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Clinical Research Article

Parathyroidectomy vs Cinacalcet Among Patients Undergoing Hemodialysis

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Abstract

Context: Parathyroidectomy (PTx) and cinacalcet are both effective treatments for secondary hyperparathyroidism in hemodialysis patients, but limited data exist comparing the long-term outcomes of these interventions.

Objective: We aimed to compare the risk of mortality among hemodialysis patients who underwent PTx and those who started treatment with cinacalcet.

Methods: In this prospective cohort study, comprising patients from the Japanese Society for Dialysis Therapy Renal Data Registry, patients who had intact parathyroid hormone (PTH) levels ≥ 300 pg/mL in late 2007 and underwent PTx or started treatment with cinacalcet in 2008 to 2009 were matched by propensity score at 1:3. PTx and cinacalcet were compared for all-cause mortality within 6 years.

Results: Among eligible patients, 894 patients who underwent PTx were matched with 2682 patients who started treatment with cinacalcet. The median baseline intact PTH levels were 588 pg/mL and 566 pg/mL in the PTx and cinacalcet groups, respectively. PTx resulted in greater reductions in intact PTH, calcium, and phosphorus levels compared with cinacalcet. During the 6-year follow-up period, 201 patients (22.5%) in the PTx group and 736 patients (27.4%) in the cinacalcet group died. PTx was associated with a lower risk of mortality compared with cinacalcet (hazard ratio, 0.78 [95% CI, 0.67-0.91]; $P = 0.002$). This association was more pronounced in patients with intact PTH levels ≥ 500 pg/mL and in patients with serum calcium levels ≥ 10.0 mg/dL (both P for interaction < 0.001).

Conclusion: PTx compared with cinacalcet is associated with a lower risk of mortality, particularly among patients with severe secondary hyperparathyroidism.

Key Words: cinacalcet, fracture, hemodialysis, mortality, parathyroidectomy, secondary hyperparathyroidism

Abbreviations: HR, hazard ratio; JRDR, Japanese Society for Dialysis Therapy Renal Data Registry; JSDT, Japanese Society for Dialysis Therapy; LVH, left ventricular hypertrophy; PTH, parathyroid hormone; PTx, parathyroidectomy; SHPT, secondary hyperparathyroidism.

Mortality rates are unacceptably high in patients undergoing hemodialysis (1). Secondary hyperparathyroidism (SHPT) is one of the predominant factors accounting for the high mortality rates. SHPT is prevalent among patients with kidney failure, with more than 70% of patients receiving treatment for this condition in Japan and in many other countries (2). If insufficiently treated, severe SHPT can contribute to high-turnover bone disease (3, 4) and may associate with vascular calcification (5, 6), left ventricular hypertrophy (LVH) (7), immune dysfunction (8), myopathy (9), and wasting (10, 11). In epidemiological studies, elevated levels of parathyroid hormone (PTH) have been associated with cardiovascular events, mortality, and fracture (12-15). It is, however, unknown whether lowering PTH levels to a specific target range improves clinical outcomes.

Until about the last decade, the primary treatment options for SHPT have been phosphate binders and activated vitamin D; however, these interventions do not always provide adequate control of SHPT, particularly among patients with advanced parathyroid hyperplasia (16). Parathyroidectomy (PTx) is the definitive therapy for uncontrolled SHPT (17). If performed successfully, this procedure drastically lowers PTH levels (18), improves high-turnover bone disease (3), and ameliorates symptoms related to SHPT (19). PTx is thus

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suggested in clinical practice guidelines for patients with severe SHPT who are refractory to medical therapy (20, 21). Recent observational studies also reported associations between PTx and improved clinical outcomes (22-26), yet most of these studies used data obtained before the introduction of calcimimetics.

Cinacalcet hydrochloride is the first calcimimetic agent; it became available in 2004 in the US, in 2005 in Europe, and in 2008 in Japan. It effectively lowers PTH levels by the allosteric activation of the parathyroid calcium-sensing receptor (27). Of note, cinacalcet is effective even in patients with advanced parathyroid hyperplasia (28), and there have been reductions in annual rates of PTx after the introduction of cinacalcet in several countries (29-31). Studies also suggested that cinacalcet may reduce the risk of cardiovascular events, mortality, and fracture (32-34). Despite the widespread use of cinacalcet, however, few studies have evaluated the clinical outcomes in patients with SHPT undergoing hemodialysis treated with cinacalcet or PTx (35).

In this study, we used data from a nationwide registry to compare the outcomes among hemodialysis patients with SHPT who underwent PTx and those who started treatment with cinacalcet.

Methods

Data Source

This study used data from the Japanese Society for Dialysis Therapy (JSDT) Renal Data Registry (JRDR), a nationwide database of dialysis patients in Japan. Details of the database have been described elsewhere (36-38). Briefly, the JSDT prospectively collects data on demographics, comorbid conditions, laboratory values, prescriptions, and clinical outcomes by sending questionnaires to all dialysis facilities in Japan at the end of each year. In addition to the routine questionnaire, the JSDT collected data on the history of PTx in 2007 and 2009 and the use of cinacalcet in 2009. These data allow the identification of individuals who underwent PTx at some point between January 1, 2008, and December 31, 2009, and those who initiated treatment with cinacalcet at some point between January 25, 2008 (the release date of cinacalcet), and December 31, 2009. The study protocol was approved by the Medicine Ethics Committee of the JSDT. Additional details of the registry are provided in Supplementary Methods (39).

Study Population

Patients were eligible for inclusion in the study if they were aged 18 years or older, had been undergoing maintenance hemodialysis or hemodiafiltration thrice weekly for more than 3 months, had moderate to severe SHPT (intact PTH level of at least 300 pg/mL), had no history of PTx as of December 31, 2007, and underwent PTx or initiated treatment with cinacalcet between January 1, 2008, and December 31, 2009.

Outcomes

The primary outcome was all-cause mortality. The secondary outcome was cause-specific mortality, defined by the JRDR classification system as described previously (38). Because the registry did not collect the date of PTx or cinacalcet initiation, mortality follow-up started on December 31, 2009, and continued until death, transplantation, loss to follow-up, or December 31, 2015, whichever came first.

We also examined incident hip fracture in a subcohort of patients with no history of hip fracture as of December 31, 2009. The JSDT collected data on the history of hip fracture starting in 2007, which allowed the identification of the first occurrence of hip fracture among individuals with no prior history of hip fracture (40).

Statistical Analyses

Propensity score matching was used to reduce potential bias due to treatment allocation (41). The propensity score was estimated by logistic regression analysis, with PTx as the dependent variable and all baseline characteristics listed in Table 1 as covariates. Patients who underwent PTx or initiated treatment with cinacalcet were matched in a 1:3 ratio according to the propensity score. Because the baseline characteristics between the 2 groups were well balanced after propensity score matching (Table 1), we used the Kaplan-Meier method and univariate Cox regression analysis to compare mortality rates between the groups. We also estimated the absolute risk difference, with 95% CIs calculated using bootstrapping with 1000 repetitions (42). Because we could not identify the exact date of fracture, we applied an interval-censored Cox model, which was developed to deal with interval-censored data (43). Statistical significance of the between-group differences in mineral metabolism parameters over time was assessed using mixed-effects models. Because intact PTH was not normally distributed, we analyzed log-transformed values in the mixed-effects models.

We performed several sensitivity analyses to test the robustness of our findings: (1) propensity score matching in a 1:1 ratio; (2) a complete case analysis that excluded all individuals with missing data; (3) a conventional multivariable Cox regression analysis in the unmatched population; (4) inverse probability of treatment weighting, in which each patient is weighted by the inverse of the probability of that patient being assigned to the treatment group; (5) overlap weighting, in which each patient is weighted by the probability of that patient being assigned to the opposite treatment group (44); and (6) restriction of the study population to individuals who were less likely to have serious comorbidities (ie, those who were younger than 60 years of age, did not have diabetes as a cause of kidney failure, and had no history of myocardial infarction, cerebral infarction, cerebral hemorrhage, amputation, or hip fracture). We also estimated the potential effect of unmeasured confounders, using an array-approach analysis (45). To further address bias due to unmeasured confounders, we performed an instrumental variable analysis (46), using the adjusted percentage of patients undergoing PTx, among those who received PTx or cinacalcet, at each prefecture (n = 46) as the instrumental variable.

We also performed several exploratory analyses. To evaluate whether the potential benefit of PTx was attenuated in the presence of postoperative persistent SHPT, we stratified patients undergoing PTx into tertiles based on their postoperative intact PTH levels and compared mortality with their respective propensity score-matched patients receiving cinacalcet. We also asked if there was a difference in mortality rates when posttreatment parameters of mineral metabolisms were comparable between the PTx and cinacalcet groups. To do this, we additionally included posttreatment

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Table 1. Baseline characteristics before and after propensity score matching[a]

Characteristic	Before matching			After matching		
	PTx (n = 955)	Cinacalcet (n = 8228)	Standardized difference, %[b]	PTx (n = 894)	Cinacalcet (n = 2682)	Standardized difference, %[b]
Age, years	57.6 ± 11.2	59.5 ± 11.7	16.3	57.8 ± 11.2	57.5 ± 11.6	2.3
Female, %	46.5	40.0	15.1	45.1	45.3	0.5
Dialysis duration, mo	154 (106–223)	132 (82–192)	28.9	151 (104–220)	152 (99–218)	1.4
Cause of kidney failure, %						
Glomerulonephritis	60.6	56.3	10.1	61.1	58.4	6.4
Diabetes	8.7	14.0	20.1	9.1	11.0	7.4
Hypertension	2.9	4.1	7.8	3.0	3.1	0.7
Others	13.4	13.3	0.3	13.2	14.4	4.0
Unknown	14.3	12.4	6.4	13.6	13.2	1.4
Hemodiafiltration, %	13.6	10.7	10.1	13.1	13.2	0.3
Body-mass index, kg/m^2	20.8 (18.9–23.2)	21.1 (19.2–23.5)	9.8	20.8 (18.9–23.2)	20.8 (19.0–23.1)	0.5
Kt/V	1.47 ± 0.27	1.44 ± 0.28	11.0	1.47 ± 0.27	1.47 ± 0.28	0.1
nPCR, g/kg/day	0.96 ± 0.17	0.96 ± 0.17	5.2	0.96 ± 0.17	0.96 ± 0.17	0.3
Past history, %						
Myocardial infarction	4.5	4.9	2.2	4.5	4.9	2.2
Cerebral infarction	4.6	6.4	9.4	4.8	4.9	0.5
Cerebral hemorrhage	3.5	3.8	1.9	3.3	3.1	1.3
Amputation	0.7	1.2	6.2	0.8	0.6	2.7
Hip fracture	1.9	1.4	4.4	1.9	1.8	0.9
PEIT	5.0	3.9	6.0	4.9	5.4	2.6
Laboratory tests						
Hemoglobin, g/dL	10.5 ± 1.3	10.5 ± 1.2	3.8	10.5 ± 1.3	10.5 ± 1.2	0.9
Albumin, g/dL	3.9 ± 0.3	3.9 ± 0.3	3.0	3.9 ± 0.3	3.9 ± 0.4	1.1
Creatinine, mg/dL	12.0 ± 2.6	12.2 ± 2.7	5.2	12.1 ± 2.7	12.2 ± 2.6	3.1
Intact PTH, pg/mL	615 (432–872)	464 (368–629)	47.3	588 (422–809)	566 (427–777)	4.0
Intact PTH, %						
300–499 pg/mL	36.0	57.2	50.5	38.4	38.4	0.0
500–999 pg/mL	47.0	36.9	23.6	50.1	50.1	0.0
≥1000 pg/mL	17.0	5.9	38.2	11.5	11.5	0.0
Calcium, mg/dL	9.9 ± 0.8	9.9 ± 0.8	7.6	9.9 ± 0.8	9.9 ± 0.7	4.0
Phosphorus, mg/dL	6.2 ± 1.4	6.0 ± 1.5	8.0	6.1 ± 1.4	6.2 ± 1.5	4.4
CRP, mg/dL	0.1 (0.1–0.3)	0.1 (0.1–0.3)	0.1	0.1 (0.1–0.3)	0.1 (0.1–0.3)	3.0

Data are percentage, mean ± SD, or median (interquartile range). Percentages do not add up to 100% in some cases because of rounding.
Abbreviations: CRP, C-reactive protein; *Kt/V*, dialysis adequacy; nPCR, normalized protein catabolic rate; PEIT, percutaneous ethanol injection therapy; PTH, parathyroid hormone; PTx, parathyroidectomy.
[a]Patients underwent PTx or initiated treatment with cinacalcet between January 2008 and December 2009. Baseline data were collected in December 2007.
[b]The standardized differences are reported as percentages; a difference of less than 10.0% indicates a relatively small imbalance.

values of intact PTH, calcium, and phosphorus as covariates for estimating the propensity score and repeated propensity score matching and survival analysis. Finally, we explored the proportion of the association of PTx vs cinacalcet with mortality that was mediated by posttreatment changes in mineral metabolism. We used a 4-way decomposition approach to estimate the controlled direct effect, the reference interaction, the mediated interaction, and the pure indirect effect. We then assessed the overall proportion due to mediation by summing the proportions due to the mediated interaction and to the pure indirect effect (47).

As the mortality follow-up started on December 31, 2009, we could not account for deaths that occurred by this time. Although early mortality after PTx is exceedingly rare in Japan (31), this might bias the results in favor of PTx. To explore to what extent early mortality after PTx affects the results, we performed a simulation study. To assume a scenario in which the potential impact of early mortality after PTx is sufficiently considered, we modeled an increased risk of early mortality after PTx using data from a study of the US Renal Data System (Supplementary Table 1) (22, 39), which reported a much higher postoperative mortality rate than in Japan (31).

The proportion of missing data was < 10% for all baseline variables except C-reactive protein (23.3%). We accounted for missing data by using multiple imputation to create 10 imputed datasets. Statistical analyses were performed on each imputed dataset and were finally pooled to achieve

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single parameter estimates. Two-sided P values of < 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics 24 (IBM), R 4.0.5 (R Foundation for Statistical Computing), and Stata 16 (StataCorp). A detailed description of the statistical analyses is provided in Supplementary Methods (39).

Results

Study Population

We identified 9183 hemodialysis patients with SHPT who met our inclusion criteria (Fig. 1), of whom 8228 (89.6%) received cinacalcet and 955 (10.4%) underwent PTx between January 2008 and December 2009. Before propensity score matching, patients who underwent PTx were younger; were more likely to be female and to be undergoing hemodiafiltration; were less likely to have diabetes as a cause of kidney failure; and had a longer dialysis duration, higher *Kt/V*, and higher intact PTH levels (Table 1). Based on their propensity scores, 2682 patients who received cinacalcet were matched with 894 patients who underwent PTx. After matching, the standardized differences for all baseline variables between the groups were less than 0.1.

Changes in Biochemical Parameters and Medications

The median levels of intact PTH, calcium, and phosphorus over time in the propensity score-matched cohort are shown in Fig. 2. PTx resulted in significantly greater reductions in intact PTH levels compared with cinacalcet: the median intact PTH levels were 83 pg/mL and 218 pg/mL in December 2009 in patients who underwent PTx and those who received cinacalcet, respectively. These levels remained relatively constant thereafter. PTx also yielded more pronounced reductions in the serum calcium and phosphorus levels, although the between-group differences were relatively small. Changes in biochemical parameters in the unmatched cohort are shown in Supplementary Figure 1 (39). In accordance

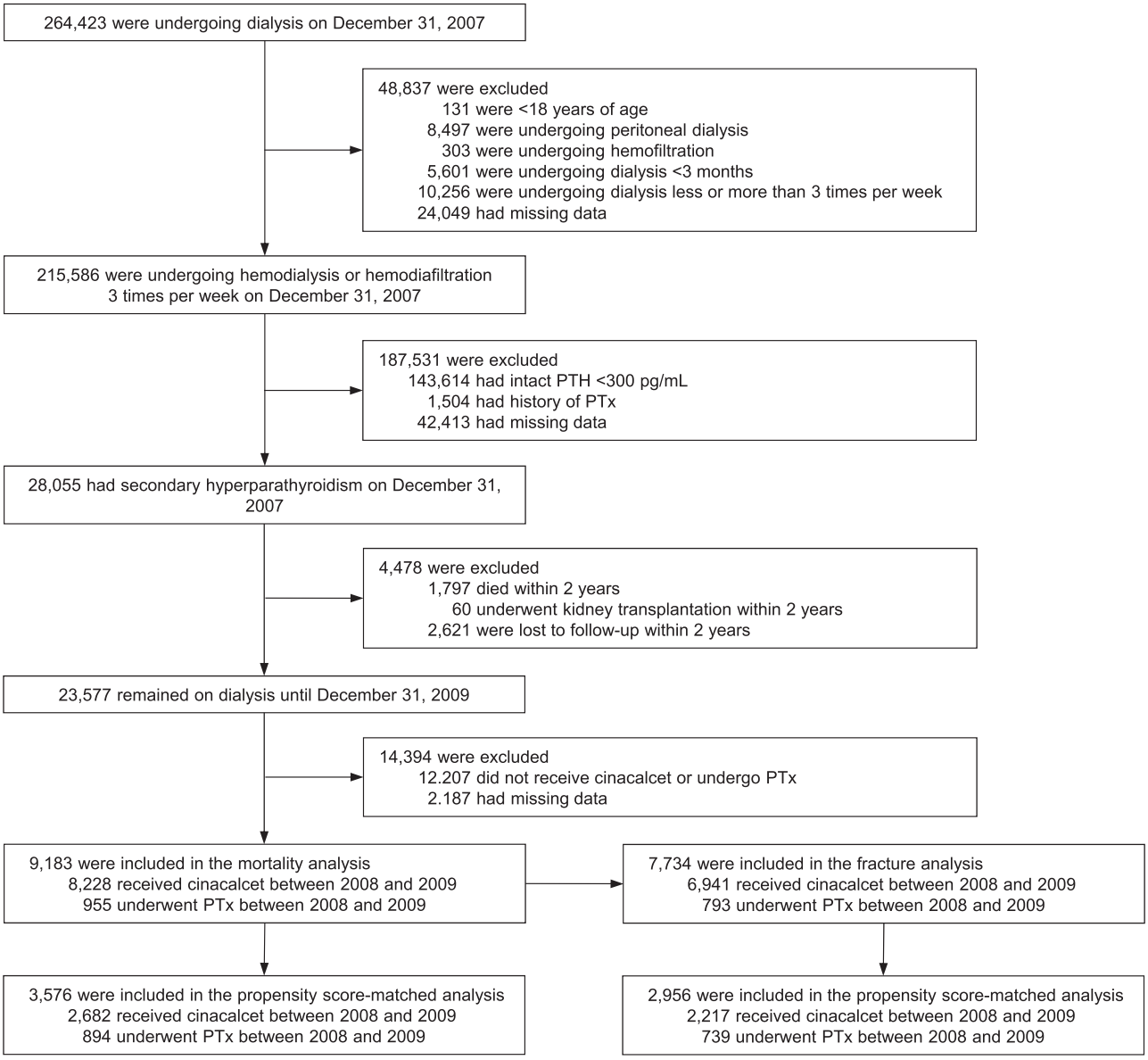

Figure 1. Study profile. Abbreviations: PTH, parathyroid hormone; PTx, parathyroidectomy.

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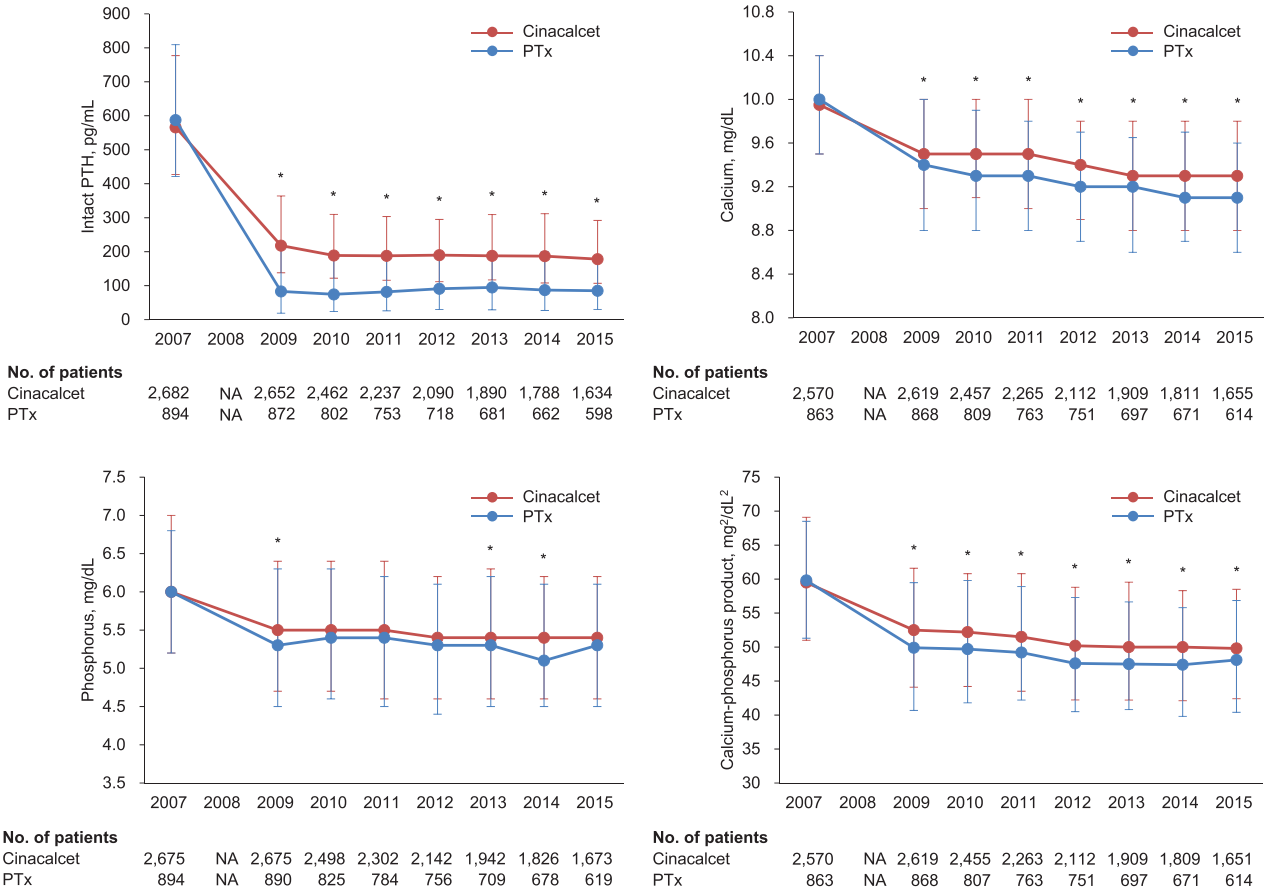

Figure 2. Biochemical parameters during the study in the matched cohort. Shown are medians (interquartile range) of intact parathyroid hormone (PTH), calcium, phosphorus, and calcium-phosphorus product in the parathyroidectomy (PTx) group and the cinacalcet group. *$P < 0.05$ between groups at each time point based on mixed-effects models.

with the changes in intact PTH, patients who underwent PTx showed lower alkaline phosphatase levels after treatment than those who received cinacalcet (Supplementary Figure 2) (39). The concomitant medications used after PTx or the initiation of treatment with cinacalcet are provided in Supplementary Table 2 (39).

Primary Outcome

During the 6-year follow-up period, 201 of 894 patients (22.5%) in the PTx group and 736 of 2682 patients (27.4%) in the cinacalcet group died. PTx was associated with a lower risk of mortality compared with cinacalcet (risk difference, –5.4% [95% CI, –6.8% to – 4.1%]; hazard ratio [HR], 0.78 [95% CI, 0.67–0.91]; $P = 0.002$) (Fig. 3). Subgroup analyses revealed that the survival benefit of PTx vs cinacalcet was more pronounced in patients with baseline intact PTH levels ≥ 500 pg/mL and in patients with baseline serum calcium levels ≥ 10.0 mg/dL (both P for interaction < 0.001) (Fig. 4).

Secondary Outcomes

The results of the cause-specific mortality analysis are shown in Supplementary Figure 3 (39). The most common cause of death was heart failure (21.3% of all deaths), and PTx was associated with a lower risk of death due to heart failure compared with cinacalcet (HR, 0.67 [95% CI, 0.47-0.96]). There were no significant associations with other causes of death.

Among the 7734 patients with no history of hip fracture as of December 2009 (Fig. 1), 739 patients who underwent PTx and 2217 patients who initiated treatment with cinacalcet were matched based on their propensity scores (Supplementary Table 3) (39). During follow-up, hip fractures occurred in 24 patients (3.2%) in the PTx group and 66 patients (3.0%) in the cinacalcet group. In the interval-censored Cox model, there was no significant difference between the groups for incident hip fracture (HR, 1.14 [95% CI, 0.65-2.00]).

Sensitivity Analyses

The results of the sensitivity analyses are presented in Table 2. The association between PTx vs cinacalcet and mortality was qualitatively unchanged when we performed propensity score matching in a 1:1 ratio (HR 0.76 [95% CI, 0.64-0.91]); when we performed a complete case analysis (HR 0.75, [95% CI, 0.62-0.90]); when we restricted the study population to individuals who were less likely to have serious comorbidities (HR, 0.66 [95% CI, 0.45-0.95]); when we performed a conventional multivariable Cox regression analysis (HR, 0.72 [95% CI, 0.63-0.83]); and when we applied inverse probability of treatment weighting (HR, 0.79 [95% CI, 0.68-0.92]) or overlap weighting (HR, 0.74 [95% CI, 0.64-0.85]). The array-approach sensitivity analysis showed that an unmeasured confounder present in 10% of the PTx group would have to be 4 times more prevalent

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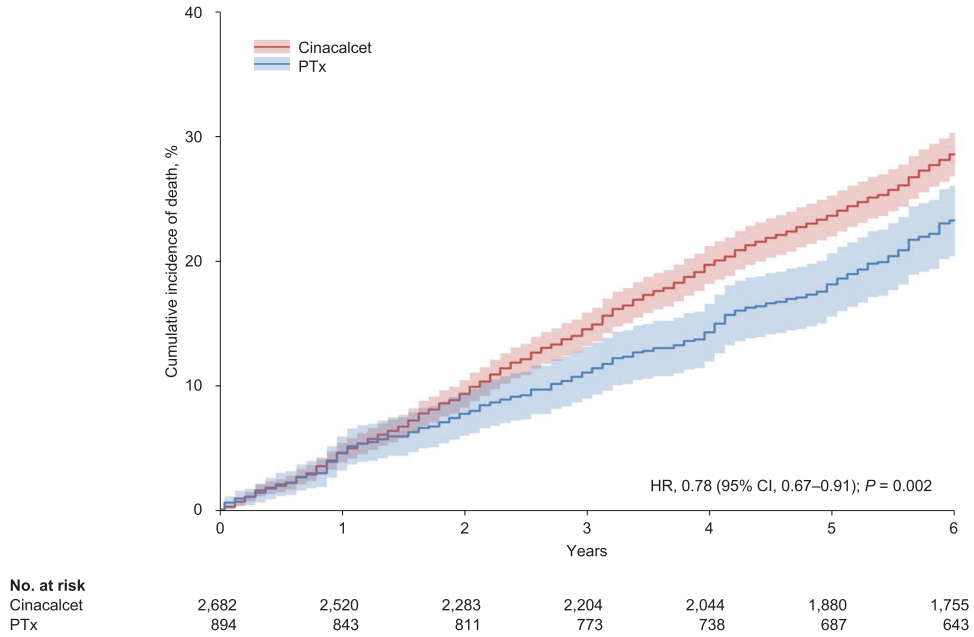

Figure 3. Kaplan-Meier cumulative incidence of death in the matched cohort. Shown are cumulative incidence curves for death in the propensity score-matched cohort. Shaded areas represent 95% CIs. Abbreviation: PTx, parathyroidectomy.

in the cinacalcet group and would itself have to increase the mortality risk by 2.0 to fully explain our estimates (Supplementary Figure 4) (39).

To further account for unmeasured confounding, we adopted an instrumental variable approach. The unadjusted proportion of patients undergoing PTx varied across regions, ranging from 2.0% to 19.3%. The first-stage F-statistic was 146.8, indicating that the instrumental variable (the adjusted percentage of patients undergoing PTx by region) strongly predicted the likelihood of undergoing PTx for each individual. In the fully adjusted model, every 10% increase in the adjusted percentage of patients undergoing PTx within a region was associated on average with a 17% lower risk of mortality (HR, 0.83 [95% CI, 0.74-0.93]).

Exploratory Analyses

Among patients undergoing PTx, lower postoperative intact PTH levels were associated with decreased mortality (Supplementary Table 4) (39). When we stratified patients undergoing PTx into tertiles based on their postoperative intact PTH levels and performed propensity score matching for each tertile, the survival benefit of PTx vs cinacalcet was most evident in patients who had sustained reductions in intact PTH levels after surgery but not in those with postoperative persistent SHPT (Table 3). When we additionally included posttreatment values of intact PTH, calcium, and phosphorus as covariates for estimating the propensity score, there was no significant survival benefit of PTx vs cinacalcet (HR, 0.94 [95% CI, 0.79-1.11]). The results of the mediation analysis showed that posttreatment reductions in intact PTH levels explained 64.1% of the association between PTx vs cinacalcet and mortality (Table 4). Estimates of each component in the 4-way decomposition are provided in Supplementary Table 5 (39).

Simulation Study

When we modeled an increased risk of postoperative mortality to the same extent as the United States, the cumulative survival probability was initially lower in the PTx group compared with the cinacalcet group, then became equal at 20 months (95% CI, 11-54 months); thereafter, the cumulative survival probability was consistently higher in the PTx group (Supplementary Figure 5) (39). The expected survival was 14.1 years (95% CI, 12.8-15.5 years) in the PTx group compared with 12.3 years in the cinacalcet group; the incremental life years gained was 1.8 (95% CI, 0.5-3.2).

Discussion

In this nationwide prospective cohort of patients undergoing hemodialysis, PTx compared with cinacalcet was associated with more aggressive control of SHPT and a substantially lower risk of mortality. This finding was consistent across several analytic approaches and robust to multiple sensitivity analyses, including an instrumental variable analysis. The survival advantage of PTx was more pronounced in patients with higher PTH levels and those with higher calcium levels. These results suggest a potential benefit of PTx with respect to mortality, particularly among patients with severe SHPT.

To our knowledge, this is the first large-scale study to compare the long-term outcomes in patients undergoing dialysis who were treated with PTx or cinacalcet. One recent study addressed this question, but the results were limited by the small sample size (35). In the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial (33), cinacalcet did not significantly reduce the risk of the primary end point; however, PTx was more frequently performed in the placebo group, and when participants were censored at the time of PTx, the relative hazard was nominally significant. This finding points to the possibility that participants in the placebo group who underwent PTx had lower rates of mortality and cardiovascular events than those in the cinacalcet group, which appears to be in line with our findings.

In the current clinical practice guidelines (20, 21), PTx is suggested for patients with severe SHPT who fail to respond to medical therapy, which may include calcimimetics.

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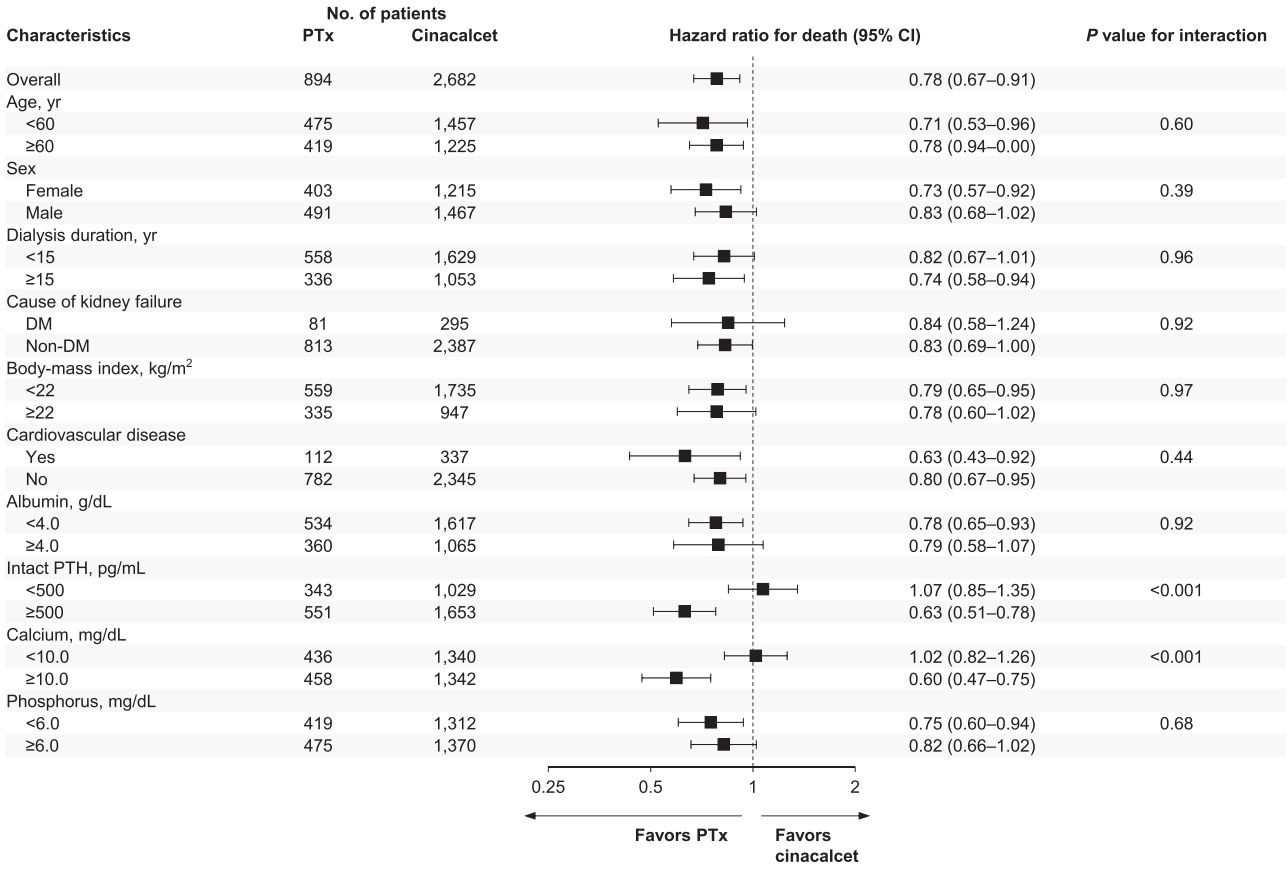

Figure 4. Subgroup analysis. Shown are the associations of parathyroidectomy (PTx) vs cinacalcet with mortality in the propensity score-matched cohort according to baseline characteristics. Squares represent point estimates for the hazard ratio, and horizontal lines indicate 95% confidence intervals. Cardiovascular disease includes myocardial infarction, cerebral infarction, cerebral hemorrhage, and amputation. Abbreviations: DM, diabetes mellitus; PTH, parathyroid hormone.

Table 2. Sensitivity analysis of the association between PTx vs cinacalcet and mortality

Model	PTx		Cinacalcet		Hazard ratio	95% CI
	No. of patients	No. of death	No. of patients	No. of death		
Propensity score matching with 1:3 ratio (base model)	894	201	2682	736	0.78	0.67–0.91
Propensity score matching with 1:1 ratio	948	215	948	269	0.76	0.64–0.91
Complete case analysis	586	134	1758	506	0.75	0.62–0.90
Excluding patients with advanced age or comorbidities[a]	381	34	1143	150	0.66	0.45–0.95
Multivariable Cox regression[b]	955	217	8228	2479	0.72	0.63–0.83
Inverse probability of treatment weighting[c]	917	230	8274	2495	0.79	0.68–0.92
Overlap weighting	824	188	823	240	0.74	0.64–0.85

Abbreviations: PTH, parathyroid hormone; PTx, parathyroidectomy.
[a]The analysis excludes patients who were 60 years of age or older, had diabetes as a cause of kidney failure, or had history of myocardial infarction, cerebral infarction, cerebral hemorrhage, amputation, or hip fracture.
[b]Adjusted for all variables listed in Table 1.
[c]Stabilized weights are used.

Studies reported reductions in rates of PTx after the introduction of cinacalcet (29-31), suggesting that in current clinical practice, clinicians favor the use of cinacalcet rather than PTx for patients who are refractory to conventional therapy, even if they are expected to tolerate surgery. This is not surprising because patients generally prefer medical to surgical treatment, and there may be a perception of surgery as an undesirable outcome. Our findings raise questions about the relevance of such patterns in clinical practice and emphasize the need for further research comparing the outcomes of PTx and cinacalcet. Our results also have implications for health care costs. Because PTx is performed only once in a lifetime in most cases, it is considered less expensive than life-long treatment with cinacalcet (48). Thus, if our findings are verified by future studies, PTx can be considered "economically dominant" over cinacalcet, further supporting the use of PTx for patients who are eligible for surgery.

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Table 3. Risk of mortality associated with PTx vs cinacalcet, stratified by postoperative PTH levels and after propensity score matching[a]

Postoperative intact PTH	*PTx*		*Cinacalcet*		*Hazard ratio*	*95% CI*
	Median (IQR) posttreatment intact PTH, pg/mL[b]	**n**	**Median (IQR) posttreatment intact PTH, pg/mL[b]**	**n**		
Tertile 1 (<35 pg/mL)	12 (7–20)	304	231 (148–401)	912	0.56	0.42–0.74
Tertile 2 (35–163 pg/mL)	83 (53–121)	304	232 (140–383)	912	0.73	0.55–0.95
Tertile 3 (≥164 pg/mL)	321 (226–522)	304	213 (135–343)	912	1.02	0.79–1.30

Abbreviations: IQR, interquartile range; PTH, parathyroid hormone; PTx, parathyroidectomy.
[a]Propensity score matching was repeated for patients who underwent PTx in each tertile of postoperative PTH and those who initiated treatment with cinacalcet.
[b]Posttreatment intact PTH values were collected in December 2009.

Table 4. Proportion of the association of PTx vs cinacalcet with mortality in the matched cohort, mediated by posttreatment change in intact PTH, calcium, or phosphorus[a]

Mediator	**Overall proportion mediated, %**	**95% CI**
Change in log intact PTH	64.1	14.8 to 113.4
Change in calcium	7.9	1.6 to 14.2
Change in phosphorus	1.7	–2.4 to 5.9

Abbreviations: PTH, parathyroid hormone; PTx, parathyroidectomy.
[a]Models adjusted for all variables listed in Table 1.

Because elevated PTH levels are associated with increased morbidity and mortality (12-14), the greater reduction in PTH levels is the most reasonable explanation for the survival advantage conferred by PTx when compared with treatment with cinacalcet. Supporting this possibility, we observed by mediation analysis that posttreatment reductions in intact PTH levels explained more than 60% of the survival benefit associated with PTx. It is known that elevated PTH increases the efflux of calcium and phosphorus from the bone and thereby contributes to vascular calcification, leading to arterial stiffness, increased afterload, and LVH. Experimental data also suggest that PTH directly induces cardiomyocyte hypertrophy (7). Additionally, PTH stimulates the production of fibroblast growth factor 23 (FGF23) by bone cells (49, 50), which has been linked to LVH and heart failure (51, 52). Thus, we speculate that the survival benefit associated with treatment with PTx compared with cinacalcet results from the more effective attenuation of vascular calcification and LVH, which contributes to reducing mortality, particularly from heart failure. Elevated PTH levels have also been implicated in the development of immune dysfunction (8), myopathy (9), and wasting (10, 11), which may also explain the survival advantage associated with PTx.

In contrast to the mortality results, there was no significant difference in the rates of hip fracture between the PTx and cinacalcet groups. There is concern that the oversuppression of PTH after PTx can lead to adynamic bone disease, which might adversely affect bone strength (53), but our results did not provide evidence to support this hypothesis. It should, however, be noted that the fracture analysis was subject to interval censoring and limited to individuals with no prior history of hip fracture, and we were only able to identify the first occurrence of hip fracture. Additional studies are needed to determine whether PTx or cinacalcet is superior with regard to fracture prevention.

A unique aspect of this study is that we included patients who underwent PTx and those who initiated treatment with cinacalcet during the first 2 years after the introduction of cinacalcet to the Japanese healthcare system, during which period cinacalcet was increasingly prescribed, whereas PTx continued to be performed in a subset of patients. This allowed us to identify a sufficient number of patients in each group during the same time frame. Other strengths of this study include the large sample size from a nationwide registry, prospective study design, long follow-up period, and robust statistical analysis.

This study has several limitations. First, the treatment strategy was not based on random assignment, and our results may be subject to selection bias and confounding. To minimize these biases, we used a range of statistical methods, including propensity score matching, and our array-approach analysis indicated that a confounder effect would need to be quite large to fully attenuate our estimates. We also confirmed the robustness of our results by applying an instrumental variable approach, which provides estimates that would be less biased even if important confounders were not measured. Second, the registry did not collect the date of PTx or cinacalcet initiation, and all participants were followed up for mortality from December 31, 2009. Although we defined patient groups in the fixed time interval, we could not fully account for immortal time bias with this study design. Specifically, our study excluded patients who died by the end of 2009, which precluded us from identifying a subset of deaths that occurred shortly after PTx or cinacalcet initiation. Our simulation results suggested that even if we modeled an increased risk of postoperative mortality to the same extent as the United States, this would not yield a large bias. Third, the registry did not collect data on PTx and cinacalcet use after 2009. It is possible that a subset of patients in the cinacalcet group underwent PTx later. However, this would reduce the observed effect size. It is also possible that a small proportion of patients in the PTx group presented with postoperative persistent SHPT and were subsequently treated with cinacalcet. This could bias the results in favor of PTx, but such uses of cinacalcet should be accepted as part of postoperative care. Fourth, because the registry collected data annually, we did not have biochemical data immediately before PTx or cinacalcet. We also lacked information on the use of activated vitamin D before either treatment. Fifth, we lacked data on medication adherence and the dose of cinacalcet. We cannot exclude the possibility that the therapeutic effect of cinacalcet was attenuated in a subset of patients by poor adherence or inappropriate dose adjustment. Sixth, we did not have access

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to information about the PTx procedure. Total PTx with autotransplantation is most commonly performed in Japan (70%-80%) (31), as contrasted with other regions (23, 25, 26). Seventh, the present study focused on the comparison of PTx and cinacalcet, so our results should not be extrapolated to other calcimimetics with different profiles.

Finally, the study population was restricted to Japanese hemodialysis patients, which may limit the generalizability of our findings. In particular, the national guideline suggests maintaining intact PTH levels in the range of 60 to 240 pg/mL (21), which is quite lower than the range suggested in the international guideline (approximately 130 to 585 pg/mL) (20). Indeed, it was reported that the median intact PTH level in patients receiving cinacalcet in the United States was greater than 400 pg/mL (54), which is approximately 2-fold higher than the level we observed in the present study. We assume that had we studied individuals in other regions where the dose of cinacalcet is titrated less aggressively, the relative benefit of PTx would have been more pronounced. One may also hypothesize that if cinacalcet is more aggressively titrated to achieve PTH levels to a similar extent as PTx, both treatments might provide similar survival benefits. Exploring this possibility would be a promising direction for future research, which will provide important implications about the optimal PTH level in patients undergoing hemodialysis.

In conclusion, in this nationwide cohort of patients undergoing hemodialysis, PTx was associated with a lower risk of mortality compared with cinacalcet, particularly among patients with severe SHPT. Our findings support the need for randomized clinical trials designed to compare the benefits of PTx and cinacalcet. More fundamentally, future research should investigate whether intensive control of SHPT improves clinical outcomes.

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Disclosures

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request and with permission of the JSDT.

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