

# Cost-effectiveness of antiosteoporosis strategies for postmenopausal women with osteoporosis in China

Na Li, MS,<sup>1,3</sup> Bin Zheng, PhD,<sup>1,3</sup> Maobai Liu, MS,<sup>1,3</sup> Haimei Zhou, MD,<sup>1</sup> Lingfen Zhao, MD,<sup>3</sup> Hongfu Cai, MS,<sup>1,3</sup> and Jingze Huang, MS<sup>2</sup>

## Abstract

**Objective:** Osteoporosis has become an important public health problem in China, especially among elderly postmenopausal women. Massive amounts of medical and health resources have been devoted to patients with osteoporosis and osteoporosis-related fractures. This study estimated the cost-effectiveness of alendronate, zoledronate, raloxifene, teriparatide, and calcium/vitamin D as treatments for osteoporosis in elderly postmenopausal women in China from the medical system perspective.

**Methods:** A Markov model was constructed by using TreeAge Pro 2015 software. This model simulated the disease process over 40 years in response to the five investigated therapeutic strategies. Each cycle lasted for 1 year. The model parameters included Chinese epidemiological data, clinical effectiveness, cost, and utility. Total treatment costs and quality-adjusted life-years (QALYs) were estimated, and incremental cost-effectiveness analysis was performed. Univariate and probabilistic sensitivity analyses were conducted to verify the model.

**Results:** The calcium/vitamin D strategy, zoledronate, alendronate, teriparatide, and raloxifene offered patients 10.24, 10.83, 10.70, 10.88, and 10.54 QALYs at the cost of \$3,799.72, \$8,425.61, \$9,849.89, \$34,843.72, and \$13,353.33 for over 40 years, respectively. The alendronate and raloxifene strategies were eliminated because they were less effective and more expensive than the other strategies. The base-case analysis revealed that the incremental cost-effectiveness ratios (ICERs) of the zoledronate strategy relative to those of the calcium/vitamin D strategy were \$7,864.59/QALY. This result indicated that the zoledronate strategy was more cost-effective than other strategies and was within the willingness-to-pay threshold of China (\$28,624/QALY). The ICERs of the teriparatide versus zoledronate strategies were \$4,70,797.08/QALY, which exceeded the threshold.

**Conclusion:** From the perspective of the Chinese medical system, zoledronate is more cost-effective than the calcium/vitamin D strategy, alendronate, raloxifene, and teriparatide for the treatment of osteoporosis in elderly postmenopausal women. Not factoring the parameters of adherence and persistence in, and consequent variability in treatment effectiveness relative risks, seems like a major limitation, but it can be speculated that it would not change the conclusion that zoledronate is the most economical strategy.

**Key Words:** Alendronate – Calcium/vitamin D – Cost-effectiveness analysis – Postmenopausal osteoporosis – Raloxifene – Teriparatide – Zoledronate.

Osteoporosis has become an important public health problem in China as the country's population continues to age. A previous epidemiological survey has shown that the prevalence rates of osteoporosis among Chinese men and women over 50 years of age are 20.7% and 14.4%, respectively. The prevalence of osteoporosis increases drastically among people over 60 years old, especially among

women.<sup>1</sup> Chinese women are more prone to osteoporotic fractures than other populations. Approximately two-fifths of Chinese women aged 50 years old will experience osteoporotic fractures in their remaining life, whereas the worldwide average for these injuries is one-third.<sup>2</sup> Osteoporotic fractures are harmful and are one of the main causes of disability and death among elderly patients. More than

Received January 6, 2019; revised and accepted March 7, 2019.

From the <sup>1</sup>Department of Pharmacy, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China; <sup>2</sup>Department of Endocrinology, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China; and <sup>3</sup>The School of Pharmacy, Fujian Medical University, Fuzhou, China.

Na Li and Bin Zheng contributed equally to this article.

Funding/support: This work was supported by National Natural Science Foundation of China (grant number 71804025), Science and Technology

Department of Fujian Province (grant number 2018R0041 and grant number 2017Y0035) of the People's Republic of China.

Financial disclosure/conflicts of interest: The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. Na Li, Bin Zheng, Mao-Bai Liu, Hai-Mei Zhou, Ling-Fen Zhao, Hong-Fu Cai, Jing-Ze Huang declare that they have no conflict of interest.

Address correspondence to: Jingze Huang, MS, Department of Endocrinology, Fujian Medical University Union Hospital, No. 29 Xinquan Road, Fuzhou 350001, Fujian Province, China. E-mail: fjhuangjingze@163.com

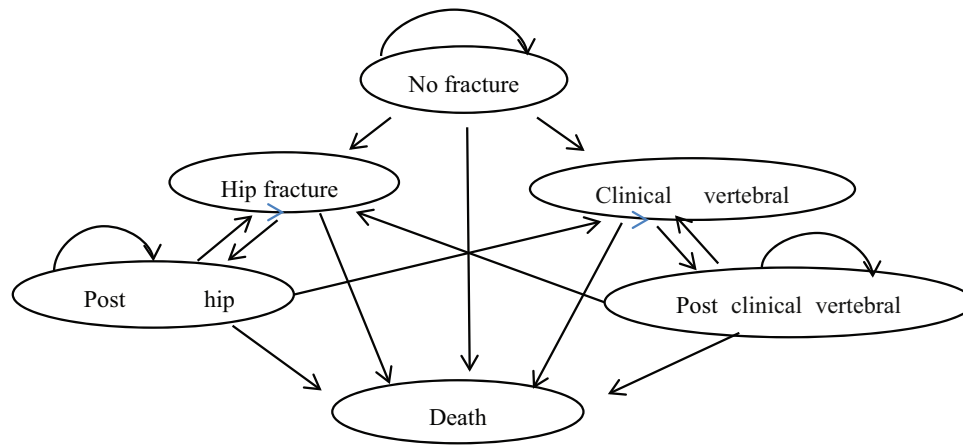


FIG. 1. Simplified structure and transitions of the Markov model.

20% of patients die within the first year after a hip fracture because of complications, and approximately 50% of patients become disabled; disability remarkably decreases the quality of life of these patients.<sup>3</sup> The medical treatment and care of osteoporosis and fractures impose a heavy familial and societal burden given their requirement for a considerable amount of manpower and material and financial resources. A forecast in 2015 showed that the medical expenses for major osteoporotic fractures (wrist, vertebral, and hip) in China will reach as high as \$19.92 billion and \$25.43 billion in 2035 and 2050, respectively.<sup>2</sup>

Effective drug therapy can help maintain the quality of life for people with osteoporosis by reducing the risk of osteoporosis-related fractures. Current approaches for the prevention and treatment of osteoporosis include the application of fundamental supplement for bone health and pharmacologic therapies. The fundamental supplement for bone health mainly comprises calcium and vitamin D. The pharmacologic therapies include antiresorptives and bone formation-stimulating regimens, such as diphosphonate, calcitonin, selective estrogen receptor modulators, estrogens, and parathyroid hormone analogs. Alendronate, zoledronate, raloxifene, and teriparatide reduce the risk of fragility fractures and are widely used in Chinese clinical practice.<sup>3</sup>

At present, the prevention of osteoporosis and osteoporosis-related fractures in China is expensive, given the high costs of antiosteoporosis drugs in the country. Given that China is a developing country with a large population and limited medical resources, Chinese policymakers must identify cost-effective drugs for the treatment of osteoporosis in elderly postmenopausal women. Therefore, in this study, we aimed to evaluate the cost-effectiveness of alendronate, zoledronate, raloxifene, teriparatide, and calcium/vitamin D in the treatment of osteoporosis in postmenopausal women in China.

## METHODS

### Model design

We revised a published Markov state-transition model<sup>4</sup> and conducted a cost-effectiveness analysis of five treatment

strategies for postmenopausal women with osteoporosis in China at different initial treatment ages (60, 65, 70, 75, 80, 85, 90, and greater than 90 years) from the medical system perspective (Fig. 1). Each cycle comprised 1 year, and the timeframe was 40 years. The model consisted of the following six health states: no fracture; hip fracture; posthip fracture; clinical vertebral fracture; postclinical vertebral fracture; and death. Our model only considered two states of fragility fractures (hip and clinical vertebral fractures) because of the lack of reliable epidemiological data on other osteoporotic fractures in the Chinese setting. The model initially assumed that patients were in a “no fracture” state that may persist for years or may enter other health states on the basis of transition probabilities. Patients who have experienced hip fractures (or clinical vertebral fractures) transition to a “hip fracture” (or “clinical vertebral fracture”) state for one cycle and then to the “posthip fracture” (or “postclinical vertebral fracture” state) or “death” state on the basis of transition probabilities. A patient may persist in the “posthip fracture” (or “postclinical vertebral fracture”) state, re-experience hip or clinical vertebral fracture, or die as a result of all-cause. Patients can experience only one fracture per cycle and can experience up to two hip fractures and an unlimited number of clinical vertebral fractures over the entirety of the study period. Quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratio (ICER) were the primary health outcomes used in this study. A discount rate of 3% was applied in cost and QALY calculation.<sup>5</sup> ICER was calculated as follows:

$$\text{ICER} = \frac{\text{cost}[\text{strategy A}] - \text{cost}[\text{strategy B}]}{\text{effectiveness}[\text{strategy A}] - \text{effectiveness}[\text{strategy B}]}$$

The cost-effectiveness threshold in this study was set as three times the per capita gross domestic product of China in 2017 (\$28,624) in accordance with WHO recommendations.<sup>6-8</sup>

TreeAge 2015 (TreeAge Software Inc., Williamstown, MA) was used to program and analyze the model.

## Patient population

The target population for this study was Chinese women over 60 years old without a history of fractures and whose bone mineral density (BMD) in the lumbar spine (L2-4) or femoral neck T value was less than or equal to  $-2.5$  standard deviations (DEXA method), which is indicative of the necessity of drug intervention.

## Treatments

Our model consisted of five strategies: fundamental supplement for bone health (daily oral administration of 600 mg of calcium and 125 IU vitamin D); once-weekly administration of 70 mg of alendronate; yearly intravenous administration of 5 mg of zoledronate; daily oral administration of raloxifene; and daily subcutaneous administration of 20  $\mu$ g of teriparatide for 2 years. The “drug holiday” theory states that drugs are continued to be released from bone for months or years after the termination of treatment. Thus, we assumed a 2-year drug holiday after 5 and 3 years of alendronate and zoledronate treatments, respectively, as suggested by the 2017 Chinese guideline and 2016 American Association of Clinical Endocrinologists guideline.<sup>3,9</sup> We also assumed that teriparatide was used for 2 years and stopped on the basis of medicine specifications.

We extracted data on the basis of the efficacy of these strategies from a recent network meta-analysis, including the risk of fracture after treatment in the target population.<sup>10</sup>

## Model parameters

### Transition probabilities

**Fracture rates.** In this study, fracture incidence was defined in reference to the epidemiological study of Bow et al,<sup>11</sup> who quantified the incidence of clinical vertebral and hip fractures among postmenopausal women of different ages. The incidence of fractures in postmenopausal osteoporosis patients would be calculated by multiplying the incidence in the general population of postmenopausal women by the relative risk of fractures in patients with osteoporosis in different age groups compared with the general population of postmenopausal women.<sup>4</sup> The BMD values of different body parts of the patients will drastically increase after drug intervention. Hence, the risk rate of fracture in different body parts of patients who have received treatment will be drastically lower than those of patients who have not taken any treatment.

A meta-analysis by Murad et al involved 116 randomized controlled trials. In this meta-analysis, the odds ratio (OR) of the relative risk of hip and vertebral fractures in different antiosteoporosis drug groups versus the placebo group was calculated.<sup>10</sup> We converted the OR value to the relative risk (RR) in reference to a study by Zhang and Yu<sup>12</sup> by using the formula  $RR = OR / ([1 - Po] + [Po \times OR])$ , where Po represents the incidence of outcome measures in the control group. Our calculation reveals that RR obtained through calculation is consistent with OR because Po is low. Therefore, OR is used as RR, which is included in the model for calculation.

The formula for the risks of fractures in the model is as follows: (fracture risk of different age groups in the general population)  $\times$  (relative risk of fracture in patients with osteoporosis)  $\times$  (relative risk of fracture after drug intervention). In addition, the relative risks of refracture associated with the same location of the previous fracture increased.<sup>13</sup> Hence, the probability of second or subsequent fractures in the same location is multiplied by the relative risk of refracture in the same site<sup>14</sup> (Table 1).

**Mortality rates.** In accordance with an epidemiological study involving the long-term follow-up surveys of 155,466 postmenopausal women in Taiwan reported by Chang et al,<sup>15</sup> we collected data on the mortality rates associated with fractures in different parts of the body at different ages. These fracture types included no fracture, hip fracture, vertebral fracture, and late hip fracture (Table 1).

## Utilities

The current analysis considered the health outcomes on the basis of preferences. Life-year was adjusted to the health-related quality-of-life year by utility value. Utility values can range from 0 (death) to 1 (perfect health). QALYs can be calculated by multiplying life-year with utility value.

The health-related quality of life of women with osteoporosis, but without fracture history, is almost identical to that of the general population.<sup>16</sup> Hence, the health utility value of the “no fracture” state in this model used the health utility value of different age groups in the general population as calculated by Sun et al<sup>17</sup> by using the EuroQol five-dimensions questionnaire. Fractures reduce the health utility value of patients. We extracted the disutility value of the hip and clinical vertebral fractures of Asian populations from the study of Mori et al.<sup>4</sup> The disutilities of “hip fractures” and “clinical vertebral fractures” states were highest in the first year of fracture and reduced in the “postfracture” state, which lasts for the rest of the patient’s life (Table 1).

## Cost

This research was conducted from the perspective of the Chinese health system. The costs involved mainly include the cost of medicine for the five treatment options, the cost of treatment for fractures at different locations, the monitoring fees for related drug treatments, BMD monitoring expenses, and zoledronate injection cost (Table 1). We searched the provincial bid price of all drugs in 2018 through Yaozh (https://yaozh.com/), which is a big-data service platform for China’s medical industry. We considered the median value as the reference prices of the drugs and calculated the annual drug cost of each strategy.

The cost of fractures in different body parts includes direct and indirect medical costs. Data were extracted from recent research on fracture burden in China.<sup>18</sup> Rehabilitation costs, auxiliary medical device costs, and hospital review fees accrued after discharge from a hospital with hip fractures are also generated each year.<sup>19</sup>

TABLE 1. Model parameters

	Value	Range	Distribution	Reference
Teriparatide				
Relative risk of hip fracture	0.42	0.10-1.82	Beta	10
Relative risk of vertebral fracture	0.30	0.16-0.55	Beta	10
Raloxifene				
Relative risk of hip fracture	0.87	0.63-1.22	Beta	10
Relative risk of vertebral fracture	0.57	0.39-0.83	Beta	10
Zoledronate				
Relative risk of hip fracture	0.50	0.34-0.73	Beta	10
Relative risk of vertebral fracture	0.35	0.20-0.64	Beta	10
Alendronate				
Relative risk of hip fracture	0.45	0.27-0.68	Beta	10
Relative risk of vertebral fracture	0.50	0.33-0.79	Beta	10
Vitamin D + calcium				
Relative risk of hip fracture	0.81	0.68-0.96	Beta	10
Relative risk of vertebral fracture	0.99	0.74-1.41	Beta	10
Incidence rate of fracture for individuals without intervention				
Hip fracture, age 60-64 years	0.00057	0.0005415-0.0005985	Beta	11
Hip fracture, age 65-69 y	0.00103	0.001235-0.001365	Beta	11
Hip fracture, age 70-74 y	0.00273	0.0025935-0.0028665	Beta	11
Hip fracture, age 75-79 y	0.00527	0.0050065-0.0055335	Beta	11
Hip fracture, age 80-84 y	0.01059	0.0100605-0.0111195	Beta	11
Hip fracture, age 85-89 y	0.01377	0.0130815-0.0144585	Beta	11
Hip fracture, age 90-94 y	0.01377	0.0130815-0.0144585	Beta	11
Vertebral fracture, age 60-64 y	0.00516	0.004902-0.005418	Beta	11
Vertebral fracture, age 65-69 y	0.00564	0.005358-0.005922	Beta	11
Vertebral fracture, age 70-74 y	0.00874	0.008303-0.009177	Beta	11
Vertebral fracture, age 75-79 y	0.01205	0.0114475-0.0126525	Beta	11
Vertebral fracture, age 80-84 y	0.02119	0.0201305-0.0222495	Beta	11
Vertebral fracture, age 85-89 y	0.02689	0.0255455-0.0282345	Beta	11
Vertebral fracture, age 90-94 y	0.02689	0.0255455-0.0282345	Beta	11
Relative risk of fractures for individuals with osteoporosis				
Hip fracture, age 65-69 y	2.39	2.16-2.60	Gamma	4
Hip fracture, age 70-74 y	1.89	1.79-1.99	Gamma	4
Hip fracture, age 75-79 y	1.57	1.52-1.62	Gamma	4
Hip fracture, age 80-84 y	1.35	1.32-1.38	Gamma	4
Hip fracture, age 85+ y	1.25	1.22-1.27	Gamma	4
Vertebral fracture, age 65-69 y	2.47	2.10-2.86	Gamma	4
Vertebral fracture, age 70-79 y	2.09	1.84-2.34	Gamma	4
Vertebral fracture, age 80+ y	1.86	1.68-2.04	Gamma	4
Relative risks of subsequent fractures associated with prior fractures at the same location				
Hip fracture	2.3	1.5-3.7	Gamma	14
Clinical vertebral fracture	4.4	3.6-5.4	Gamma	14
The mortality rate of different health status changes with age				
Hip fracture, age 60-69 y	0.062	0.0496-0.0744	Beta	15
Hip fracture, age 70-79 y	0.108	0.086-0.13	Beta	15
Hip fracture, age 80-89 y	0.167	0.134-0.20	Beta	15
Hip fracture, age ≥90 y	0.279	0.223-0.335	Beta	15
Vertebral fracture, age 60-69 y	0.020	0.016-0.024	Beta	15
Vertebral fracture, age 70-79 y	0.044	0.0352-0.0528	Beta	15
Vertebral fracture, age 80-89 y	0.086	0.069-0.103	Beta	15
Vertebral fracture, age ≥90 y	0.185	0.148-0.222	Beta	15
No fracture, age 60-69 y	0.010	0.008-0.012	Beta	15
No fracture, age 70-79 y	0.033	0.0264-0.0396	Beta	15
No fracture, age 80-89 y	0.086	0.0688-0.103	Beta	15
No fracture, age ≥90 y	0.155	0.124-0.186	Beta	15
Post hip fracture, age 60-69 y	0.040	0.032-0.048	Beta	15
Post hip fracture, age 70-79 y	0.081	0.0648-0.0972	Beta	15
Post hip fracture, age 80-89 y	0.136	0.109-0.163	Beta	15
Post hip fracture, age ≥90 y	0.235	0.188-0.282	Beta	15
Post vertebral fracture, age 60-69 y	0.019	0.0152-0.228	Beta	15
Postvertebral fracture, age 70-79 y	0.042	0.336-0.0504	Beta	15
Postvertebral fracture, age 80-89 y	0.086	0.0688-0.103	Beta	15
Postvertebral fracture, age ≥90 y	0.178	0.142-0.214	Beta	15
Cost (in 2018 US dollars)				
Teriparatide at a dose of 20 µg/d subcutaneously, annual cost	11220.23	10212.99-12913.31	Beta	Yaozh
Oral daily Raloxifene, annual cost	611.5823	580.741-680.247	Beta	Yaozh
Zoledronate at a dose of 5 mg/y intravenously, annual cost	525.80629	407.78-593.86	Beta	Yaozh
Oral daily Risedronate, annual cost	250.7971	186.21-330.5221	Beta	Yaozh
Oral weekly alendronate, annual cost	545.328	447.58-501.99	Beta	Yaozh

(Continued on next page)

TABLE 1 (Continued)

	Value	Range	Distribution	Reference
Oral calcium + vitamin D, annual cost	55.6301	48.88-101.193	Gamma	Yaozh 18
Hip fracture, hospitalization costs	5263.14	4999.52-5526.76	Gamma	18
Vertebral fracture, hospitalization costs	3705.56	3520.28-3890.84	Gamma	19
Posthospital discharge of hip fracture	1296.78	674.26-2453.56	Triangular	20
Dual-energy x-ray absorptiometry	28.7876	N/A	N/A	20
Renal function test	8.1565	N/A	N/A	20
Biochemical tests	28.7876	N/A	N/A	20
Examinations of bone metabolism	19.1917	N/A	N/A	20
Electrolytes test	4.158	N/A	N/A	20
Zoledronate injection cost	1.28	N/A	N/A	20
Utility				
Age 60-64 y	0.728	0.582-0.874	Triangular	17
Age 65-69 y	0.702	0.562-0.842	Triangular	17
Age 70-74 y	0.685	0.548-0.822	Triangular	17
Age 75-79 y	0.669	0.535-0.803	Triangular	17
Age 80-84 y	0.655	0.524-0.786	Triangular	17
Age 85+ y	0.643	0.514-0.772	Triangular	17
Disutilities				
Hip fracture, first year	0.776	0.720-0.844	Beta	4
Hip fracture, beyond first year	0.855	0.800-0.909	Beta	4
Vertebral fracture, first year	0.724	0.667-0.779	Beta	4
Vertebral fracture, beyond first year	0.868	0.827-0.922	Beta	4

N/A, not applicable.

According to the drug instructions and the Guidelines for the Diagnosis and Treatment of Primary Osteoporosis (2017 version),<sup>3</sup> the patient's creatinine clearance rate should be monitored when using alendronate for the first time. Serum calcium, phosphorus, magnesium, and creatinine levels, and renal function before each dose should be monitored when using zoledronate for the first time. Creatinine clearance and blood calcium levels during treatment should be monitored when using teriparatide for the first time. In China, bone mineral density (BMD) is measured annually during antio-osteoporosis treatment. The costs of tests were obtained from the Fujian Provincial Price Bureau.<sup>20</sup> The costs were converted into US dollars (CYN 6.2527 = US \$12,018).

### Sensitivity analyses

We performed univariate and probability sensitivity analyses. We used a wide range of drug costs, hospitalization costs, and utility, and varied the transition probability of each health state within 95% CIs. We performed second-order Monte Carlo probabilistic sensitivity analysis to estimate the total influence of the uncertainty of model parameters on the model. We used beta, gamma, and triangular and beta distribution to analyze probability, relative risk and cost, and utility parameters.

## RESULTS

### Base case analyses

Rollback analysis was conducted. Alendronate and raloxifene strategies were eliminated because they had lower utility and were more expensive than the other strategies. The zoledronate and calcium/vitamin D strategies were subjected to incremental cost-effectiveness analysis. The zoledronate strategy had an ICER of \$7864.59/QALY. Thus, this strategy was more cost-effective relative to thresholds applied in

China (\$28,624/QALY). Then, incremental cost-effectiveness analysis was conducted on teriparatide and zoledronate strategies. The teriparatide strategy yielded an ICER of \$470797.08/QALY. In contrast to that of the zoledronate strategy, the ICER of teriparatide strategy exceeded the threshold. Thus, this strategy was not cost-effective and was eliminated.

### Sensitivity analyses

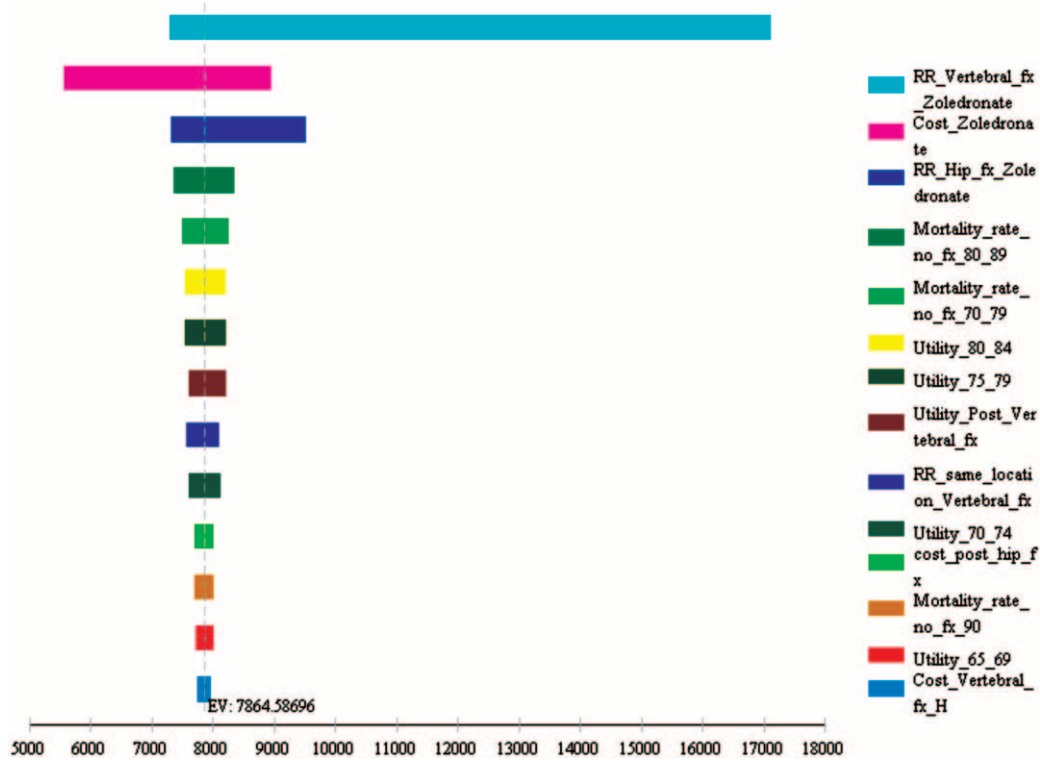
Sensitivity analyses show that the results were robust. The most sensitive parameter in the model was the relative risk of vertebral fracture of zoledronate (Fig. 2). Model parameters were simulated by Monte Carlo 1,000 times in accordance with the distributions and value ranges shown in Table 2.

The scatter plot comparing the zoledronate and calcium/vitamin D strategies shows that most of the scatter localized below the dotted diagonal line, indicating that zoledronate had a high probability of being economical (Fig. 3A). The scatter plot for the comparison of the teriparatide and zoledronate strategies shows that most of the scatter localized above the dotted diagonal line. This pattern indicates that teriparatide strategy had a very low probability of being economical within the acceptable threshold (Fig. 3B). The cost-effectiveness acceptability curves show that zoledronate had 95% probability of being cost-effective at a willingness-to-pay threshold of \$28,624/QALY (Fig. 4).

### Threshold analysis

Threshold analysis was performed by adjusting the range of teriparatide price. Teriparatide obtained an ICER of \$28571.87/QALY, which is less than the threshold and demonstrates cost-effectiveness when the annual drug cost is \$2620 (ie, the unit price of teriparatide is reduced from \$935/2.4 to \$218/2.4 mL).

**Tornado Analysis (ICER)**



**FIG. 2.** One-way sensitivity analysis. RR\_Vertebral\_fx\_Zoledronate, relative risk of vertebral fracture of zoledronate; Cost\_Zoledronate, annual cost of zoledronate at a dose of 5 mg/year intravenously; RR\_Hip\_fx\_Zoledronate, relative risk of hip fracture of zoledronate; Mortality\_rate\_no\_fx\_80\_89, mortality rate of “no fracture” status in 80 to 89-year-olds; Mortality\_rate\_no\_fx\_70\_79, mortality rate of “no fracture” status in 70 to 79-year-olds; Utility\_80\_84, health utility value of the “no fracture” status in 80 to 84-year-olds; Utility\_75\_79, health utility value of the “no fracture” status in 75 to 79-year-olds; Utility\_Post\_Vertebral\_fx, health utility value of the “Vertebral fracture, beyond first year” status; RR\_same\_location\_Vertebral\_fx, relative risks of subsequent fractures associated with prior fractures at the same vertebral location; Utility\_70\_74, health utility value of the “no fracture” status in 70-74 years old; Cost\_post\_hip\_fx, post hospital discharge of hip fracture; Mortality\_rate\_no\_fx\_90, mortality rate of “no fracture” status in more than 90 years old; Utility\_65\_69, health utility value of the “no fracture” status in 65 to 69-year-olds; Cost\_Vertebral\_fx\_H, hospitalization costs of vertebral fracture.

**DISCUSSION**

We evaluated the cost-effectiveness of five different strategies for the treatment of osteoporosis in postmenopausal Chinese women. We identified the zoledronate strategy as the superior strategy on the basis of ICER. The base case analysis revealed that compared with the ICER of the calcium/vitamin D strategy, that of the zoledronate strategy was \$7864.59/QALY. This result indicates that the zoledronate strategy was cost-effective on the basis of the thresholds applied in China (\$28,624/QALY). Although the teriparatide strategy had better therapeutic effect and offered better quality-of-life advantages than the zoledronate strategy, its ICER remarkably

exceeded the threshold. The teriparatide strategy would be cost-effective only if its price was reduced by 76.7% (from \$935/2.4 to \$218/2.4 mL). Teriparatide was recommended for the prevention of fractures in people with previous fractures or at especially high risk of fractures in the 2016 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines, given its better efficacy than other strategies.<sup>9</sup> Therefore, teriparatide may be a cost-effective antiosteoporosis strategy for people with a history of fractures or at especially high risk of fractures. However, no head-to-head study is available on the efficacy of teriparatide and other strategies in high-risk populations. Model

**TABLE 2.** Base case results

Strategy	Cost (\$)	QALYs	ICER (vs calcium/vitamin D)	ICER (vs zoledronate)
Calcium/vitamin D	3799.72	10.24	—	—
Zoledronate	8425.61	10.83	7864.59	—
Alendronate	9849.89	10.70	13235.40	Dominated
Teriparatide	34843.72	10.88	48181.76	470797.08
Raloxifene	13353.33	10.54	32238.67	Dominated

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

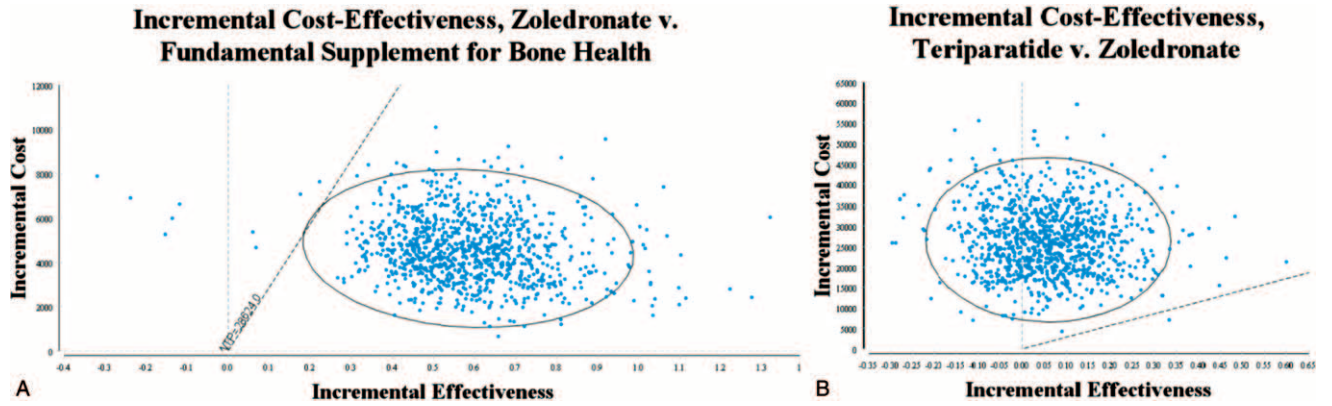


FIG. 3. Probabilistic sensitivity analyses for zoledronate first versus foundation treatment (A) and teriparatide first versus zoledronate (B).

parameters and results will need to be updated when relevant data become available.

This study applied epidemiological data, costs, and utility values for the Chinese population. Hence, the results of the study could be applicable to postmenopausal women with osteoporosis in China. We applied the time-dependent Markov model in this study. Our model is consistent with reality and could be applied to simulate the long-term outcome of a patient’s mortality from osteoporosis because the fracture risk

rate, relative risk rate, and utility value of patients with osteoporosis change with age in the model.

Our study focuses on the most cost-effective medication plan for menopausal women who are older than or equal to 60 years and suffering from osteoporosis. The study population includes patients who suffer from osteoporosis but have never had a fracture. The study population in clinical trials included in the meta-analysis used in our study comprises patients who have osteoporosis, but have never had a fracture.

### CE Acceptability Curve

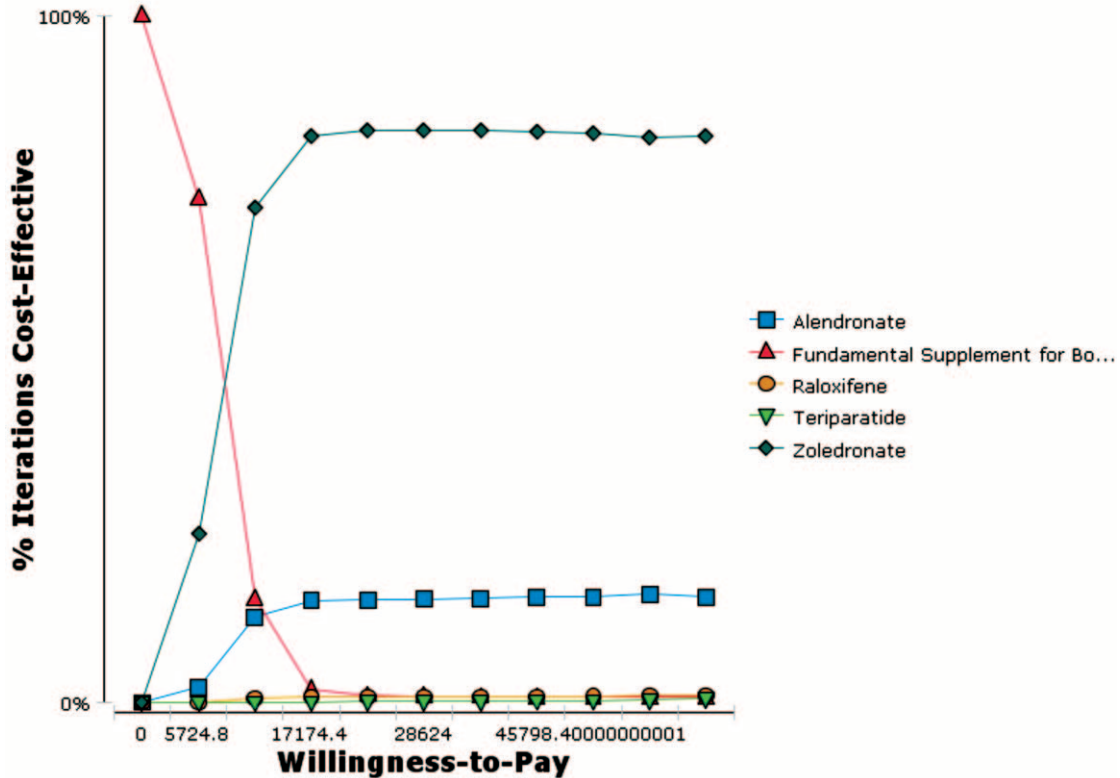


FIG. 4. Cost-effectiveness acceptability curves shows the probability of being cost-effective for competing strategies at different willingness-to-pay for quality-adjusted life-years (QALYs).

If the initial treatment is administered when patients are 70 or 80 years old, fracture events may occur in 10 or 20 years without treatment. Afterwards, antiosteoporosis therapy is performed. Its effect cannot be compared with that of patients without fracture events at the same baseline. Therefore, 60 years is selected as the age of initial treatment without a cross-sectional comparison of the ages of different initial treatments.

Our data and study design have several limitations. First, given that no head-to-head study on the five strategies for the treatment of osteoporosis in elderly postmenopausal women is available, the data on the effectiveness of the treatments used in this study were obtained from a recent network meta-analysis, which involved an indirect comparison of five competing strategies and placebos in reducing the incidence of fragility fractures in a population of patients with osteoporosis. The instructions on the use of teriparatide and raloxifene suggest that their effects on reducing the risk of hip fracture have not been confirmed. The network meta-analysis did not find statistically significant reductions in odds of hip fracture among women using teriparatide or raloxifene (teriparatide OR 0.42 [0.10; 1.82] and raloxifene OR 0.87 [0.63; 1.22]). Therefore, we conduct uncertainty analyses, which showed that the result of cost-effectiveness analysis is robust, and the overall result does not change because of the wide variation in this parameter. Second, our results may only apply to postmenopausal women in China and may not be applicable to women in other countries or to men. All cost parameters were set for China, which may be different from other countries. Meanwhile, the parameters “relative risks of subsequent fractures associated with prior fractures at the same location” and “relative risk of fractures for individuals with osteoporosis,” were obtained from foreign data given the absence of data relevant to the Chinese population. Third, our decision-analytic model was a simplification of the actual disease outcome. Therapeutic strategies and clinical practice were based on Chinese guidelines and the recommendations of a clinical expert on metabolism. Our model did not reflect individual treatment decisions. Apart from this, because no relevant data about the Chinese population are available, only hip fracture and clinical vertebral fracture are set up, and no other osteoporotic fracture states, such as humerus and distal forearm fractures, are present. The effects of these states on treatment costs and quality of life are also disregarded. Fourth, only branded drugs were evaluated in this study because, in contrast to that of branded drugs, the quality of the Chinese generics of zoledronate, alendronate, teriparatide, and raloxifene cannot be determined. Finally, the persistence and adherence of patients to osteoporosis treatment affect the treatment and the risk of fracture.<sup>21-23</sup> Medication persistence and adherence parameters have been used in other studies. For example, Mori et al<sup>4</sup> performed univariate sensitivity analysis and showed that the results were sensitive to the RR value of nonpersistence of denosumab relative to alendronate. However, variations in the effect on ICER do not exceed the willingness of patients to pay for their treatment, that is, the

conclusion remains unchanged. Mori et al<sup>24</sup> also considered the influence of medication persistence and adherence on the result. The univariate sensitivity analysis shows that the result is not sensitive to persistence and adherence parameters. The adherence and persistence were not considered in this study, and we assumed that patients would continue to receive standardized treatment as prescribed. The zoledronate strategy involves an intravenous infusion once a year and has a low frequency of administration and slightly adverse reactions. Thus, patient compliance for the zoledronate strategy is superior to that for the other four regimens.<sup>25,26</sup> Hence, it can be speculated that the parameters of adherence and persistence would not change the conclusion that zoledronate is the most economical strategy.

## CONCLUSION

From the perspective of the Chinese medical system, zoledronate is more cost effective than the calcium/vitamin D strategy, alendronate, raloxifene, and teriparatide for the treatment of osteoporosis in elderly postmenopausal women.

## REFERENCES

1. Editorial board of white paper on osteoporosis on China Health Promotion Foundation. Chinese white paper on osteoporosis. *Chin J Health Manage* 2009;3:148-154.
2. Si L, Winzenberg TM, Chen M, et al. Residual lifetime and 10 year absolute risks of osteoporotic fractures in Chinese men and women. *Curr Med Res Opin* 2015;31:1149-1156.
3. The Chinese Medical Association of Osteoporosis, Bone Mineral Disease. Guidelines for the diagnosis and treatment of primary osteoporosis (2017). *Chin J Pract Intern Med* 2018;38:127-150.
4. Mori T, Crandall CJ, Ganz DA. Cost-effectiveness of denosumab versus oral alendronate for elderly osteoporotic women in Japan. *Osteoporos Int* 2017;28:1733-1744.
5. Guo-en Liu. *China guidelines for Pharmacoeconomic Evaluations and Manual (2015 edition)*. Beijing: Science Press Co Ltd; 2015.
6. List of Chinese Administrative Divisions by GDP Per Capita. Available at: [http://en.wikipedia.org/wiki/List\\_of\\_Chinese\\_administrative\\_divisions\\_by\\_GDP\\_per\\_capita](http://en.wikipedia.org/wiki/List_of_Chinese_administrative_divisions_by_GDP_per_capita). Accessed May 20, 2018.
7. Eichler HG, Kong SX, Gerth WC, et al. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge. *Value Health* 2004;7:518-528.
8. Murray CJ, Evans DB, Acharya A, et al. Development of WHO guidelines on generalized cost-effectiveness analysis. *Health Econ* 2000;9:235-251.
9. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis: 2016. *Endocr Pract* 2016;22:1-42.
10. Murad MH, Drake MT, Mullan RJ, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab* 2012;97:1871-1880.
11. Bow CH, Cheung E, Cheung CL, et al. Ethnic difference of clinical vertebral fracture risk. *Osteoporos Int* 2012;23:879-885.
12. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 1998;280:1690-1691.
13. Kanis JA, Brazier JE, Stevenson M, et al. Treatment of established osteoporosis: a systematic review and cost-utility analysis. *Health Technol Assess* 2002;6:1-146.
14. Klotzbuecher CM, Ross PD, Landsman PB, et al. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res* 2000;15:721-739.
15. Chang CY, Tang CH, Chen KC, et al. The mortality and direct medical costs of osteoporotic fractures among postmenopausal women in Taiwan. *Osteoporos Int* 2016;27:665-676.

16. Si L, Winzenberg TM, de Graaff B, Palmer AJ. A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. *Osteoporos Int* 2014;25:1987-1997.
17. Sun S, Chen J, Johannesson M, et al. Population health status in China: EQ-5D results, by age, sex and socio-economic status, from the National Health Services Survey 2008. *Qual Life Res* 2011;20:309-320.
18. Qu B, Ma Y, Yan M, et al. The economic burden of fracture patients with osteoporosis in western China. *Osteoporos Int* 2014;25:1853-1860.
19. Luo LZ, Xu L. Study on direct economic-burden and its risk factors of osteoporotic hip fracture. *Chin J Epidemiol* 2005;26:669-672.
20. Fujian Provincial Price Bureau. Available at: <http://wjf.fujian.gov.cn/>. Accessed May 20, 2018.
21. Cotte FE, Mercier F, de Pouvourville G. Relationship between compliance and persistence with osteoporosis medications and fracture risk in primary health care in France: a retrospective case-control analysis. *Clin Ther* 2008;30:2410-2422.
22. Rabenda V, Reginster JY. Overcoming problems with adherence to osteoporosis medication. *Expert Rev Pharmacoecon Outcomes Res* 2010;10:677-689.
23. Rabenda V, Mertens R, Fabri V, et al. Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. *Osteoporos Int* 2008;19:811-818.
24. Mori T, Crandall CJ, Ganz DA. Cost-effectiveness of combined oral bisphosphonate therapy and falls prevention exercise for fracture prevention in the USA. *Osteoporos Int* 2017;28:585-595.
25. McClung M, Recker R, Miller P, et al. Intravenous zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. *Bone* 2007;41:122-128.
26. Durden E, Pinto L, Lopez-Gonzalez L, et al. Two-year persistence and compliance with osteoporosis therapies among postmenopausal women in a commercially insured population in the United States. *Arch Osteoporos* 2017;12:22-30.