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ORIGINAL ARTICLE

Comparison of the efficacy between once-monthly oral ibandronate and risedronate among Korean women with osteoporosis: a nationwide population-based study

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Abstract

Summary Using a nationwide database from the Korean National Health Insurance Service, this study showed that once-monthly oral ibandronate (150 mg) had better anti-fracture efficacy than once-monthly oral risedronate (150 mg), as seen on assessing overall and non-vertebral fractures among Korean elderly women with osteoporosis.

Introduction Once-monthly oral bisphosphonates have been used widely without appropriate comparison. Therefore, we aimed to compare the anti-fracture efficacy of once-monthly ibandronate (150 mg) and once-monthly risedronate (150 mg).

Methods We conducted a retrospective cohort study among Korean women aged ≥ 60 years from 2006 to 2015 using a nationwide database from the National Health Insurance Service Senior Cohort. The primary outcome was the first occurrence of fracture related to osteoporosis after the initial prescription of bisphosphonates. A Cox proportional model was used to estimate the incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for overall and site-specific fractures between the two treatments, after adjusting for possible confounding factors.

Results After propensity score matching, the ibandronate and risedronate groups, with 3454 patients each, were assembled from 36,701 new once-monthly ibandronate or risedronate users. After 4 years of follow-up, the ibandronate group had significantly lower incidence rates of overall and non-vertebral fractures than the risedronate group (IRR 0.822, 95% CI 0.698–0.968, $P = 0.919$ and IRR 0.798, 95% CI 0.647–0.985, $P = 0.036$, respectively).

Conclusions Once-monthly ibandronate (150 mg) shows better anti-fracture efficacy than once-monthly risedronate (150 mg). However, further large-scale studies are required to confirm our findings and to determine site-specific differences, especially regarding the vertebral and hip areas.

Keywords Bisphosphonate · Fracture · Ibandronate · Osteoporosis · Risedronate

Introduction

Osteoporosis and osteoporosis-related fractures are major public health problems globally [1]. As the population worldwide ages at an unprecedented rate, the incidence of osteoporotic fractures is expected to increase accordingly, contributing to rapid growth in the related social and economic burden in the future. For hip fractures alone, the incidence worldwide is expected to increase from 1.7 million in 1990 to 6.3 million in 2050, with corresponding annual costs increasing from $34.8 billion in 1990 to $131.5 billion by 2050 [2]. Given the other types of osteoporosis-related fractures, the social and economic burdens are expected to be very high.

To prevent osteoporotic fractures, diverse agents have been developed, such as bisphosphonates, selective estrogen receptor modulators, calcitonin, parathyroid hormone agonists, and receptor activator of nuclear factor-κB ligand (RANKL) inhibitors. Among these, bisphosphonates are the mainstay of treatment for osteoporosis and account for almost half of the global drug market [3]. Despite the proven efficacy and safety of the daily regimen, the stringent administration method prompted the development of a weekly regimen. However, only half of the patients

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following the weekly regimen achieved adequate adherence [4]. To further improve adherence, a once-monthly regimen was developed. This long intermittent dosing was possible because of the high binding affinity of bisphosphonates to bone [5]. Patients also preferred the once-monthly regimen to the once-weekly regimen, mainly because of its convenience [6]. Currently, once-monthly ibandronate and risedronate are used widely in clinical practice; however, the anti-fracture efficacy of these two drugs has not been compared. Therefore, we aimed to compare the fracture prevention efficacy between once-monthly ibandronate and risedronate in overall and site-specific fractures.

Methods

Study design and population

The Korean National Health Insurance Service (KNHIS) covers almost 100% of the population for any medical procedure with the exception of cosmetic surgery and medical services for injuries due to traffic accidents. We used data acquired from the National Health Insurance Service Senior Cohort 2002–2015 (NHIS-Senior 2002–2015), a nationwide representative sample of approximately 5,500,000 adults aged 60 years or older. The NHIS-Senior is a random sample representing approximately 10% of the population of the corresponding age. The database contains all claim data (demographic information, diagnoses, prescriptions, inpatient and outpatient healthcare use, and medical costs), health outcomes (death for the respective years), and biennial national health examination results. The KNHIS classifies diagnoses based on the Korean Classification of Diseases, which is similar to the International Classification of Diseases, Tenth Revision (ICD-10).

New bisphosphonate users were defined as those persons initiating therapy after at least a 12-month period without zoledronic acid and a 6-month period without prescription for any other bisphosphonates. The date of the first filled bisphosphonate prescription after this 6-month period was defined as the index date. In Korea, the prescription of bisphosphonates is permitted only for osteoporosis; thus, we regarded all bisphosphonate users as having osteoporosis.

We excluded patients with conditions that may affect bone integrity or the effectiveness of bisphosphonates (i.e., Cushing syndrome, hypercalcemia, hyperparathyroidism, celiac disease, osteomalacia, osteopetrosis, Paget disease, bone malignancy, multiple myeloma, renal impairment, and organ transplant). We also excluded patients who discontinued therapy within the first 3 months, which is the minimum period of therapy adherence.

Ethics statement

The study protocol was approved by the institutional review board of Wonkwang University Sanbon Hospital (WUSH-7302-201641). The need for informed consent was waived by the board.

Follow-up

Cohorts were followed for up to 4 years. Follow-up for each subject in either the ibandronate group or the risedronate group was censored according to the date of other bisphosphonate prescriptions, date of death, low adherence to bisphosphonates, and end of the study period. Low adherence to bisphosphonate therapy was defined according to the proportion of days covered (PDC) < 80% based on systematic review regarding the impact of osteoporosis treatment adherence [7]. The PDC was calculated as the number of days covered by the prescription divided by the total number of follow-up days [8].

Study covariates and outcome

Among the baseline characteristics, age and household income were assessed during the year of cohort entry. Previous fracture was defined as any history of clinical fracture of the hip, vertebra, wrist, humerus, clavicle, pelvis, or lower leg, including the ankle, within 5 years before the index date. Comorbidities, medications, and health service use were examined over 6 months before the index date. Because the insurance coverage for bisphosphonates was changed on October 1, 2011, in Korea, the index date was categorized accordingly (before or after October 1, 2011). Teriparatide and denosumab, two strong anti-osteoporotic agents, were excluded from the recent medications because they were introduced in Korea after 2015, which was not included in the NHIS-Senior database. Among the recent medications, glucocorticoid use was defined as receipt of 450 mg of prednisone-equivalent pills 6 months before the index date—an approximation based on the American College of Rheumatology guideline for 5 mg of prednisone for at least 90 days [9].

The first occurrence of a fracture after the index date was the study endpoint. A fracture related to bisphosphonate use was defined using the following ICD-10 codes: S22.0 and S22.1 (fracture of the thoracic spine); S32.0, S32.7, and 32.8 (fracture of the lumbar spine); S42.0 (fracture of the clavicle); S22.3 and S22.4 (fracture of the ribs); S32.1–32.5 (fracture of the pelvis); S42.2–42.4 and S42.7–S42.9 (fracture of the humerus), S52 (fracture of the forearm), S62.0–62.4 and S62.8 (fracture of the wrist), S72.0–S72.2 and S72.9 (fracture of the femur); and S82 (fracture of the lower leg, including the ankle) [10, 11]. Hip fracture was restricted to only inpatients; the other fractures were not restricted by inpatient or outpatient.

Individuals who had a fracture within the 180 days before the first use of bisphosphonates were excluded to avoid the misclassification of follow-up visits for a recent fracture. Individuals who concurrently experienced trauma (ICD-10 codes: T05, T09, T11, T13, T14, T75, T79, V01–V99, W11–W17, W50–W52, W64, X34–X39, Y01–Y04, and Y30–Y32), seizure (G40, G41, and R56), or pathological fracture (M80, M84.4, and M90.7) during the study period were also excluded from the outcome and were censored on the day on which the event occurred [12].

Statistical analyses

To reduce the bias caused by differences between the two groups, propensity score matching analysis was used [13]. Covariates included in the propensity scores were factors that could affect the fracture risk, such as age at the index date, household income level, history of fracture, Charlson comorbidity index, comorbidities, recent medications, health service use, and classification of the index date.

We evaluated the baseline characteristics of the matched cohorts with the chi-square test and Student's *t* test as appropriate (Table 1). The incidence rate ratio (IRR) between the two drugs was estimated using the Cox proportional model, after adjusting for baseline. The appropriateness of the proportional hazard assumption was assessed by graphical and numerical methods [14]. All tests were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). *P* values less than 0.05 were considered significant.

Results

Baseline characteristics

Among the patients comprising the NHIS-senior cohort, 36,701 women started once-monthly oral ibandronate or once-monthly oral risedronate. After the exclusion criteria were applied, 7785 patients were eligible for the present study. Finally, 6908 patients were included in the propensity score matched analysis (3454 per group) (Fig. 1). Baseline characteristics of the patients are presented in Table 1. The ibandronate and risedronate groups were similar in most baseline characteristics; however, there were significant differences in the distribution of the history of hip fracture, diagnosis of dyslipidemia, and corticosteroid use between the groups ($P = 0.038$, 0.003, and 0.042, respectively).

The ibandronate group was followed for a mean 384.1 ± 336.0 days. At the end of 1 and 4 years after the initiation of follow-up, 34.9% and 2.9% of the original patients remained. The alendronate group was followed for a mean 351.5 ± 317.3 days. At the end of 1 and 4 years after the start of follow-up, 29.9% and 1.7% of the original patients remained. The main reason for censoring in each cohort was non-adherence to medication.

Risks of fracture (overall and at each anatomical site)

Table 2 presents the number of new fractures, incidence rate per 1000 person-years according to treatment, and crude and adjusted rate ratios of ibandronate compared with those of risedronate. For fractures at any site, the incidence rate of new fractures was lower in the ibandronate group than in the risedronate group (77.4 and 92.4 per 1000 person-years, respectively). The difference was also noted in Kaplan-Meier curves with statistical significance (log rank test $P = 0.034$) (Fig. 2). The multivariate-adjusted Cox proportional model showed that the ibandronate group had a 17.8% lower incidence rate than the risedronate group (IRR 0.822, 95% confidence interval [CI] 0.698–0.968, $P = 0.019$).

Regarding non-vertebral fractures, the incidence rate of new fracture was lower in the ibandronate group than in the risedronate group (45.4 and 54.4 per 1000 person-years, respectively). The multivariate-adjusted Cox proportional model showed a 20.2% lower incidence rate in the ibandronate group than in the risedronate group (IRR 0.798, 95% CI 0.647–0.985, $P = 0.036$).

Concerning vertebral fractures, the incidence rate of new fracture was numerically lower in the ibandronate group than in the risedronate group (36.7 and 41.2 per 1000 person-years, respectively). The multivariate-adjusted Cox proportional model showed a similar but insignificantly lower incidence rate in the ibandronate group than in the risedronate group (IRR 0.897, 95% CI 0.709–1.135, $P = 0.366$).

Regarding hip fractures, only a small number of events occurred in each treatment group (ibandronate and risedronate groups: 4.9 and 4.7 per 1000 person-years, respectively). Therefore, it was difficult to compare the efficacy of the drugs.

Discussion

In this study, we found that after about 1 year of treatment, the once-monthly ibandronate (150 mg) group had a lower incidence of overall and non-vertebral fractures than the once-monthly risedronate (150 mg) group among Korean osteoporotic women aged 60 and older. Based on the absolute incidence rate difference between the two groups, the number of patients who needed to be treated with once-monthly ibandronate compared to those treated with once-monthly risedronate to prevent one event was approximately 67 for overall fractures and 111 for non-vertebral fractures.

For agents to be effective with a long dosing interval, bisphosphonates must have a high affinity to bone tissue. In this regard, ibandronate is more effective than risedronate [15]. In addition, the manufacturer doubled the dose of

Table 1 Baseline characteristics of the matched cohorts

	Ibandronate group ($n = 3454$)		Risedronate group ($n = 3454$)		P value[a]
	N (%)		N (%)		
Age (years, mean ± SD)	71.7	(6.2)	71.6	(6.2)	0.464
Household income level, deciles	6.1	(5.9)	6.1	(5.9)	0.954
History of fracture[b]					
Any site	1586	(45.9)	1582	(45.8)	0.923
Hip	148	(4.3)	115	(3.3)	0.038
Vertebra	694	(20.1)	679	(19.7)	0.651
Non-hip, non-vertebra	878	(25.4)	876	(25.3)	0.956
Charlson comorbidity index (mean ± SD)[c]	2.2	(2.1)	2.2	(2.1)	0.516
Comorbidities[c]					
Rheumatoid arthritis	245	(7.1)	262	(7.6)	0.432
Hyperthyroidism	82	(2.4)	76	(2.2)	0.629
Diabetes mellitus	941	(27.2)	947	(27.4)	0.871
Hypertension	2289	(66.3)	2352	(68.1)	0.107
Dyslipidemia	1740	(50.4)	1677	(46.8)	0.003
Recent medications[c]					
Corticosteroids	60	(1.7)	39	(1.1)	0.042
Anticoagulants	38	(1.1)	34	(1.0))	0.636
Antidepressants	295	(8.5)	260	(7.5)	0.121
Benzodiazepines	1239	(35.9)	1260	(36.5)	0.617
Proton pump inhibitors	552	(16.0)	528	(15.3)	0.427
Thiazolidinediones	73	(2.1)	65	(1.9)	0.490
Estrogen, oral or intramuscular	11	(0.3)	10	(0.3)	0.827
SERM	84	(2.4)	78	(2.7)	0.633
Calcitonin	0	(0.0)	0	(0.0)	NA
Tibolone	27	(0.8)	21	(0.6)	0.385
Health service use[c]					
Outpatient visit, number (mean ± SD)	18.4	(16.1)	18.3	(15.0)	0.827
Any hospitalization	878	(25.4)	860	(24.9)	0.618
Classification of the index date[d]					0.652
Before Oct. 1, 2011	1250	(36.2)	1232	(35.7)	
Oct. 1, 2011 or after	2204	(63.8)	2222	(64.3)	

SD standard deviation, *SERM* selective estrogen receptor modulator, *NA* not applicable

[a] Student's *t* test was used to analyze continuous variables, and the chi-square test was used to analyze categorical variables

[b] Assessed within 5 years before the index date (the date of the first bisphosphonate prescription without a recent 6-month bisphosphonate medication)

[c] Assessed within 6 months before the index date

[d] The index date was classified by the date of the insurance criteria revision about bisphosphonate use (Oct. 1, 2011)

once-monthly ibandronate compared with the daily regimen in terms of annual cumulative exposure (ACE), because previous studies have demonstrated that when the ACE is identical, the anti-fracture efficacy of the intermittent regimen is lower than that of the daily regimen [16, 17]. In contrast, once-monthly risedronate was manufactured to have the same ACE as the daily dose. These facts can serve as additional evidence that support the superior efficacy of once-monthly ibandronate to once-monthly risedronate. However, compared to ibandronate, risedronate is a stronger inhibitor of the farnesyl pyrophosphate synthase enzyme, a key enzyme in the anti-resorptive activity of bisphosphonates, by which it may exhibit better anti-osteoporotic efficacy than ibandronate [15]. Hence, it is difficult to predict the relative efficacy between ibandronate and risedronate based on their pharmacologic properties.

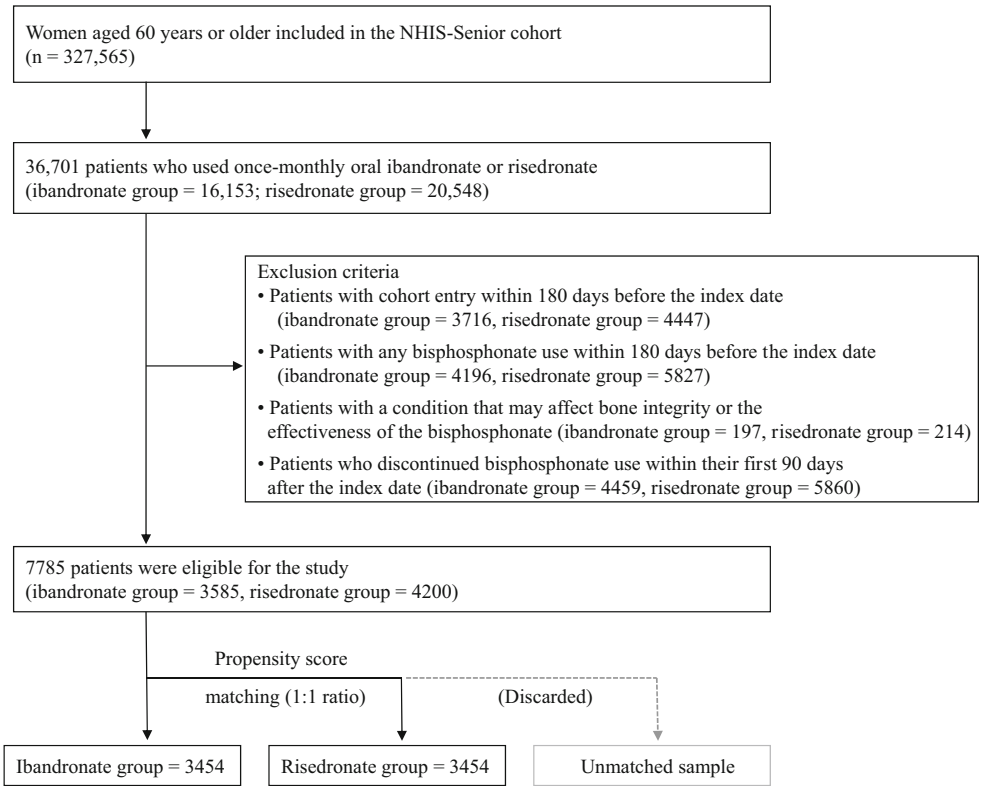

Fig. 1 Flow diagram for the selection of the study population

Regarding epidemiologic studies, no head-to-head trials have compared the efficacy between once-monthly oral ibandronate and risedronate. Although the dose and dosage form were different, a well-designed study (the MOVER trial) compared the efficacy between ibandronate and risedronate [18]. By combining the results of the MOVER trial with the findings of related ibandronate and risedronate studies, it is possible to confirm our observations indirectly.

The MOVER study

The MOVER study evaluated the relative anti-fracture efficacy between once-monthly intravenous (IV) ibandronate (1 mg) and daily oral risedronate (2.5 mg) in Japanese patients with primary osteoporosis [18]. In this study, at 3 years, the mean relative increases from baseline bone mineral densities (BMDs) of the lumbar spine and total hip were significantly

Table 2 Incidence of new fracture per 1000 person-years according to treatment

Fracture type	Number of new fractures		Incidence rate[a]		Crude rate ratio[b] (95% CI)	Adjusted rate ratio[c] (95% CI)	*P* value for the adjusted result
	Ibandronate group	Risedronate group	Ibandronate group	Risedronate group			
Any fracture	281	307	77.4	92.4	0.839 (0.713–0.966)	0.822 (0.698–0.968)	0.019
Vertebral fracture	138	143	36.7	41.2	0.893 (0.707–1.129)	0.897 (0.709–1.135)	0.366
Non-vertebral fracture[d]	169	087	45.4	54.4	0.830 (0.674–1.023)	0.798 (0.647–0.985)	0.036
Hip fracture	19	17	4.9	4.7	1.020 (0.530–1.963)	1.064 (0.549–2.060)	0.855

CI confidence interval

[a] New fracture incidence per 1000 person-years

[b] Based on the Cox proportional model

[c] Based on the Cox proportional model, which was adjusted for age, household income level, history of fracture, Charlson comorbidity index, comorbidity, recent medication, health service use, and classification of the index date

[d] Non-vertebral fracture includes fractures of the hip, forearm/wrist, humerus, clavicle, rib, and lower leg

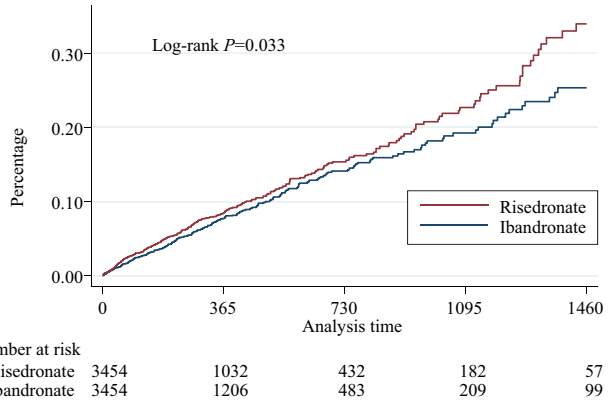

Fig. 2 Cumulative percentage of new osteoporotic fractures according to the treatment group *NHIS-Senior*, National Health Insurance Service Senior Cohort 2002–2015

greater with once-monthly IV ibandronate (1 mg) than with daily oral risedronate (2.5 mg). In addition, significant differences were noted between the two treatments in the mean reductions of bone turnover markers. Thus, the MOVER study suggested that once-monthly IV ibandronate (1 mg) may show better anti-fracture efficacy than once-monthly oral risedronate (2.5 mg).

Related ibandronate studies

The MOVEST study, the bridging study of the MOVER study, assessed the efficacy of once-monthly oral ibandronate (100 mg) versus once-monthly IV ibandronate (1 mg) in Japanese osteoporotic patients. This study demonstrated that lumbar spine BMD gain after 12 months was similar between the treatments (oral 5.22% and IV 5.34%). Given the dose-response anti-osteoporotic effect of ibandronate documented by pharmacokinetic and epidemiologic studies [19, 20], oral ibandronate (150 mg), which was the dosage assessed in the current study, may provide a more protective effect than 100-mg oral or 1-mg IV ibandronate.

Related risedronate studies

In a randomized, double-blind, comparative study with multiple dose levels of risedronate among Japanese osteoporotic patients, the percent increase in lumbar spine BMD after 6 months of treatment was similar in patients taking 2.5 mg and 5 mg of risedronate [21]. In a 2-year randomized, double-blind study among postmenopausal osteoporotic women, the efficacy of 5-mg daily oral risedronate compared with a 150-mg once-monthly regimen was comparable in lumbar spine and hip BMD [22]. Therefore, the anti-osteoporotic efficacy of once-monthly oral risedronate (150 mg) in the current study may be similar to that of daily oral risedronate (2.5 mg) at least in lumbar BMD.

Combining the MOVER study and related studies

Based on the aforementioned evidence of the MOVER and related studies, we can summarize the relative efficacy as follows:

$$\begin{aligned}&\text{Once–monthly oral ibandronate (150 mg)}\\ &\quad \geq \text{monthly oral ibandronate (100 mg)}\\ &\quad = \text{monthly IV ibandronate (1 mg)}\\ &\quad > \text{daily oral risedronate (2.5 mg or 5 mg)}\\ &\quad = \text{once–monthly oral risedronate (150 mg)}\end{aligned}$$

Thus, our observations (the superior efficacy of 150 mg ibandronate to 150 mg risedronate) coincide with current evidence, although these inferences are based on studies with different populations and protocols. Because direct comparative trials on the efficacy of once-monthly oral ibandronate and risedronate are lacking currently, clinicians should pay attention to the different efficacy between once-monthly ibandronate (150 mg) and risedronate (150 mg) herein.

Strengths and limitations

Several limitations to this study should be acknowledged. First, fractures were identified according to diagnostic codes of health insurance claim data without standardization or validation. However, we increased the accuracy of identifying osteoporotic fracture by excluding traumatic or pathologic fracture using ICD-10 codes. Second, although we used propensity score matching and adjusted for accessible factors to minimize confounding factors, such as BMD, we could not control for calcium and vitamin D intake, cigarette smoking, heavy alcohol drinking, exercise, and balance impairment between the groups. Third, we set 12 and 6 months as washout periods for zoledronic acid and other bisphosphonates. However, residual anti-fracture effect may persist beyond these periods according to the durations of treatments. Thus, the unbalanced residual effect may have influenced the results. Fourth, some of the baseline characteristics, such as a history of hip fracture, diagnosis of dyslipidemia, and corticosteroid use, were not balanced between the two treatment groups. Interestingly, all these characteristics were more common in the ibandronate group than in the risedronate group. As a result, this imbalance may possibly support our observation instead of weakening it. Fifth, the current study's results were based on data obtained from Korean elderly women with osteoporosis. Accumulating evidence has shown that the pharmacokinetics and efficacy of bisphosphonates may be different between Caucasians and Asians [20, 23, 24]. For example, the bioavailability of oral ibandronate was different in Japanese subjects versus Western subjects (0.91% and 0.63%, respectively) [20]. Additionally, although the effect of the 2.5-mg dose was smaller than the 5-mg dose of

risedronate in the Caucasian population [23, 24], the effect was similar between the two doses in the Japanese population [21]. Therefore, clinicians should be cautious in generalizing the current observation to other populations, especially Caucasians. Finally, the sample size was relatively small to detect a difference in site-specific fractures, especially of the vertebral and hip areas.

Despite the aforementioned limitations, our study has some important strengths. First, this is the first study to compare the anti-fracture efficacy between once-monthly oral ibandronate and risedronate based on a nationwide representative sample with a relatively long follow-up duration. Additionally, although our study design was retrospective and observational, it has an advantage over randomized controlled trials (RCTs) in generalizability. RCTs are recognized as the gold standard in establishing the efficacy and safety of a treatment; however, an observational study includes various individuals who have been excluded from the RCTs because of strict inclusion and exclusion criteria (for e.g., age, comorbidities, concomitant medications) [25]. For example, Dowd et al. found that most patients with osteoporosis (79% or more) who are candidates for treatment did not meet the eligibility for RCTs [26]. Moreover, because our results were drawn from a nationally representative cohort, they are more likely to be generalizable.

In conclusion, we found that once-monthly ibandronate (150 mg) provides clinical benefit over once-monthly risedronate (150 mg). Given the potential limitations of current study, further large-scale studies are warranted to confirm our findings and to determine the site-specific differences, especially regarding the vertebral and hip areas.

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Compliance with ethical standards

Conflicts of interest None.

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