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Original Article

Cost-Effectiveness of Denosumab for the Treatment of Postmenopausal Osteoporosis in South Korea

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Background: Osteoporosis is a progressive skeletal disease associated with an increased risk of bone fracture. This study aimed to estimate the cost-effectiveness of denosumab for osteoporotic fracture prevention compared to bisphosphonates (alendronate, ibandronate, risedronate, and zoledronate) and selective estrogen receptor modulators (raloxifene) in a cohort of postmenopausal women with osteoporosis. **Methods:** A Markov model was used to evaluate the cost and effectiveness of denosumab versus comparators. The model had a cycle length of 6 months and was run from the age of 68 years to individual patients' lifetime or the age of 100 years. The health states considered in the model were well, hip fracture, vertebral fracture, wrist fracture, other osteoporotic fracture, post-hip fracture, post-vertebral fracture, and death. Recent local data were used as inputs for the model parameters. A discount rate of 4.5% was applied to both costs and outcomes. **Results:** From the perspective of the healthcare system, denosumab was cost-effective or cost-saving compared to all comparators, considering one unit of Korea's gross domestic product per capita, USA dollar (USD) 34,870. Denosumab was cost-saving compared to ibandronate (oral) and raloxifene. Compared to alendronate, denosumab was cost-effective with an incremental cost-effectiveness ratio (ICER) of USD 767.10 per quality-adjusted life year (QALY). The ICER of denosumab vs. ibandronate IV, risedronate, and zoledronate was USD 685.63, USD 1,469.71, USD 4,668.53 per QALY, respectively. **Conclusions:** The findings of this analysis suggest that denosumab is a cost-effective therapeutic option for preventing fractures in postmenopausal women with osteoporosis in South Korea.

Key Words: Cost-benefit analysis · Denosumab · Fractures, bone · Korea · Osteoporosis

INTRODUCTION

Osteoporosis is a systemic and progressive skeletal disease, which leads to a reduction in bone mass and quality.[1] Epidemiological data from 2020 Health Insurance Review & Assessment Service (HIRA) suggest approximately 22% of adults in Korea suffer from osteoporosis.[2] Low bone mineral density (BMD) reduces bone strength which makes bones more susceptible to fracture. The clinical sequelae of osteoporotic fractures are serious. Osteoporosis is associated with significant fracture-related morbidity [3] since the majority of fractures occur at the hip, spine, and distal radius, which leads to loss of body function and acute pain.

[4,5] Patients who experienced a fracture were more likely to have a re-fracture, and patients who experienced a re-fracture within 3 years of the first fracture have a 20% higher mortality rate than those who did not.[6] According to the 2020 report of the Korean Society for Bone and Mineral Research osteoporotic fractures are associated with functional limitations and excess mortality of 17%, meaning preventing fractures has important implications for public health.[7]

In addition to negative clinical effects of osteoporosis-induced fracture, including increased mortality, reduced quality of life, and increased subsequent fracture rate, osteoporosis is accompanied by a considerable burden on healthcare resources. As the elderly population, the major age group with osteoporosis in Korea, continues to expand, and the social costs associated with osteoporotic fractures are also expected to increase. A recent study predicted that if the treatment and diagnosis rates of osteoporosis increase by 50% and 44%, respectively, from 2020 to 2040, 4.3 million osteoporotic fractures would be avoided, which will save the healthcare system up to 13.5 billion USA dollar (USD).[8] Thus, improving the treatment effectiveness of osteoporosis and preventing fractures is an important treatment goal that not only provides clinical benefits to patients but also reduces the economic burden on the healthcare system.

Denosumab is an antiresorptive agent targeting the receptor activator of nuclear factor-κB ligand. In the Future REvascularization Evaluation in patients with Diabetes mellitus: optimal management of Multivessel disease (FREEDOM) clinical trial and its extension trials, long-term use of denosumab for (up to 10 years) has been reported to be effective in preventing fractures.[9,10] Unlike most oral osteoporotic drugs that should be taken daily / weekly / monthly, denosumab is subcutaneously injected every 6 months. Due to its convenience, adherence to medication is superior in denosumab compared to other oral drugs. In Korea denosumab has been reimbursed as the first-line treatment for osteoporosis since 2019.[11] In addition, the list price of denosumab decreased by 17.6% in December 2020 compared to the initial list price in 2017.[12] Nevertheless, there is a lack of research comparing the cost-effectiveness of denosumab at the new list price with alternative treatments in Korea. The purpose of this study was to estimate the cost-effectiveness of denosumab for osteoporotic fracture prevention compared with bisphosphonates (alendronate, ibandronate, risedronate, zoledronate) and selective estrogen receptor modulator (SERM; raloxifene) in a cohort of postmenopausal women in Korea.

METHODS

For this cost-effectiveness analysis, the previously published Markov model for cost-effectiveness analysis,[13] was utilized. The Markov model is useful when a decision problem involves continuous risk over time, when the timing of events is important, and when important events may happen more than once.[14]

1. Analysis

The current Markov model presented the cost per quality-adjusted life years (QALYs) and the incremental cost-effectiveness ratio (ICER). ICER is expressed as the ratio of the difference in total cost between denosumab and each comparator to the difference in health outcomes. The difference in health outcomes was measured in QALYs between denosumab and each comparator. If the ICER of denosumab compared to other anti-osteoporosis drugs was lower than the willingness to pay threshold of 1 gross domestic product (GDP), denosumab will be suggested to be a cost-effective option. Also, suppose the cost of denosumab group was lower than the other drug group, since denosumab decreased the number of fractures, ICER will be negative. In that case, denosumab will be suggested as a cost-saving option. One unit of Korea's GDP per capita was applied for willingness to pay threshold in accordance with the World Health Organization (WHO) recommendations.[15]

2. Sensitivity analysis

We conducted a one-way deterministic sensitivity analysis for each comparison. Sensitivity analyses were performed by changing the key model inputs and assumptions. Also, the weighted average drug costs of each comparator were applied for sensitivity analysis. The results are presented as the costs per QALY gained.

3. Model structure

The current model was used to evaluate the costs and effectiveness of denosumab and other comparators (alen-

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dronate, risedronate, ibandronate, zoledronate, raloxifene) for the treatment of osteoporosis in postmenopausal women. The comparator drugs have been selected considering their reimbursement criteria and line of therapy in the recent Korean market situation. The model has a cycle length of 6 months and was run from age 68 years, the average age of postmenopausal women with osteoporosis in South Korea, to individual patients' lifetime or the age of 100 years. The model utilized a healthcare system perspective to include direct medical costs. The model is a cohort-based model designed in Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

The model was comprised of eight health states: (1) well; (2) hip fracture; (3) vertebral fracture; (4) wrist fracture; (5) other osteoporotic fracture (non-hip/ non-vertebral/ non-wrist osteoporotic fracture); (6) post-hip fracture; (7) post vertebral fracture; and (8) dead (Fig. 1).

The target population in the model is defined as average postmenopausal women with osteoporosis in Korea. Based on 2014 HIRA-National Patients Sample data, the average age of postmenopausal women with osteoporosis patients was 68 years.[16] All people entered the model in the 'well' state. From there, probabilities of sustaining a fracture, remaining healthy, or dying determined transitions to other health states in each cycle. After one cycle in a given fracture state, patients had a risk of sustaining a subsequent fracture, moving to the post-fracture state (either post-hip or post-vertebral fracture) or dying, depending on the previous healthy state.

We assumed that patients with wrist fractures or other osteoporotic fractures could transition to the 'well' state and do not move to the 'dead' state, while patients in the hip fracture and vertebral fracture state cannot move to the 'well' state but can move to the 'dead' state. A patient who has already experienced a hip fracture was only at risk of dying or sustaining subsequent hip fractures (not other fracture types). The model also assumed patients who had sustained a vertebral fracture are at risk of sustaining subsequent vertebral fractures, hip fractures, or dying. Since the model assumed that the patient who sustains a hip fracture or vertebral fracture may not incur future wrist or other osteoporotic fractures ever again, the model slightly underestimated less severe fractures (wrist fracture, other fractures). Therefore, this limitation was addressed by estimating and adding the number of these missed downstream fractures based on the method previously used.[13,17]

It was assumed that health statuses did not affect drug administration, and an adverse event (e.g., gastrointestinal [GI] disorder) was not considered in the model.

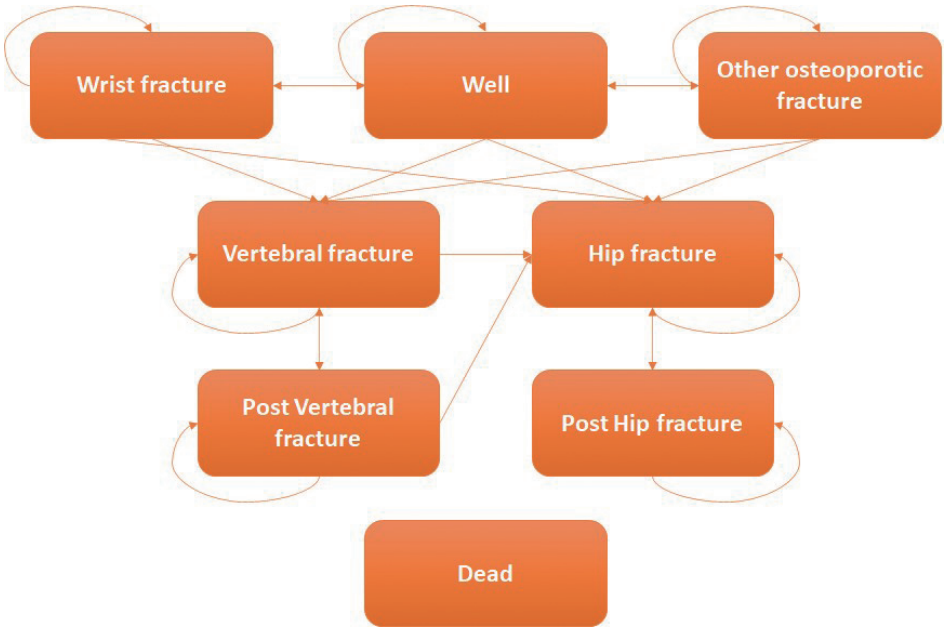

Fig. 1. Structure of the denosumab Markov cohort model. Arrows to the health state "dead" were excluded for simplification, cycle length was 6 months.

4. Model input

1) Incidence of fracture and mortality

General population mortality was estimated using the Korean statistical information service (KOSTAT) complete life table from 2019 for 50 years and older women. The baseline fracture prevalence of osteoporosis patients was calculated from the 2020 National Health Insurance Service (NHIS) Ilsan hospital report.[18] The incidence of each fracture type according to the age group was extracted from the HIRA report about healthcare utilization of osteoporosis and prescription status (Supplementary Table 1).[19] The mortality rate after vertebral fracture was calculated at 5-year intervals based on Lee et al. [20]. The mortality rate after hip fracture was based on 10-year intervals of standardized mortality ratio from data presented in Yoon et al. [21]. The mortality rate of fractures at other sites was calculated by combining the results of studies by Barret et al. [22] and Kanis et al. [23] (Supplementary Table 1). We assumed that 30% of the excess mortality (compared to normal mortality) after hip, vertebral, and other fractures were associated with the fracture event, which is a widely accepted assumption in previous studies.[13,24] However, wrist fracture was assumed to not be associated with excess mortality, and the excess mortality of hip and vertebral fractures lasts for 8 years.

2) Cost

According to HIRA pharmacoeconomics guideline, only direct medical costs and transportation cost were considered in the model. Direct medical costs included in this study were cost of: drug therapy, osteoporotic fracture treatment, nursing home costs, BMD measurement, physician visits, subcutaneous (SC) infusion, intravenous (IV) infusion, and pharmacy visits. The regimen of each drug therapy was extracted from the Korean Ministry of Food and Drug Safety, and the cost was extracted from HIRA drug ceiling price list. It was assumed that BMD is measured once a year in patients receiving treatment. Denosumab was associated with 2 physician visits and 2 SC infusions yearly in the model. Drugs delivered intravenously (zoledronate, ibandronate IV) were assumed to be associated with IV infusion and physician visits (once a year for zoledronate, four times yearly for ibandronate). Oral drugs (alendronate, ibandronate [oral], risedronate, raloxifene) were assumed to be associated with physician visits and pharmacy visits four times yearly. Indirect costs were not included in the model. All costs were presented in Korean won (KRW) and converted to USD using the average exchange rate during the first half of 2021 (1 USD=1,117.73 KRW).[25] A discount rate of 4.5% per annum was applied to both costs and outcomes according to the most recent Korean guidelines for economic evaluation from 2021.[26] The cost of treatment of direct clinical events, fractures, and medical resource utilization in the first year after fracture for each fracture type were extracted from HIRA big data of 2021.[27] The cost of physician visits, IV and SC injections, and BMD measurement were informed by HIRA fee-for-service prices for 2020 (Supplementary Table 2).[28] The out-of-pocket copayment rate was based on the average rate of orthopedics departments in tertiary hospitals derived from the NHIS report in 2019.[29] Drug cost was based on the ceiling price of the original drug of each comparator,[30] and the original drug prices were applied in the base-case analysis (Supplementary Table 2). The weighted average drug costs of each comparator based on HIRA weighted average drug cost table 2021 [27,28,31] were applied for sensitivity analysis (Supplementary Table 2). Transportation cost was derived from the KOSTAT 2020 transportation price index.[32]

3) Treatment efficacy

Barrionuevo et al. [33], a recently published network meta-analysis, was used to inform treatment-specific fracture reduction efficacy because of its robustness as a systematic review of osteoporosis treatment efficacy of denosumab and comparators. Freemantle et al. [34], another network meta-analysis including denosumab and comparators' efficacy, was applied in the sensitivity analysis, although it does not report efficacy values for ibandronate and raloxifene to hip fracture (Supplementary Table 3). Maximum treatment duration for a fully persistent patient was assumed to be 5 years. Persistence data were based on Li et al. [35] using their long-term estimates through 5 years. When patients discontinue drug administration, the model assumed the treatment effect does not stop immediately but continues through the "offset time" after treatment is stopped. In the model, offset time was assumed to be as long as the time on treatment, up to a maximum of 2 years. Even though differential effects for treatments should be based on solid evidence, very few

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studies have evaluated offset time, and the findings were inconsistent. Thus, since there is not robust evidence to support differential offsets, we assumed the same period for all treatments. This is a limitation of this analysis and should be taken into account.

4) Utility

Utility values for the general population of 50 years or older was sourced from the 2014 Korea National Health and Nutrition Examination Survey result.[16] Reduction in quality of life within one year after hip, vertebral, and wrist fracture and within the second or following years after hip or vertebral fracture was based on a meta-analysis and clinician experience.[16] Wrist fractures and "other fractures" were estimated to have no quality-of-life reduction in the second and subsequent years (Supplementary Table 2). The gained life years (quantity) and quality of life were combined into a single measure of health, which is the QALYs.

RESULTS

1. Base-case analysis

In the base-case scenario applying efficacy input based on Barrionuevo et al. [33], we examined the cost-effectiveness of denosumab compared to other comparators. Denosumab was found to be cost-effective compared to alendronate, ibandronate IV, risedronate, and zoledronate or cost-saving compared to ibandronate (oral) and raloxifene considering the willingness-to-pay threshold of one GDP per capita, USD 34,870 (International Monetary Fund, 2021) (Table 1).

2. Sensitivity analysis

One-way sensitivity analysis showed that the model results were most sensitive to a variation of utility values within 10% and a variation of efficacy values within the confidence interval (CI) (Table 2). A range of 10% was determined in consultation with investigators of this study. If the utility values were increased by 10%, or if the upper boundary of CI in efficacy input were applied, the cost per QALY gained increased substantially. If medical costs were high as 10%, the costs per QALY gained would increase. Assuming decreased discount rate for cost and effect, the cost per QALY gained would decrease. Applying lower fracture prevalence decreased the costs per QALY relative to the base case level.

The sensitivity analysis using efficacy input based on Freemantle et al. [34] also showed the cost-effectiveness of denosumab compared to comparators. Denosumab was cost-saving compared to ibandronate IV, ibandronate (oral), and raloxifene. Denosumab was cost-effective compared to alendronate, risedronate, and zoledronate. In the sensitivity analysis where drug cost is based on a weighted average cost, and efficacy is based on Barrionuevo et al. [33], denosumab was also cost-effective (alendronate, ibandronate IV, risedronate, zoledronate) or cost-saving (ibandronate [oral], raloxifene) compared to all comparators considering willingness to pay threshold. This result aligns with the result of the base-case scenario. In the sensitivity analysis where drug cost is based on weighted average price and efficacy is based on Freemantle et al. [34], denosumab was found to be cost-effective (alendronate, risedronate, zoledronate) or cost-saving (ibandronate IV, ibandronate [oral], raloxifene). The sensitivity analysis ICER from each comparison is presented in Table 2. Overall, there was no result that exceeded the willingness-to-pay threshold (USD 34,870), which is in line with the base-analysis, showing the robustness of the cost-effectiveness analysis result.

Table 1. Base-case analysis result

	Denosumab vs. Alendronate	Denosumab vs. Ibandronate (IV)	Denosumab vs. Ibandronate (oral)	Denosumab vs. Risedronate	Denosumab vs. Raloxifene	Denosumab vs. Zoledronate
Cost difference (KRW)	43,230	41,260	-16,787	97,809	-128,888	161,674
QALY	0.050	0.054	0.053	0.060	0.055	0.031
Life years	0.010	0.010	0.010	0.012	0.012	0.007
ICER (KRW)	856,407	766,354	Cost-saving	1,642,742	Cost-saving	5,218,159
ICER (USD)	767.10	685.63	Cost-saving	1,469.71	Cost-saving	4,668.53

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Table 2. Sensitivity analysis result (cost [KRW] per quality-adjusted life year gained)

One-way sensitivity analyses	Alendronate	Ibandronate (IV)	Ibandronate (oral)	Risedronate	Raloxifene	Zoledronate
Base case	856,407	766,354	Cost-saving	1,642,742	Cost-saving	5,218,159
Cost+10%	283,739	110,548	Cost-saving	1,081,777	Cost-saving	4,628,109
Cost-10%	1,429,076	1,422,160	333,827	2,203,707	Cost-saving	5,808,208
Utility+10%	2,115,287	1,955,354	Cost-saving	3,855,952	Cost-saving	11,360,991
Utility-10%	540,470	479,673	Cost-saving	1,051,157	Cost-saving	3,413,807
Efficacy+10%	720,936	698,040	Cost-saving	1,604,863	Cost-saving	6,023,533
Efficacy-10%	120,601	838,676	Cost-saving	1,011,613	Cost-saving	4,468,643
Efficacy lower CI	Cost-saving	1,952,804	451,894	Cost-saving	Cost-saving	2,253,057
Efficacy upper CI	4,038,533	Cost-saving	Cost-saving	5,548,484	Cost-saving	11,529,533
Discount rate 0%	86,644	120,158	Cost-saving	528,758	Cost-saving	2,726,020
Discount rate 3%	569,902	525,130	Cost-saving	1,240,317	Cost-saving	4,326,451
Discount rate 5%	957,462	851,544	Cost-saving	1,782,320	Cost-saving	5,526,808
Fracture prevalence 5.54%	1,578,635	1,495,353	314,746	2,427,148	Cost-saving	6,291,162
Fracture prevalence 7.10%	1,351,179	1,265,753	116,137	2,180,178	Cost-saving	5,952,464
GP visit 5 times/year	419,613	766,354	Cost-saving	1,306,973	Cost-saving	5,218,159
Efficacy input (Freemantle)	1,638,252	Cost-saving	Cost-saving	2,519,481	Cost-saving	11,732,008
Drug cost: weighted average cost (Barrionuevo)	813,679	489,572	Cost-saving	1,937,564	Cost-saving	5,218,159
Drug cost: weighted average cost (Freemantle)	1,593,003	Cost-saving	Cost-saving	2,826,111	Cost-saving	11,732,008

DISCUSSION

This study estimated the cost-effectiveness of denosumab compared with alendronate, risedronate, ibandronate, zoledronate, and raloxifene from the South Korean healthcare system's perspective. The base-case population was post-menopausal women with osteoporosis. The model structure is well validated and similar chosen to represent the average patient treated for postmenopausal osteoporosis in Korea. In this analysis, the model structure is consistent with previously published model.[16] However, in this model, model has been updated with all currently reimbursable drug options in Korea as comparators. The results of this analysis demonstrated that denosumab is a cost-effective treatment option to reduce the risk of fracture in postmenopausal Korean women with osteoporosis compared to other osteoporosis agents. Specifically, denosumab is cost-effective compared with alendronate, ibandronate IV, risedronate, zoledronate and cost-saving compared with ibandronate (oral) and raloxifene. The ICER of denosumab compared to other antiosteoporosis drugs was below the willingness to pay threshold of 1 GDP, as recommended by WHO. Therefore, considering the threshold, denosumab is suggested to be a cost-effective option for treating postmenopausal osteoporotic women.

The findings from this study provide insights into the cost-effectiveness of denosumab versus alendronate, ibandronate IV, ibandronate (oral), risedronate, raloxifene and zoledronate, all the reimbursed drugs for treating osteoporosis in Korea. The results from our models are consistent with previous economic evaluations in Japan that have found denosumab to be cost-effective in the treatment of postmenopausal osteoporosis with a willingness to pay of USD 50,000.[36] Likewise, denosumab has been shown to be cost-effective in different settings such as the USA, Canada, several countries in the European Union, and Australia.[13,17,36-40]

There are unmet therapeutic needs for treating osteoporotic postmenopausal women since some patients are forced to discontinue bisphosphonates and SERM agents due to their complexity of administration or side effects. Individuals with limited public health literacy, for example, were shown to have poor oral bisphosphonates persistence [41] and the poor persistence rate of bisphosphonates for osteoporosis treatment is associated with increased fracture risk.[42] Bisphosphonates also have a contraindication for use in patients with renal impairment.[43] However, the pharmacokinetics and pharmacodynamics of denosumab at the standard dose are not affected by renal impairment.[44] The findings from Mosca et al.

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[45], showed that raloxifene, a SERM agent used as one of the comparators in our analysis, is associated with an increased risk for fatal stroke and venous thromboembolism while another study showed denosumab could be used without the risk of stroke and venous thromboembolism. [44] Although discontinuation of denosumab can lead to reversal of bone turnover suppression and rapid loss of BMD gained during treatment, denosumab has confirmed long-term efficacy and safety in 10 years extension to the FREEDOM study. According to the FREEDOM study, denosumab treated patients not only showed increases in BMD without plateau, but also showed low rates of adverse events. Furthermore, previous studies reported that denosumab treated patients improved BMD significantly more than bisphosphonates.[46,47] In our analysis, although denosumab had relatively high cost among compared drugs, it showed considerably lower cost per QALY estimates, which can be explained due to the superior efficacy of denosumab compared to other treatments. Thus, denosumab could be a cost-effective therapeutic alternative to bisphosphonates and raloxifene for postmenopausal women with osteoporosis.

There are several limitations to the generalizability of our findings. GI disorder, the common adverse reaction to bisphosphonates, was not considered in the model. The model excluded GI disorder as a conservative approach for denosumab. However, this limitation should have a minimum impact on the ICER, according to a cost-effectiveness analysis in a Swedish setting, in which GI disorder of alendronate was included in a sensitivity analysis.[13]

Secondly, even though this analysis applied recent data from the Korean clinical settings and market changes such as post-evaluation on drug cost or market share, utility value [16] and the mortality rate of other fractures (non-hip / non-vertebral / non-wrist osteoporotic fracture) [22,23] were calculated using data from other countries due to the lack of local data. Thus, sensitivity analysis was conducted to assess these limitations. The results from varying the utility values by 10% suggested a similar conclusion, which in turn demonstrated the model's robustness.

Despite limitations, this study is the first study to demonstrate the cost-effectiveness of denosumab compared with all the other drugs reimbursed as first-line therapy in osteoporotic postmenopausal women in Korea. Specifically, this analysis considered up-to-date Korean reimbursement circumstances and drug costs. The model showed the cost-effective feature of denosumab which is in alignment with studies from other countries.[13,38-40] Also, the efficacy data included in the model was from a network meta-analysis.[35] According to the HIRA economic evaluation guideline,[26] network meta-analysis is recommended for indirect treatment comparison if head-to-head randomized controlled trial results are not available.

The findings of this study offer important evidence for public health policymakers and healthcare providers to ensure adequate access to appropriate therapies to deal with Korea's increasing burden of osteoporosis and fracture risk.

DECLARATIONS

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Authors' contributions

Conceptualization: JYK and HY; Data curation: JYK and LC; Formal analysis: LC; Methodology: BJ; Writing - original draft: JYK and HY; Writing - review & editing: JYK, LC, BJ, and HY; All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Conflict of interest

JYK and HY are employees of Amgen Inc. Except for that, no potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Incidence of fracture and mortality rate (relative risk)

Age	Incidence (per 10,000)				Mortality rate (relative risk)			
	Vertebral	Hip	Wrist	Others	Vertebral	Hip	Post-vertebral	Post-hip
50-54	16.57	1.26	34.76	27.72	6.85	2.81	4.86	1.75
55-59	37.02	2.31	59.78	38.18	9.08	2.66	6.44	1.84
60-64	78.05	5.10	72.19	41.03	5.31	2.22	3.68	1.56
65-69	178.86	14.11	83.99	44.08	5.26	1.85	3.64	1.30
70-74	273.76	28.98	79.49	41.75	2.77	1.69	2.02	1.25
75-79	367.65	55.37	78.92	39.73	3.60	1.83	2.62	1.38
80-84	409.07	93.12	81.21	38.33	2.59	2.10	1.86	1.56
85-89	400.30	136.93	89.98	42.30	3.65	2.34	2.62	1.79
90-94	327.01	146.31	84.52	39.83	7.53	3.51	5.48	2.81
95-100	186.13	112.59	48.81	35.14	7.53	2.95	5.48	2.21

Supplementary Table 2. Cost inputs and utility inputs

Variable	Value (KRW)	References
Cost input		
Drug cost (yearly) (original)		Korean National Health Insurance Service [30]
Denosumab	355,300	
Alendronate	276,442	
Ibandronate (IV)	206,220	
Ibandronate (oral)	231,552	
Zoledronate	214,592	
Risedronate	218,088	
Raloxifene	257,136	
Drug cost (yearly) (weighted average cost)		Korean National Health Insurance Service [31]
Denosumab	355,300	
Alendronate	277,955	
Ibandronate (IV)	214,964	
Ibandronate (oral)	229,752	
Zoledronate	214,592	
Risedronate	204,108	
Raloxifene	257,501	
Direct cost of clinical event (per year) (considering copayment rate)		Health Insurance Review & Assessment Service [27]
Vertebral fracture	4,651,492	
Wrist fracture	5,538,351	
Hip fracture	15,363,707	
Other fracture	6,327,605	
Other unit cost		Health Insurance Review & Assessment Service [28]
Daily cost of nursing home/long-term care	7,136	
Cost of BMD measurement	35,604	
Cost of physician visit	8,411	
Cost of IV per injection	1,622	
Cost of a pharmacy visit	5,142	
Utility input		The 2014 Korea National Health and Nutrition Examination Survey
Utility of normal population (age)		
50	0.94	
55	0.93	
60	0.91	
65	0.88	
70	0.85	
75	0.79	
80	0.75	
85	0.82	
90	0.90	
Utility multipliers (fracture type/period)		Bae and Kwon [16]
First year after fracture		
Hip fracture 1st year	0.700	
Vertebral fracture 1st year	0.590	
Wrist fracture	0.956	
Other fracture	0.902	
Second and following years after fracture		
Hip fracture 2nd and following years	0.800	
Vertebral fracture 2nd and following years	0.929	

BMD, bone mineral density.

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Supplementary Table 3. Treatment efficacy inputs

Drug	Barrionuevo et al. [33][a]				Freemantle et al. [34][a]			
	Hip fracture	Vertebral fracture	Wrist fracture	Other fracture	Hip fracture	Vertebral fracture	Wrist fracture	Other fracture
Alendronate	0.61	0.57	0.84	0.84	0.63	0.57	0.82	0.83
Ibandronate (IV)	0.62	0.67	1.06	1.06	1	0.50	1	1.11
Ibandronate (oral)	0.62	0.67	1.06	1.06	1	0.50	1	1.11
Risedronate	0.73	0.61	0.78	0.78	0.75	0.62	0.67	0.80
Raloxifene	0.91	0.59	0.94	0.94	1	0.63	1	0.87
Zoledronate	0.60	0.38	0.79	0.79	0.58	0.30	0.76	0.75
Denosumab	0.56	0.32	0.80	0.80	0.60	0.32	0.84	0.81

[a]Network meta-analysis studies which provides comparative effective estimates for various antiosteoporosis drugs in reducing the risk of osteoporotic fractures.