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ORIGINAL ARTICLE

# Association between renal function and fracture incidence during treatment with teriparatide or alendronate: an exploratory subgroup analysis of the Japanese Osteoporosis Intervention Trial-05

Yasuhiro Takeuchi[1,2] · Shiro Tanaka[3] · Tatsuhiko Kuroda[4] · Hiroshi Hagino[5] · Satoshi Mori[6] · Satoshi Soen[7]

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## Abstract

**Summary** The association of renal function with fracture incidence during teriparatide or alendronate treatment in elderly Japanese women was examined. Fracture incidence differed by fracture type, renal function, and treatment protocol. The results provide important information on pharmacotherapy in clinical practice for osteoporosis.

**Purpose** Incidence rate of morphometric vertebral fracture was lower under treatment with once-weekly teriparatide (TPTD) followed by alendronate (ALN) than under treatment with ALN throughout the study among elderly Japanese women at high fracture risk in JOINT-05. This is an exploratory subgroup analysis according to chronic kidney disease (CKD) status at baseline.

**Methods** Participants received sequential therapy with TPTD for 72 weeks, followed by ALN for 48 weeks (TPTD-ALN group, $N=483$) or ALN monotherapy for 120 weeks (ALN group, $N=496$). Baseline CKD status was classified by the estimated glomerular filtration rate (eGFR) and categorized as: CKD 1/2 (eGFR ≥ 60 mL/min/1.73 $m^2$), CKD 3a (eGFR 45–59 mL/min/1.73 $m^2$), or CKD 3b/4 (eGFR < 45 mL/min/1.73 $m^2$). Incidences of vertebral fractures including morphometric fractures, non-vertebral fractures, and all fractures were evaluated during follow-up.

**Results** Baseline characteristics were not different between treatment groups. Higher stages of CKD were associated with age and number of prevalent vertebral fracture. In CKD 1/2 patients ($N=556$ with 90 incidents of morphometric vertebral fracture), the incidence of vertebral fractures was lower in the TPTD-ALN group than in the ALN group ($p=0.01$). In CKD 3b/4 patients ($N=112$ with 10 incidents of non-vertebral fracture), the incidence of non-vertebral fractures was lower in the ALN group than in the TPTD-ALN group, although the number of fractures was small. In the ALN group, the incidences of vertebral fractures, non-vertebral fractures, and all fractures remained constant across CKD stages.

**Conclusion** This exploratory analysis showed that fracture incidence on ALN was constant regardless of renal function. It also suggested that the incidence of vertebral fractures on TPTD-ALN was lower than ALN monotherapy in CKD 1/2 patients. These results provide important information for drug selection in the clinical practice of osteoporosis.

**Keywords** Alendronate · Chronic kidney disease · Fracture incidence · Osteoporosis · Teriparatide

✉ Yasuhiro Takeuchi
takeuchi-tky@toranomon.gr.jp

[1] Toranomon Hospital Endocrine Center, 2-2-2 Toranomon, Minato-Ku, Tokyo 105-8470, Japan

[2] Okinaka Memorial Institute for Medical Research, Minato-Ku, Tokyo, Japan

[3] Department of Clinical Biostatistics, Graduate School of Medicine, Kyoto University, Kyoto, Japan

[4] Public Health Research Foundation, Shinjuku-Ku, Tokyo, Japan

[5] Department of Rehabilitation, Sanin Rosai Hospital, Yonago, Tottori, Japan

[6] Seirei Hamamatsu General Hospital, Hamamatsu, Japan

[7] Soen Orthopaedics, Osteoporosis and Rheumatology Clinic, Kobe, Hyogo, Japan

## Introduction

Osteoporosis is a systemic bone disorder characterized by low bone mass, poor bone integrity, and increased fracture risk. It is a global burden for the elderly population [1]. Renal function decreases progressively with age. Chronic kidney disease (CKD) is another emerging health problem in elderly people. Both health issues are entangled because CKD is associated with impaired bone integrity through dysregulation of calcium and phosphorus metabolism [2, 3]. CKD presents with increased circulating levels of fibroblast growth factor-23 (FGF23) and secondary hyperparathyroidism, both of which contribute to abnormalities in bone metabolism, increasing fracture incidence [2–4].

The prevalence and comorbidity of CKD and osteoporosis both increase with age, and they result in an elevation of fracture risk [5]. It has been reported that CKD patients at stage G5 have a 4.4-fold higher risk of fractures than the general population [6]. It has also been established that even CKD stage G3 (CKD 3) is an independent risk factor for fractures [7].

Bisphosphonates are the first-line drugs for the treatment of osteoporosis, but there are some concerns about renal toxicity. Intravenous administration of bisphosphonates may cause acute renal tubular necrosis, and their long-term oral administration may also have a negative effect on renal function [8]. Nevertheless, it is common to prescribe bisphosphonates to patients with CKD 3 or worse, because a significant proportion of elderly patients with osteoporosis have poor renal function. Teriparatide (TPTD) is an active fragment of parathyroid hormone (PTH). Treatment with TPTD is an option for osteoporotic patients with very high fracture risk [9, 10]. Circulating PTH levels above the reference range with normocalcemia, that is, secondary hyperparathyroidism, are common in patients with CKD 3 or worse as GFR decreases [8]. Thus, there remains uncertainty about whether treatment with TPTD significantly reduces fracture incidence in osteoporotic patients with CKD 3 or worse. Unfortunately, most anti-osteoporosis drugs have not been evaluated in prospective clinical studies to assess safety and efficacy by CKD stage, so sub-analyses using data from large pivotal clinical trials have been conducted [11–15]. As for once-weekly administration of TPTD, no clinical data of participants with different CKD stages are available, although it has been approved in Japan based on safety and efficacy data for fracture risk reduction [10].

The incidence rate of morphometric vertebral fracture was lower under treatment with once-weekly TPTD followed by alendronate (ALN) than under treatment with ALN throughout the study among elderly Japanese women at high fracture risk in JOINT-05 study [16–18]. In this clinical investigation, we conducted exploratory subgroup analysis according to CKD status at baseline using data from JOINT-05.

## Materials and methods

### Participants and treatment

JOINT-05 enrolled Japanese women aged 75 years or older with primary osteoporosis [16]. The participants were randomly assigned (1:1) to receive sequential therapy with once-weekly TPTD for 72 weeks followed by ALN for 48 weeks (TPTD-ALN group) or monotherapy with ALN for 120 weeks (ALN group). TPTD 56.5 μg was injected once-weekly, and ALN was provided as a 5-mg tablet (once daily), 35-mg tablet or jelly (once weekly), or 900-μg infusion (once every 4 weeks). Native vitamin D 400 IU/day supplements were provided to both groups throughout the entire treatment period.

### Measurements

Data for bone mineral density (BMD) at the lumbar spine (L2-4) and bone turnover markers [osteocalcin, procollagen type I amino-terminal propeptide (P1NP), and tartrate-resistant acid phosphatase-5b (TRACP-5b)] measured at 0, 12, 24, 48, 72, and 120 weeks from the JOINT-05 study [16–18] were used for this analysis.

### Stages of CKD

Participants were stratified according to kidney function at baseline, as determined by the estimated glomerular filtration rate (eGFR). The eGFR was calculated using the equation: $194*\text{serum creatinine}^{-1.094}*\text{age}^{-0.287}*0.739$ [19]. The CKD stages were categorized as: CKD stages G1 and G2 (CKD 1/2) (eGFR $\geq 60$ mL/min/1.73 $m^2$); CKD stage G3a (CKD 3a) (eGFR 45–59 mL/min/1.73 $m^2$); or CKD stages G3b and G4 (CKD 3b/4) (eGFR $< 45$ mL/min/1.73 $m^2$). Patients with CKD stage G5 were not included in the present study.

### Fracture evaluation

The endpoints for this analysis were the incidences of vertebral fractures including morphometric fractures, non-vertebral fracture, and the incidences of all fractures and BMD at L2-4 at 0, 24, 48, 72, and 120 weeks. The thoracic and lumbar vertebrae were imaged in two directions at 0 (baseline), 24, 48, 72, and 120 weeks. For the assessment of prevalent vertebral fractures, anteroposterior and lateral radiographs of the thoracic and lumbar spine were examined

by the investigators. They assessed the grade of vertebral fractures from Th4 to L4 according to the semiquantitative (SQ) technique [20]. These assessments were reviewed centrally by one evaluator of the fracture assessment committee blinded to the assigned treatment.

The committee also adjudicated the presence/absence of a new vertebral fracture by comparing radiographs of Th4 to L4 between baseline and post-treatment. After the X-ray films were collected, two evaluators blinded to the assigned treatment reviewed the films independently according to the SQ technique mentioned above. If inconsistencies arose between the evaluators, three evaluators reviewed the films simultaneously. The presence/absence of other fractures such as nonvertebral fractures and clinical fractures was assessed by the investigators. Thereafter, three evaluators of the fracture assessment committee reviewed the assessment made by the investigators using the collected X-ray films.

### Statistical analysis

This was a prespecified, subgroup analysis of the primary endpoint and secondary fracture endpoints [16]. A multivariable Poisson regression model was fit to calculate the rate ratios between the TPTD-ALN group and the ALN group and their 95% confidence intervals (CIs) using the generalized estimating equation (GEE). The GEE-Poisson regression included age, counts and maximum grades of prevalent vertebral fractures, history of proximal femur fractures, and BMD at baseline as covariates and individual and institute as clusters. BMD at L2-4 was summarized by mean and SD values, and the differences between the TPTD-ALN group and the ALN group were assessed using the unpaired *t*-test. All data were analyzed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). All reported *p* values are two-tailed without multiplicity adjustment, with a *p* value of less than 0.05 indicating a significant difference.

## Results

Full analysis dataset of original JOINT-05 consisted of the TPTD group ($N=489$) and ALN group ($N=496$). Baseline measurements of eGFR were available for 979 patients out of the 985 patients in the full analysis set, and this subgroup analysis therefore included 483 patients in the TPTD-ALN group and 496 patients in the ALN group, respectively. The baseline characteristics by CKD stage are shown in Table 1. The numbers of patients with normal kidney function (CKD 1/2), mild reduction in kidney function (CKD 3a), and moderate reduction in kidney function (CKD3b/4) were 556, 311, and 112, respectively. The mean ages of the CKD 1/2, CKD 3a, and CKD 3b/4 groups were 80.6, 82.2, and 84.0 years, respectively, and the mean numbers of prevalent vertebral fractures were 1.5, 1.9, and 2.3, respectively. Serum osteocalcin, P1NP, and TRACP-5b levels were higher in patients with eGFR less than 45 ml/min/1.73 $m^2$ than in the rest of the participants.

BMD at the lumbar spine was not different between the two treatment protocols at any time point through 120 weeks in each category of renal function (Table 2).

The differences in the three types of incident fractures by treatment group and CKD stage are shown in Fig. 1a–c (full data in Table 3). In CKD 1/2 patients ($N=556$ with 90 incidents of morphometric vertebral fracture), the incidence of vertebral fractures was lower in the TPTD-ALN group than in the ALN group ($p=0.01$). The incidence of all fractures was also lower in the TPTD-ALN group than in the ALN group in CKD 1/2 patients. As for non-vertebral fractures, only 48 incidents were observed in total. The incidence of non-vertebral fracture was lower in the ALN group than in the TPTD-ALN group in the CKD 3b/4 patients, although the CKD 3b/4 stage included only 112 patients with 10 incidents of non-vertebral fracture. In the ALN group, the incidences of vertebral fractures, non-vertebral fractures, and all fractures remained constant across the degrees of kidney function status.

## Discussion

As an exploratory sub-analysis of JOINT-05, the effect of treatment on fracture risk reduction by CKD stage was evaluated. The results showed that renal function was an important clinical parameter contributing to fracture incidence in patients treated with sequential TPTD-ALN. The risk of vertebral fracture was less in patients in the TPTD-ALN group with better renal function in whom eGFR was 60 ml/min/1.73 $m^2$ or greater (CKD 1/2), than in the ALN group. In contrast, the incidence of fractures at any site was not different between TPTD-ALN and ALN group of patients with eGFR of 45–59 ml/min/1.73 $m^2$ (CKD 3a). In addition, the incidence was constant in the ALN group regardless of renal function. These results suggest that the efficacy for fracture risk reduction with TPTD is dependent on renal function, although the efficacy of ALN is independent of it.

Renal function is critically involved in parathyroid function. Circulating levels of PTH increase as renal function worsens at CKD 3 or worse. Therefore, intermittent administration of TPTD might not have similar pharmacological effects on bone metabolism in patients with CKD 3 or worse than in those with CKD 1/2. Data shown here suggest that the efficacy of sequential TPTD-ALN is more effective for the prevention of vertebral fractures to that of ALN alone in CKD 1/2 patients. The non-physiological effects of PTH contribute to exaggeration of cortical porosity, as seen in hyperparathyroidism [21]. Greater PTH activity with

**Table 1** Baseline characteristics by CKD stage

| | CKD 1/2 eGFR ≥ 60 mL/min/1.73 $m^2$ ($N$ = 556) | CKD 3a eGFR from 45 to 59 mL/min/1.73 $m^2$ ($N$ = 311) | CKD 3b/4 eGFR < 45 mL/min/1.73 $m^2$ ($N$ = 112) |
|---|---|---|---|
| eGFR, mL/min/1.73 $m^2$ | 74.5 ± 12.5 | 53.0 ± 4.2 | 35.5 ± 7.0 |
| Age, y | 80.6 ± 4.2 | 82.2 ± 4.8 | 84.0 ± 4.6 |
| Age at menopause, y | 49.5 ± 4.2 | 49.3 ± 4.5 | 49.3 ± 5.0 |
| BMI, kg/$m^2$ | 21.7 ± 3.6 | 22.6 ± 3.6 | 23.2 ± 3.7 |
| Number of prevalent vertebral fractures | | | |
| 0 | 36.0% | 28.9% | 22.3% |
| 1 | 27.5% | 28.0% | 22.3% |
| 2 | 15.3% | 17.0% | 17.0% |
| 3 | 9.4% | 10.0% | 14.3% |
| 4 | 5.0% | 4.5% | 9.8% |
| ≥ 5 | 6.8% | 11.6% | 14.3% |
| History of proximal femoral fractures | 13.3% | 12.5% | 19.6% |
| BMD at L2-4, T-score | − 2.43 ± 1.34 | − 2.22 ± 1.52 | − 2.25 ± 1.55 |
| Prior treatment for osteoporosis | 51.3% | 59.2% | 56.3% |
| Prior bisphosphonates | 30.8% | 31.1% | 23.2% |
| Osteocalcin, ng/mL | 16.9 ± 8.7 | 18.2 ± 10.6 | 26.5 ± 18.3 |
| P1NP, ng/dL | 56.3 ± 41.3 | 52.0 ± 35.3 | 71.7 ± 65.9 |
| TRACP 5b, mU/dL | 484.4 ± 219.1 | 446.9 ± 202.6 | 519.5 ± 269.2 |
| Creatinine, mg/dL | 0.6 ± 0.1 | 0.8 ± 0.1 | 1.2 ± 0.3 |
| Calcium, mg/dL | 9.5 ± 0.4 | 9.5 ± 0.4 | 9.6 ± 0.7 |
| Urine calcium, mg/g-creatinine | 222.0 ± 144.3 | 152.3 ± 100.4 | 126.8 ± 130.1 |

Values are indicated as means ± SD

*CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *BMI*, body mass index; *BMD*, bone mineral density; *P1NP*, procollagen type I amino-terminal propeptide; *TRACP 5b*, tartrate-resistant acid phosphatase 5b

administration of TPTD to patients with poor renal function may aggravate cortical structure, although it has not yet been proven in human studies that once-weekly TPTD causes such aggravation. In contrast, intermittent administration of TPTD to patients with physiological parathyroid function may improve bone integrity to reduce the risk of vertebral fractures with its pharmacologically anabolic effect on bone.

In this study, serum osteocalcin, P1NP, and TRACP-5b levels were higher in patients with CKD3b/4 than in the rest of the participants. This observation was consistent with the assumption that patients with poor renal function had secondary hyperparathyroidism, which continuously stimulates bone metabolism. In particular, serum TRACP-5b level has been reported to be independent of renal function but positively correlated with circulating PTH level [22]. Serum osteocalcin level is also positively correlated with circulating PTH level after multiple regression analysis including GFR, even though it is negatively correlated with GFR [22]. However, the assumption was not confirmed because plasma PTH levels were not measured in this study. Thus, the mechanism for higher non-vertebral fracture incidence among CKD 3b/4 patients in the TPTD-ALN group than in the ALN group was unclear.

Treatment with ALN has been reported to reduce fracture incidence in osteoporosis patients with CKD 3 or better [11]. The present results are consistent with previous reports demonstrating that fracture incidence in patients treated with ALN was similar regardless of renal function, but not in the case of end-stage renal failure. The most important finding of this study was uncovering how renal function was implicated in a head-to-head trial of two different therapeutic options, both of which are efficacious in reducing fracture incidence. Based on the present data, renal function is an essential parameter when choosing anti-osteoporosis drugs. In CKD 1/2 patients, TPTD followed by ALN may be more effective than ALN monotherapy in preventing vertebral fractures, although it may be less effective in preventing non-vertebral fracture in CKD 3b/4 patients. Since BMD at the lumbar spine was not different between the two treatment protocols at any time point through 120 weeks in each category of renal function, BMD alone might not explain the lower

**Table 2** BMD changes at L2-4 by CKD stage

| | TPTD-ALN group | ALN group | *p* |
|---|---|---|---|
| CKD 1/2: eGFR ≥ 60 mL/min/1.73 $m^2$ | | | |
| 0 weeks | −2.44 ± 1.30 (*N* = 158) | −2.41 ± 1.38 (*N* = 153) | - |
| 24 weeks | −2.24 ± 1.23 (*N* = 113) | −2.23 ± 1.38 (*N* = 131) | 0.96 |
| 48 weeks | −2.10 ± 1.24 (*N* = 100) | −2.17 ± 1.42 (*N* = 125) | 0.68 |
| 72 weeks | −2.14 ± 1.22 (*N* = 82) | −2.09 ± 1.37 (*N* = 108) | 0.78 |
| 120 weeks | −1.87 ± 1.28 (*N* = 67) | −2.19 ± 1.41 (*N* = 94) | 0.15 |
| CKD 3a: eGFR from 45 to 59 mL/min/1.73 $m^2$ | | | |
| 0 weeks | −2.14 ± 1.51 (*N* = 80) | −2.29 ± 1.54 (*N* = 88) | - |
| 24 weeks | −1.83 ± 1.55 (*N* = 57) | −2.02 ± 1.54 (*N* = 78) | 0.48 |
| 48 weeks | −2.11 ± 1.41 (*N* = 45) | −1.92 ± 1.53 (*N* = 75) | 0.49 |
| 72 weeks | −2.02 ± 1.57 (*N* = 35) | −1.88 ± 1.58 (*N* = 53) | 0.68 |
| 120 weeks | −1.89 ± 1.70 (*N* = 31) | −1.71 ± 1.62 (*N* = 36) | 0.66 |
| CKD 3b/4: eGFR < 45 mL/min/1.73 $m^2$ | | | |
| 0 weeks | −1.94 ± 1.74 (*N* = 28) | −2.61 ± 1.26 (*N* = 25) | - |
| 24 weeks | −1.73 ± 1.85 (*N* = 21) | −2.41 ± 0.90 (*N* = 19) | 0.15 |
| 48 weeks | −1.56 ± 1.84 (*N* = 19) | −2.34 ± 0.92 (*N* = 20) | 0.10 |
| 72 weeks | −1.42 ± 2.05 (*N* = 15) | −2.38 ± 0.92 (*N* = 15) | 0.11 |
| 120 weeks | −1.21 ± 2.22 (*N* = 12) | −2.31 ± 0.83 (*N* = 13) | 0.11 |

*BMD*, bone mineral density; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate; *TPTD*, teriparatide; *ALN*, alendronate

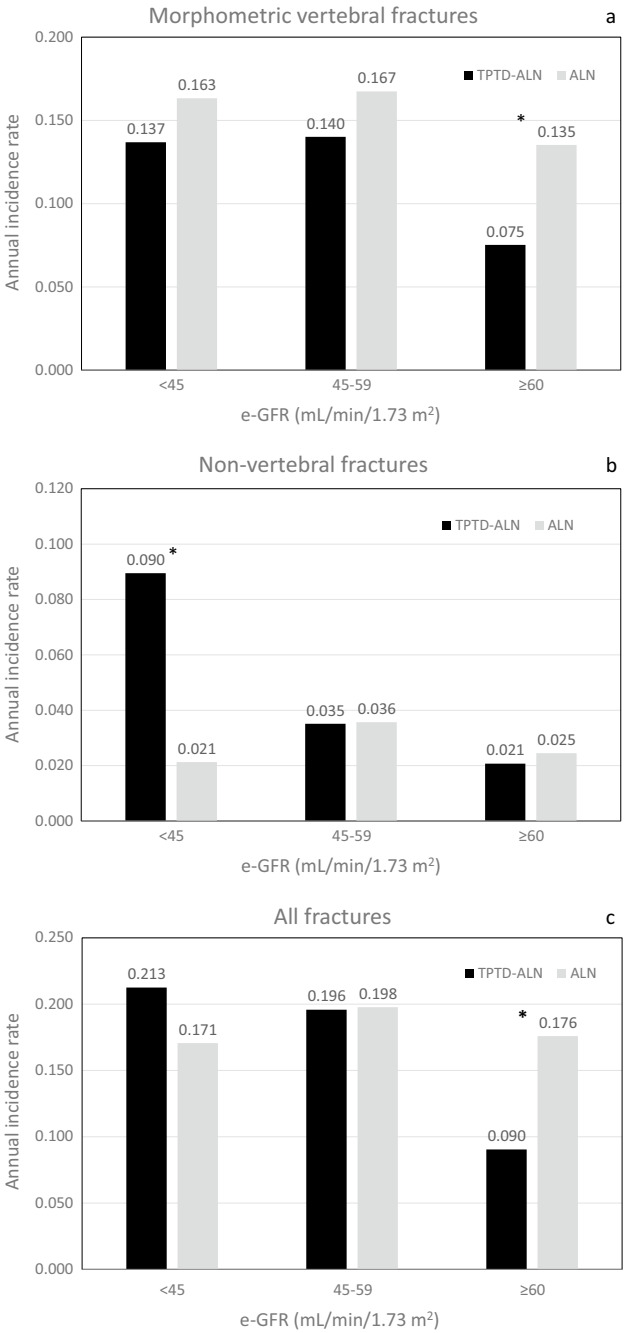


**Fig. 1** Differences in **a** morphometric vertebral fractures, **b** non-vertebral fractures, and **c** all fractures by treatment group and CKD stage

vertebral fracture incidence in the TPTD-ALN group than in the ALN group with CKD1/2. Unfortunately, BMD at the distal radius as a cortical bone parameter was not available in the present study.

This analysis had limitations. The current analysis was a subgroup analysis of data from JOINT-05, a randomized, controlled trial, which excluded patients with severe renal dysfunction. Therefore, evidence for fracture prevention in patients with severe renal dysfunction needs to be confirmed in a study designed for that purpose. Approximately 30% of the patients enrolled in the present study had been treated with bisphosphonates before their participation. Although there was no difference in prior use of bisphosphonates between the proportion of the participants assigned to the TPTD-ALN group and the ALN group, and among the CKD 1/2, 3a, and 3b/4 groups, the effect of history of bisphosphonates use on fracture incidence in each subgroup is unknown. Finally, although this analysis is one of prespecified subgroup analyses in JOINT-05 [16], power for the comparisons within CKD stage is limited. The power to detect the observed effect size in CKD 3b/4 is only 50%. This implies that the apparent difference in non-vertebral fracture should be carefully interpreted and further studies are needed to confirm their reproducibility.

## Conclusion

This exploratory analysis showed that fracture incidence on ALN was constant regardless of renal function. It also suggested that the incidence of vertebral fractures on TPTD-ALN was lower than ALN monotherapy in CKD 1/2 patients. These results provide important information for drug selection in the clinical practice of osteoporosis.

**Table 3** Fracture incidence by treatment group and CKD stage

| | TPTD-ALN group | | | | ALN group | | | | Rate ratio* | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Count | Persons | Person-years | Annual incidence rate | Count | Persons | Person-years | Annual incidence rate | | | |
| CKD 1/2: eGFR ≥ 60 mL/min/1.73 $m^2$ | | | | | | | | | | | |
| Morphometric vertebral fractures | 27 | 21 | 359.2 | 0.0752 | 63 | 44 | 465.8 | 0.1353 | 0.55 | 0.35–0.84 | 0.01 |
| Clinical vertebral fractures | 0 | 0 | 359.2 | 0 | 11 | 7 | 465.8 | 0.0236 | † | | |
| Progression of vertebral fractures | 16 | 15 | 359.2 | 0.0445 | 23 | 21 | 465.8 | 0.0494 | † | | |
| Non-vertebral fractures | 8 | 8 | 387.3 | 0.0207 | 12 | 12 | 489.0 | 0.0245 | 0.78 | 0.34–1.81 | 0.57 |
| All fractures | 35 | 29 | 387.3 | 0.0904 | 86 | 52 | 489.0 | 0.1759 | 0.58 | 0.37–0.93 | 0.02 |
| CKD 3a: eGFR from 45 to 59 mL/min/1.73 $m^2$ | | | | | | | | | | | |
| Morphometric vertebral fractures | 26 | 19 | 185.6 | 0.1401 | 49 | 34 | 292.7 | 0.1674 | 0.90 | 0.49–1.66 | 0.73 |
| Clinical vertebral fractures | 6 | 5 | 185.6 | 0.0323 | 1 | 1 | 292.7 | 0.0034 | † | | |
| Progression of vertebral fractures | 10 | 9 | 185.6 | 0.0539 | 16 | 14 | 292.7 | 0.0547 | 1.04 | 0.37–2.96 | 0.94 |
| Non-vertebral fractures | 7 | 3 | 199.2 | 0.0351 | 11 | 11 | 308.5 | 0.0357 | 1.23 | 0.38–4.03 | 0.73 |
| All fractures | 39 | 21 | 199.2 | 0.1958 | 61 | 43 | 308.5 | 0.1977 | 0.96 | 0.57–1.61 | 0.88 |
| CKD 3b/4: eGFR < 45 mL/min/1.73 $m^2$ | | | | | | | | | | | |
| Morphometric vertebral fractures | 11 | 8 | 80.4 | 0.1369 | 14 | 12 | 85.7 | 0.1633 | 0.84 | 0.43–1.65 | 0.61 |
| Clinical vertebral fractures | 0 | 0 | 80.4 | 0 | 0 | 0 | 85.7 | 0 | † | | |
| Progression of vertebral fractures | 4 | 4 | 80.4 | 0.0498 | 5 | 5 | 85.7 | 0.0583 | † | | |
| Non-vertebral fractures | 8 | 6 | 89.4 | 0.0895 | 2 | 2 | 93.8 | 0.0213 | 6.42 | 1.15–6.02 | 0.03 |
| All fractures | 19 | 11 | 89.4 | 0.2125 | 16 | 14 | 93.8 | 0.1706 | 1.28 | 0.61–2.71 | 0.52 |

*GEE-Poisson regression adjusted for age, counts and maximum grade of prevalent vertebral fractures, history of proximal femur fractures, and bone mineral density at baseline as covariates and individual and institute as clusters

†Not converged

*CKD*, chronic kidney disease; *TPTD*, teriparatide; *ALN*, alendronate, *eGFR*, estimated glomerular filtration rate, *CI*, confidence interval

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**Data availability** The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Declarations

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and its later amendments or comparable ethical standards.

**Conflicts of interest** Y. Takeuchi has received consulting fees, speaking fees, and/or honoraria from Amgen Inc., Asahi Kasei Pharma Corp., Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Mochida Pharma Co., Ltd., and Teijin Pharma Ltd.
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T. Kuroda and S. Mori declare no competing interests.

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