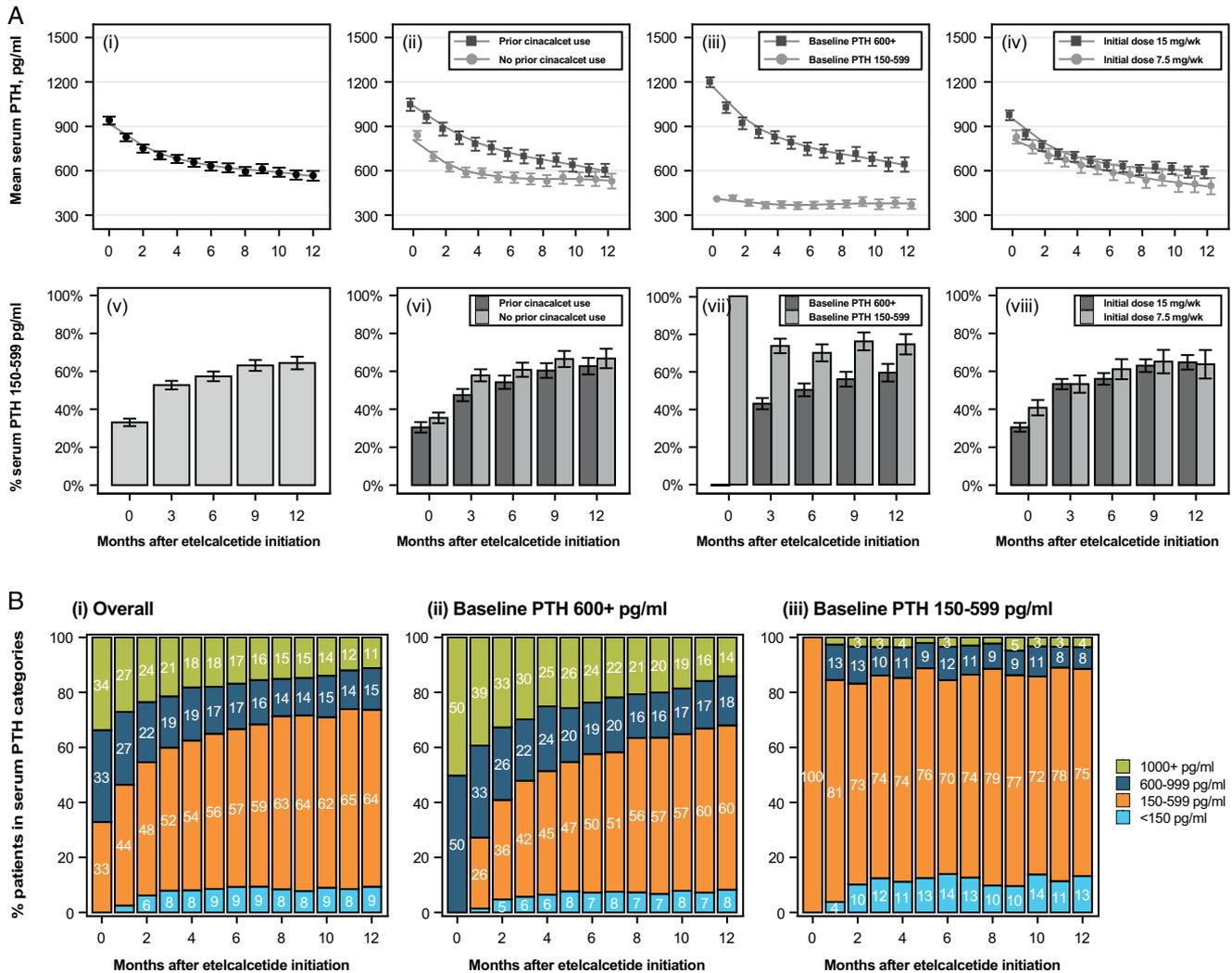
Figure 4. (A) Trajectories of mean serum PTH values and percentage in target PTH range (150-599 pg/mL) before and after initiation of etelcalcetide. Month 0 values are pretreatment; later values are during treatment. PTH is shown only among patients with an active etelcalcetide prescription in a given month. Error bars indicate 95% CI. (B) Trajectories of serum PTH values, in categories, before and after initiation of etelcalcetide. Month 0 values are pretreatment; later values are during treatment. PTH is shown only among patients with an active etelcalcetide prescription in a given month. Sample sizes at 0 and 12 months in each panel were (i) 2,126 and 715, (ii) 1,427 and 375, and (iii) 699 and 227. Abbreviation: PTH, parathyroid hormone.

the 3 months after etelcalcetide initiation, and subsequently declined to 21% after 12 months; the prevalence of low serum albumin-corrected calcium (<7.5 mg/dL) remained 1% to 2% in the first year after etelcalcetide initiation (Fig S5). Serum albumin-corrected calcium trajectories were roughly parallel by patient demographics (Fig S6).

Serum Phosphorus Trajectory After Etelcalcetide Initiation

Mean serum phosphorus levels declined from 5.9 to 5.6 mg/dL in the first 2 months after etelcalcetide initiation (Fig S7). The proportion of patients with high serum phosphorus (>5.5 mg/dL) declined from 55% to 45% in the 12 months after etelcalcetide initiation (Fig S8). Serum

phosphorus trajectories were roughly parallel by patient demographics (Fig S9).

Total Alkaline Phosphatase Trajectory After Etelcalcetide Initiation

In the 12 months after etelcalcetide initiation, mean total ALP levels declined from 131 to 107 U/L (Fig S10), and the proportion of patients with total ALP ≥ 120 U/L decreased from 40% to 23% (Fig S11).

MBD Medication Use After Etelcalcetide Initiation

Trajectories of noncalcimimetic MBD medications in the 12 months after etelcalcetide initiation are illustrated in Figure 5. The proportion of patients prescribed active
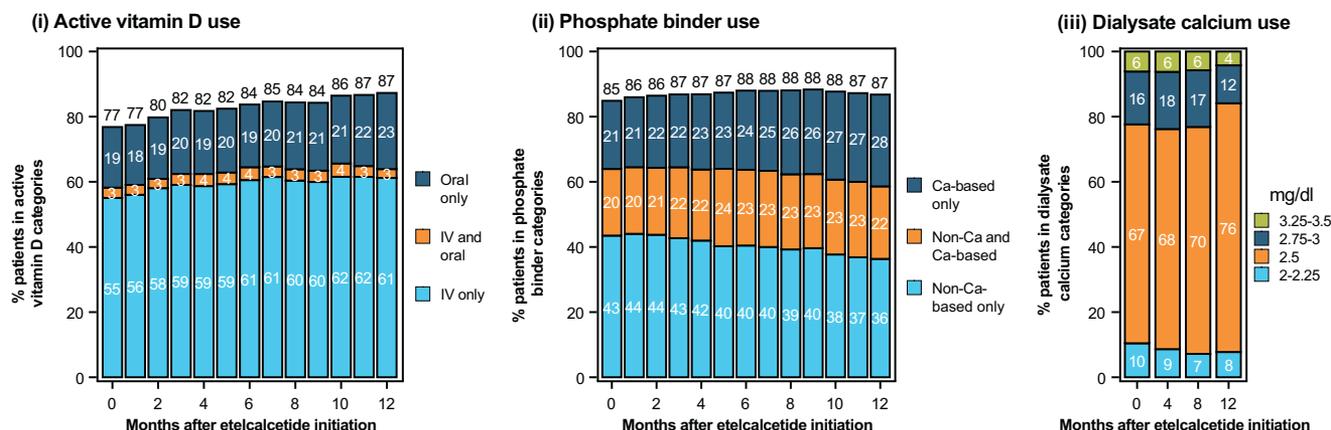
Figure 5. Trajectories of mineral bone disorder medication use, in categories, after initiation of etelcalcetide. Medication use is shown only among patients with an active etelcalcetide prescription in a given month. Active vitamin D and phosphate binder use were assessed monthly, and dialysate calcium was assessed every 4 months. Sample sizes at 0 and 12 months in each panel were (i) 2,596 and 809, (ii) 2,596 and 809, and (iii) 2,520 and 799. Abbreviations: Ca, calcium; IV, intravenous.

vitamin D each month steadily increased from 77% at etelcalcetide initiation to 87% after 12 months. Overall phosphate binder use remained steady at 85% to 88% throughout the 12 months, though the use of calcium-based phosphate binders increased from 41% to 50%. Oral calcium supplements outside of phosphate binders were rarely prescribed. In the 12 months after etelcalcetide initiation, the proportion of patients prescribed a dialysate calcium > 2.5 mEq/L ranged from 16% to 24%.

Discussion

This study of >2,500 new users of etelcalcetide demonstrates the real-world effectiveness of etelcalcetide in managing secondary hyperparathyroidism and improving achievement of KDIGO-suggested PTH target levels for HD patients. We found that patients had large and sustained improvements in the achievement of PTH target levels in the 12 months after etelcalcetide initiation, including those with high baseline PTH or prior cinacalcet use.

Prevalence of etelcalcetide use increased from its first observed use in April 2017 to up to 6% by August 2019. Etelcalcetide use was 20% in SDO/IND facilities but only 4% in LDO/MDO facilities, in which etelcalcetide use appeared to be reserved for patients with extremely high PTH levels (median of 1,048 [interquartile range, 703-1,578] pg/mL at initiation). Etelcalcetide use was also high among Black patients and those with dialysis vintage greater than 3 years—characteristics known to be associated with higher PTH levels.[11,19,35-37] In the 3 months before etelcalcetide initiation, over 80% of patients had been prescribed active vitamin D, and half had been prescribed cinacalcet. Yet new users of etelcalcetide still had very high PTH levels; the proportion of patients with baseline PTH ≥ 1,000 pg/mL was 34% overall and 43% among patients with prior cinacalcet use (Table 1). Wide

variation in PTH target upper limits across US facilities[10] help explain the heterogeneity in terms of PTH levels and SHPT treatment history of etelcalcetide initiators.

Despite such high PTH levels at etelcalcetide initiation, the majority of patients appeared to be responsive to etelcalcetide. The proportion of patients with PTH in target (150-599 pg/mL) 1 year after initiation was 64% overall, and 60% among patients who initiated etelcalcetide with PTH ≥ 600 pg/mL. Although patients prescribed versus not prescribed cinacalcet in the 3 months before etelcalcetide initiation had 200 pg/mL higher mean PTH at initiation (1,046 vs 838 pg/mL), achievement of PTH 150-599 pg/mL after 12 months differed minimally by prior cinacalcet use.

Block et al demonstrated the greater efficacy of etelcalcetide in reducing PTH levels compared with both placebo[21] and cinacalcet[22] in a double-blind, randomized control trial. Our results extend these findings by illustrating the real-world effectiveness of etelcalcetide in a large stratified random national sample of US HD patients. Although direct comparisons of etelcalcetide to cinacalcet or no calcimimetic therapy were beyond the scope of the current study, they are investigated in a recent systematic review and meta-analysis by Palmer et al,[38] who found that etelcalcetide was more effective at lowering PTH than cinacalcet but with an increased risk of hypocalcemia. A large observational study of cinacalcet initiators in France[39] showed that the proportion of patients with PTH out of target range (>9 times the upper limit) after 12 months was 41%, compared with 26% with PTH > 600 pg/mL after 12 months in our study of etelcalcetide initiators. In both studies, however, the likelihood of PTH in-target after 12 months was highly dependent on baseline SHPT severity, suggesting the potential benefit of treating SHPT at earlier stages. Our results are consistent with 3 recent prospective observational studies (N < 200) from Italy and

Spain demonstrating the effectiveness of etelcalcetide for managing SHPT.[26-28] Our study extends results from these European studies to the United States, where PTH levels tend to be higher.[2,13]

High levels of serum albumin-corrected calcium (≥9.5 mg/dL), previously shown in an observational study to be associated with cardiovascular mortality,[7] were present in 38% of new users of etelcalcetide and declined to 15%-20% during the subsequent 12 months. The proportion of patients with moderately low serum albumin-corrected calcium (7.5-8.3 mg/dL) increased from 8% to 27% in the 3 months after etelcalcetide initiation, supporting the need to monitor serum calcium levels after etelcalcetide initiation to avoid hypocalcemia. However, the prevalence of serum albumin-corrected calcium <7.5 mg/dL was very low (1%-2%) in the first year after etelcalcetide initiation. These results are consistent with recent safety studies suggesting low frequency of symptomatic hypocalcemia with etelcalcetide use or hypocalcemia-induced discontinuation of etelcalcetide.[24,25] Furthermore, the etelcalcetide label indicates that serum albumin-corrected calcium should be at or above the lower limit of normal when initiating therapy.[40]

The observed decline in serum albumin-corrected calcium levels after etelcalcetide initiation were likely responsible for the increased use of active vitamin D (from 77% to 87%) and calcium-based phosphate binder use (from 41% to 50%) over the subsequent 12 months, potentially due to fewer concerns about hypercalcemia and/or as a means to avoid hypocalcemia. This is consistent with the medication label recommending to "use concomitant therapies to increase corrected serum calcium in patients with a corrected serum calcium below the lower limit of normal."[40] Changes in serum phosphorus were also observed after etelcalcetide initiation, especially among patients with baseline PTH ≥ 600 pg/mL. In this subgroup, the prevalence of hyperphosphatemia (serum phosphorus > 5.5 mg/dL) declined from 60% to 45% in the 12 months after etelcalcetide initiation. A decline in mean total alkaline phosphatase, from 131 to 107 U/L, was also observed in the 12 months after etelcalcetide initiation.

We found that 27% of patients discontinued etelcalcetide within 12 months; the reasons for discontinuation were unknown but likely include tolerability, adherence, and achievement of the PTH goal. Tolerability, as measured by the frequency of self-reported nausea and vomiting, was reported to be similar for patients randomized to etelcalcetide versus cinacalcet.[22] Even with no difference in symptoms, we would expect that outside a controlled trial setting, medications administered intravenously at the HD facility would have better adherence than oral medications prescribed to be taken daily at home. Indeed, the proportions of patients who discontinued oral cinacalcet within 12 months in real-world studies of US HD patients by Kilpatrick et al[19] (40%; using provider-based medication lists) and by Reams et al[20] (73%;

using Medicare Part D claims data) were higher than found for etelcalcetide in our study. Better calcimimetic adherence may in turn improve SHPT management[41] and has been associated with fewer hospitalizations.[42] Further, because calcimimetics are often co-prescribed with an active vitamin D analog in the United States,[1] etelcalcetide discontinuation may also reflect intermittent use of etelcalcetide as a second-line therapy to help manage SHPT or prevent hypercalcemia.[37]

By effectively lowering PTH levels, etelcalcetide can serve as another tool to manage SHPT and improve achievement of KDIGO-recommended targets, which has been relatively poor in the United States. In contrast to the 2003 KDOQI guideline's target of 150-300 pg/mL,[8] the 2009 KDIGO CKD-MBD guideline (and 2017 update) suggested maintaining PTH levels between 2 and 9 times the upper limit of normal according to the PTH assay used (ie, ~130-585 pg/mL).[9,43] In the 10 years since, the overall proportion of US HD patients with PTH ≥ 600 pg/mL has increased from 11% to 23% overall, and from 17% to 31% among US Black patients.[1] Large observational studies have consistently shown higher mortality risks for HD patients at PTH levels ≥ 600 pg/mL.[7,11-13] Although the EVOLVE trial of cinacalcet versus placebo failed to demonstrate a survival benefit in the primary (intent-to-treat) analyses (hazard ratio, 0.93 [95% CI, 0.85-1.02]), substantial reductions in PTH levels were achieved.[44]

The above guidelines and study findings raise the question of why PTH levels have been allowed to increase to such high levels for a large fraction of US HD patients. Prior DOPPS research has shown the prevalence of high PTH (≥600 pg/mL) to be substantially lower in Europe (13%) and Japan (1%).[45] Our results provide supporting evidence for recommending initiation of etelcalcetide therapy earlier, before PTH levels increase to the point it becomes more difficult to reduce them back to target range.

A key strength of our study is the large and randomly selected sample of US HD facilities, allowing the inclusion of >2,500 new users of etelcalcetide. Another strength is the availability of laboratory data as collected during routine clinical practice, which is often unavailable when using claims data.

Our study also had some limitations. First, we do not have access to provider protocols; although we received information on the start and end dates for medication prescriptions, dose holds may not have been recorded if the prescription was unchanged. Second, information on the prescription was available in DOPPS, but not adherence to the prescription. Third, specific reasons for etelcalcetide initiation and discontinuation were not collected, preventing further investigation of the motivations for prescription and the causes of discontinuation. Fourth, given the scale of our study, including data from >150 US HD facilities from both LDOs plus many SDO/IND facilities, the PTH assay was not standardized across participating US DOPPS facilities. Because KDIGO guideline recommendations are based on 2-9 times the upper limit

of normal and not on absolute values, interassay variability may have contributed to measurement error in assessing PTH levels. Assuming this measurement error was random, it would have likely led to increased variability in PTH levels and the proportion of patients who achieved the target PTH, but would be unlikely to bias results in either direction. Fifth, although serum 25-hydroxyvitamin D levels would have been of interest to report, these data are rarely measured in routine US HD facility practice, and thus DOPPS data on 25-hydroxyvitamin D levels are sparse. Finally, information on hospitalization diagnosis and procedure codes was not available in the current data, so we could not report on rates of parathyroidectomy, fracture, or any other event in the months after etelcalcetide initiation.

We first observed etelcalcetide prescriptions in US DOPPS in April 2017; prevalence increased to 6% by mid-2019, though uptake was much greater in small/independent versus large dialysis organizations. In the 12 months after etelcalcetide initiation, patients had large and sustained reductions in PTH levels, especially among those with high baseline PTH or prior cinacalcet use. Decreases in serum phosphorus (especially for patients with baseline PTH ≥ 600 pg/mL) and serum calcium were also observed, with minimal risk of hypocalcemia. Potentially due to the decline in serum calcium levels, use of active vitamin D and calcium-based phosphate binders increased in the 12 months after etelcalcetide initiation. These results support the utility of etelcalcetide as an effective therapy to achieve the KDIGO recommendations[9] for CKD-MBD markers in HD patients.

Supplementary Material

Supplementary File (PDF)

Article Information

Authors' Full Names and Academic Degrees: Angelo Karaboyas, PhD, Daniel Muenz, PhD, Douglas S. Fuller, MS, Pooja Desai, PhD, Tzu-Chieh Lin, PhD, Bruce M. Robinson, MD, Sandro Rossetti, MD, and Ronald L. Pisoni, PhD.

Authors' Affiliations: Arbor Research Collaborative for Health, Ann Arbor, Michigan (AK, DM, DSF, BMR, RLP); and Amgen, Inc, Thousand Oaks, California (PD, T-ZL, SR).

Address for Correspondence: Angelo Karaboyas, PhD, Arbor Research Collaborative for Health, 3700 Earhart Rd, Ann Arbor, MI 48105. Email: angelo.karaboyas@arborresearch.org

References

1. Arbor Research Collaborative for Health. Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor. Accessed on January 23, 2020. https://www.dopps.org/dpm

2. Hedgeman E, Lipworth L, Lowe K, Saran R, Do T, Fryzek J. International burden of chronic kidney disease and secondary hyperparathyroidism: a systematic review of the literature and available data. *Int J Nephrol*. 2015;2015:184321.

3. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: pathogenesis, disease progression, and therapeutic options. *Clin J Am Soc Nephrol*. 2011;6:913-921.

4. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. *Kidney Int*. 2008;74(3):276-288.

5. Covic A, Kothawala P, Bernal M, Robbins S, Chalian A, Goldsmith D. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. *Nephrol Dial Transplant*. 2009;24:1506-1523.

6. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15:2208-2218.

7. Tentori F, Blayney MJ, Albert JM, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2008;52:519-530.

8. Eknoyan G, Levin A, Levin NW. Bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42:1-201.

9. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Workgroup. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)*. 2017;7(1):1-59.

10. Tentori F, Fuller DS, Port FK, Bieber BA, Robinson BM, Pisoni RL. The DOPPS practice monitor for US dialysis care: potential impact of recent guidelines and regulatory changes on management of mineral and bone disorder among US hemodialysis patients. *Am J Kidney Dis*. 2014;63(5):851-854.

11. Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. *Kidney Int*. 2005;67:1179-1187.

12. Kalantar-Zadeh K, Kuwae N, Regidor DL, et al. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int*. 2006;70(4):771-780.

13. Tentori F, Wang M, Bieber BA, et al. Recent changes in therapeutic approaches and association with outcomes among patients with secondary hyperparathyroidism on chronic hemodialysis: the DOPPS study. *Clin J Am Soc Nephrol*. 2015;10:98-109.

14. Nemeth EF, Heaton WH, Miller M, et al. Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. *J Pharmacol Exp Ther*. 2004;308(2):627-635.

15. Cunningham J, Floege J, London G, Rodriguez M, Shanahan CM. Clinical outcomes in secondary hyperparathyroidism and the potential role of calcimimetics. *NDT Plus*. 2008;1(suppl 1):i29-i35.

16. Valle C, Rodriguez M, Santamaría R, et al. Cinacalcet reduces the set point of the PTH-calcium curve. *J Am Soc Nephrol*. 2008;19(12):2430-2436.

17. Lee A, Song X, Khan I, et al. Association of cinacalcet adherence and costs in patients on dialysis. *J Med Econ*. 2011;14:798-804.

18. Fuller DS, Hallett D, Dluzniewski PJ, et al. Predictors of cinacalcet discontinuation and reinitiation in hemodialysis patients: results from 7 European countries. *BMC Nephrol*. 2019;20(1):169.

19. Kilpatrick RD, Newsome BB, Zaun D, et al. Evaluating real-world use of cinacalcet and biochemical response to therapy in U.S. hemodialysis patients. *Am J Nephrol*. 2013;37:389-398.

20. Reams BD, Dluzniewski PJ, Do TP, et al. Dynamics of cinacalcet use and biochemical control in hemodialysis patients: a retrospective new-user cohort design. *BMC Nephrol*. 2015;16:175.

21. Block GA, Bushinsky DA, Cunningham J, et al. Effect of etelcalcetide vs placebo on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: two randomized clinical trials. *JAMA*. 2017;317(2):146-155.

22. Block GA, Bushinsky DA, Cheng S, et al. Effect of etelcalcetide vs cinacalcet on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: a randomized clinical trial. *JAMA*. 2017;317:156-164.

23. Cunningham J, Block GA, Chertow GM, et al. Etelcalcetide is effective at all levels of severity of secondary hyperparathyroidism in hemodialysis patients. *Kidney Int Rep*. 2019;4(7):987-994.

24. Block GA, Chertow GM, Sullivan JT, et al. An integrated analysis of safety and tolerability of etelcalcetide in patients receiving hemodialysis with secondary hyperparathyroidism. *PLoS One*. 2019;14(3):e0213774.

25. Bushinsky DA, Chertow GM, Cheng S, et al. One-year safety and efficacy of intravenous etelcalcetide in patients on hemodialysis with secondary hyperparathyroidism. *Nephrol Dial Transplant*. 2020;35(10):1769-1778. Published correction appears in Nephrol Dial Transplant. 2019;35(9):1642.

26. Russo D, Tripepi R, Malberti F, et al. Etelcalcetide in patients on hemodialysis with severe secondary hyperparathyroidism: multicenter study in "real life. *J Clin Med*. 2019;8(7):1066.

27. Xipell M, Montagud-Marrahi E, Rubio MV, et al. Improved control of secondary hyperparathyroidism in hemodialysis patients switching from oral cinacalcet to intravenous etelcalcetide, especially in nonadherent patients. *Blood Purif*. 2019;48(2):106-114.

28. Arenas MD, Rodelo-Haad C, de Mier MVP, Rodriguez M. Control of hyperparathyroidism with the intravenous calcimimetic etelcalcetide in dialysis patients adherent and nonadherent to oral calcimimetics. *Clin Kidney J*. 2020;14(3):840-846.

29. Young EW, Goodkin DA, Mapes DL, et al. The Dialysis Outcomes and Practice Patterns Study (DOPPS): an international hemodialysis study. *Kidney Int*. 2000;57(suppl 74):S74-S81.

30. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA. The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. *Am J Kidney Dis*. 2004;44(5)(suppl 2):7-15.

31. Robinson B, Fuller D, Zinsser D, et al. The Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor:

rationale and methods for an initiative to monitor US bundled dialysis payment system. *Am J Kidney Dis*. 2011;57:822-831.

32. Arbor Research Collaborative for Health. Dialysis Outcomes and Practice Patterns Study (DOPPS) Practice Monitor Methods. Accessed on April 30, 2020. https://www.dopps.org/DPM/Data_Sources_Methods.pdf

33. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res*. 2013;22(3):278-295.

34. Cleveland WS. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc*. 1979;74:829-836.

35. Fuller DS, Xing S, Belozeroff V, et al. Variability in cinacalcet prescription across US hemodialysis facilities. *Clin J Am Soc Nephrol*. 2019;14(2):241-249.

36. Newsome BB, Kilpatrick RD, Liu J, et al. Racial differences in clinical use of cinacalcet in a large population of hemodialysis patients. *Am J Nephrol*. 2013;38:104-114.

37. St Peter WL, Li Q, Liu J, et al. Cinacalcet use patterns and effect on laboratory values and other medications in a large dialysis organization, 2004 through 2006. *Clin J Am Soc Nephrol*. 2009;4:354-360.

38. Palmer SC, Mavridis D, Johnson DW, Tonelli M, Ruospo M, Strippoli GFM. Comparative effectiveness of calcimimetic agents for secondary hyperparathyroidism in adults: a systematic review and network meta-analysis. *Am J Kidney Dis*. 2020;76(3):321-330.

39. Rottembourg J, Ureña-Torres P, Toledano D, et al. Factors associated with parathyroid hormone control in haemodialysis patients with secondary hyperparathyroidism treated with cinacalcet in real-world clinical practice: Mimosa study. *Clin Kidney J*. 2019;12(6):871-879.

40. Parsabiv (etelcalcetide) injection, for intravenous use [package insert]. KAI Pharmaceuticals Inc/Amgen; 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208325Orig1s000Lbledt.pdf

41. Friedl C, Zitt E. Role of etelcalcetide in the management of secondary hyperparathyroidism in hemodialysis patients: a review on current data and place in therapy. *Drug Des Devel Ther*. 2018;12:1589-1598.

42. Roggeri A, Conte F, Rossi C, Cozzolino M, Zocchetti C, Roggeri DP. Cinacalcet adherence in dialysis patients with secondary hyperparathyroidism in Lombardy Region: clinical implications and costs. *Drugs Context*. 2020;9:2020-2021-1.

43. Kidney Disease: Improving Global Outcomes (KDIGO) CKD MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2009;113:S1-S130.

44. EVOLVE Trial Investigators. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*. 2012;367(26):2482-2494.

45. Bikbov B, Bieber B, Andrusev A, et al. Hemodialysis practice patterns in the Russia Dialysis Outcomes and Practice Patterns Study (DOPPS), with international comparisons. *Hemodial Int*. 2017;21(3):393-408.