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Cost-utility analysis of drugs for secondary bone fracture prevention among post-menopausal osteoporotic patients in Thailand

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ABSTRACT

This study assessed the cost utility of medications used to prevent recurrent bone fractures among post-menopausal osteoporotic Thai women with a history of fractures. Economic evaluation was conducted using the Markov model-based cost-utility analysis approach under the societal perspective. Women age 50 and over with bone mass density T-score of less than or equal to 2.5 standard deviations and a history of fractures were included in the model, with a 1-year cycle length, until deceased. The model compared the expected costs and outcomes of calcium plus vitamin D alone (standard regimen) with those of calcium plus vitamin D with adjunct bisphosphonates (alendronate or risedronate), raloxifene, strontium, denosumab, or teriparatide. Bisphosphonates provided added health benefits whereas the other drugs did not. The incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained were approximately 92,995 Baht (US$2,997) for bisphosphonates and 1,701,932 Baht (US$54,848) for denosumab. Teriparatide was the most expensive with an ICER of 10,354,673 Baht (US$333,699) per QALY gained. The cost of drugs was the major expense. In conclusion, bisphosphonates are the most cost-effective adjunct interventions for post-menopausal osteoporotic women with a history of fractures treated under the Thai healthcare system.

Keywords: bone fracture; economic evaluation; osteoporosis; post-menopause; secondary prevention

1. INTRODUCTION

Osteoporosis is characterized by a reduction in the density and quality of bone, which greatly increases the risk of fractures. The incidence of osteoporotic fractures increases with age because of a progressive decrease in bone formation and an increase in bone resorption. This bone resorption is further exacerbated in post-menopausal women because estrogen is a vital factor for maintaining bone health. Bone mass density (BMD) is the cardinal indicator for bone condition evaluation, and a significant BMD reduction is a major risk factor for bone fracture (World Health Organization, 2015). Falls are the predominant cause of such fractures in osteoporotic patients. For instance, approximately 90% of hip fractures in osteoporotic patients are due to falls, whereas the rest occur during normal daily activities (Cummings and Melton, 2002). Fractures can occur at the same location or at any location

with decreased BMD (Looker et al., 1997). There are three risk categories based on the incidence of hip fractures in women as follows: high (>300 events per 100,000 population), moderate (200-300/100,000), and low (<200/100,000). Most osteoporotic women in Europe are in the high-risk category, whereas most women in North America and Asia are in the moderate-risk category (Kanis et al., 2012). The Asian Osteoporosis Study (AOS) reported an incidence of hip fractures of 289 per 100,000 population among Thai women, which is at the high end of the moderate-risk category (Lau et al., 2001). Moreover, the 1-month mortality rate is approximately 10% among post-hip fracture patients in Thailand (Chariyalertsak et al., 2001; Kanis et al., 2012), and patients with fracture history are at a greater risk of recurrent fractures (relative risk: 1.92-3.88 compared with fracture-naïve patients) (Kanis et al., 2004; Lawrence et al., 2010). Therefore, post-menopausal women with fracture history are the primary target of interventions designed to reduce the risk of hip fractures in Thailand.

The goal of osteoporosis treatment is to prevent any fracture, particularly secondary hip fractures. Standard guidelines for preventing subsequent fractures among post-menopausal women with osteoporosis and fracture history recommend bisphosphonate drugs, such as alendronate, risedronate, and etidronate, in addition to calcium and vitamin D as first-line treatment. Other drugs, including strontium ranelate, raloxifene, teriparatide, and denosumab are indicated for more complex and severe fractures considering patient age, BMD value and additional risk factors (National Institute for Health and Care Excellence, 2014; Thai Osteoporosis Foundation, 2000).

Bone fracture care is expensive because of direct drug expenses and productivity losses as well as informal care costs, particularly when a home caregiver is needed. One Thai study reported that 22% of post-hip fracture patients were unable to walk, whereas 23% needed a wheelchair and relied on caregivers for daily activities (Chariyalertsak et al., 2001). A previous analysis has reported a total yearly cost of approximately 120,000 Baht (US$3,500), with approximately 50% accounting for direct medical costs (Woratanarat et al., 2005).

Two previous studies evaluated the costs and benefits of preventive drugs for bone fractures in Thailand. The first study did not find any drug whose value was cost-effective, and the lowest ICER was for alendronate at 6,100,000 Baht (US$169,000) per QALY gained (Chaiyasong et al., 2013). However, the study was performed taking a healthcare provider perspective which included only direct costs. The second study (Kingkeaw et al., 2013) also found that alendronate had the lowest ICER of 336,000 Baht (US$9,333) per QALY gained for patients aged 50 years. The study recommended a price reduction for alendronate to meet the threshold; however, side effects of therapeutic drugs were not considered. Alternatively, a study from the UK indicated that alendronate is likely to be a cost-effective intervention against the threshold of 20,000 pounds per QALY gained (Kanis et al., 2008). Policy makers should be informed of all costs and health outcomes. At present, bisphosphonate has seen a reduction in cost, and alternative drugs for bone fracture prevention have been launched in Thailand (Thai Osteoporosis Foundation, 2000). Therefore, an economic evaluation considering all treatment costs and drug side effects among post-menopausal Thai osteoporotic women is warranted to make informed decisions on the inclusion of drugs for bone fracture prevention in the National List of Essential Medicine (NLEM), which includes drugs reimbursable by third-party payers under Thailand's health system. This study aimed to evaluate the cost-utility of preventive drugs among post-menopausal Thai women with osteoporosis and bone fracture history using a Markov model.

2. MATERIALS AND METHODS

2.1 Overall description

A model-based cost-utility analysis (CUA) was undertaken to estimate costs and health outcomes of bone fracture preventive drugs compared with those of a standard comparator (Table 1) using a lifetime horizon with a 1-year cycle length. The target population was patients aged 50 years with BMD T-score of <2.5 standard deviations (SD). In addition, the cohort population aged 50-90 years was entered to the model based on age and BMD T-score. A discount rate of 3% per year was used for costs and health outcomes. Results are presented as ICER values in Thai currency (Baht) per QALY gained. A societal perspective was adopted based on Thailand's Heath Technology Assessment (HTA) guidelines (Teerawattananon and Chaikledkaew, 2008). Based on the National Institute for Health and Care Excellence (NICE) guidelines (National Institute for Health and Care Excellence, 2014) and Thai clinical practice guidelines for osteoporosis (Thai Osteoporosis Foundation, 2000), bisphosphonates, strontium ranelate, raloxifene, teriparatide, and denosumab were added to calcium plus vitamin D as study interventions and compared to calcium plus vitamin D alone.

A Markov model with 16 health states was constructed based on the natural history of bone fracture in osteoporosis and prior studies (Kingkeaw et al., 2013) to compare the costs and benefits of calcium plus vitamin D alone (the comparator) with the addition of preventive drugs (bisphosphonates, raloxifene, strontium ranelate, denosumab, and teriparatide) (Figure 1). The model flow was validated and approved by experts and stakeholders during a consultation meeting according to HTA guidelines. Female osteoporotic patients with a history of fractures were entered into the model in one of the following three health states: post-hip, post-vertebral, or post-wrist fracture. In each of the 1-year follow-up cycles, the patient stays in the same health state or moves to another based on transitional probabilities until all modeled patients are deceased. Health states of first hip fracture, first vertebral fracture, or first wrist fracture mean that the patient has a fracture at hip, vertebrae or wrist at the first time after entering to the model. The assumptions used include 1) hip and wrist fractures which are limited to two, with no lifetime limit on spinal fractures, 2) bisphosphonate maintains its preventive efficacy for 5 years after stopping drug administration (Black et al., 2006; Fraser, 2011), whereas the other drugs have no therapeutic effect immediately after termination, 3) when a drug side effect happens, that drug will be discontinued, 4) there is no more than one side effect per patient, and 5) side effects have no role in mortality.

Table 1. Input parameters used in the model (Baht, annual costs: 2019)

Parameters	Point estimate	Range	Distribution	Source
Epidemiological data				
Probability of hip fracture from age 50 years onward				
BMD = -2.5	0.009	0.002-0.017	beta	(Strom et al., 2010)
BMD = -3	0.013	0.005-0.026	beta	(Strom et al., 2010)
BMD = -3.5	0.020	0.009-0.038	beta	(Strom et al., 2010)
BMD = -4	0.031	0.018-0.056	beta	(Strom et al., 2010)
Probability of vertebral fracture from age 50 years onward				
BMD = -2.5	0.051	0.024-0.070	beta	(Jitapunkul et al., 2008; Strom et al., 2010)
BMD = -3	0.053	0.025-0.075	beta	(Jitapunkul et al., 2008; Strom et al., 2010)
BMD = -3.5	0.057	0.027-0.081	beta	(Jitapunkul et al., 2008; Strom et al., 2010)
BMD = -4	0.062	0.030-0.088	beta	(Jitapunkul et al., 2008; Strom et al., 2010)
Probability of wrist fracture from age 50 years onward	0.003	0.002-0.004	beta	(Hagino et al., 1999)
Effectiveness of drug in prevention of hip osteoporotic fracture				
Risk ratio of raloxifene	1.00	-	log normal	(Kingkeaw et al., 2013)
Risk ratio of bisphosphonates	0.70	0.56-0.87	log normal	(Kingkeaw et al., 2013)
Risk ratio of strontium ranelate	0.89	0.67-1.18	log normal	(Kingkeaw et al., 2013)
Risk ratio of denosumab	0.84	0.65-1.09	log normal	(McClung et al., 2012)
Risk ratio of teriparatide	0.50	0.09-2.75	log normal	(Kingkeaw et al., 2013)
Effectiveness of drug in prevention of vertebral osteoporotic fracture				
Risk ratio of raloxifene	0.78	0.44-1.38	log normal	(Kingkeaw et al., 2013)
Risk ratio of bisphosphonates	0.57	0.49-0.68	log normal	(Kingkeaw et al., 2013)
Risk ratio of strontium ranelate	0.73	0.63-0.85	log normal	(Kingkeaw et al., 2013)
Risk ratio of denosumab	0.38	0.26-0.54	log normal	(McClung et al., 2012)
Risk ratio of teriparatide	0.31	0.19-0.52	log normal	(Kingkeaw et al., 2013)
Effectiveness of drug in prevention of wrist osteoporotic fracture				
Risk ratio of Raloxifene	1	-	log normal	(Kingkeaw et al., 2013)
Risk ratio of bisphosphonates	0.61	0.45-0.83	log normal	(Kingkeaw et al., 2013)
Risk ratio of strontium ranelate	0.98	0.73-1.31	log normal	(Kingkeaw et al., 2013)
Risk ratio of denosumab	0.84	0.65-1.09	log normal	(McClung et al., 2012)
Risk ratio of teriparatide	0.54	0.21-1.35	log normal	(Kingkeaw et al., 2013)
Incidence of drug's side effect per year				
Bisphosphonates				
Atypical femur fracture	0.00013	0.00012-0.00015	beta	(Dell et al., 2012)
Osteonecrosis of the jaw	0.00003	0.00002-0.00006	beta	(Fellow et al., 2011)
Denosumab				
Atypical femur fracture	0.0001	0.00009-0.00011	beta	(Papapoulos et al., 2015)
Osteonecrosis of the jaw	0.00042	0.0003-0.0005	beta	(Papapoulos et al., 2015)
Raloxifene				
Venous thromboembolism	0.00187	0.00114-0.00498	beta	(Adomaityte et al., 2008)
Strontium ranelate				
Venous thromboembolism	0.0026	0.00590-0.01180	beta	(European Medicines Agency, 2013)
Cost data				
Direct medical care cost				
Drug cost (Baht/year)				
Bisphosphonates (Alendronate 70 mg/week or Risedonate 35 mg/week)	2,490	2,241-2,739	gamma	(Drug Medical Supply Information Center (DMSIC), 2001)
Raloxifene (60 mg/day)	20,640	-	gamma	(Drug Medical Supply Information Center (DMSIC), 2001)
Strontium ranelate (2 g/day)	27,327	-	gamma	(Drug Medical Supply Information Center (DMSIC), 2001)
Denosumab prefill syring 60 mg/6 months)	23,568	-	gamma	(Drug Medical Supply Information Center (DMSIC), 2001)
Teriparatide (20 mcg/day sc)	239,375	-	gamma	(Drug Medical Supply Information Center (DMSIC), 2001)
Calcium carbonate tablet (1,500 mg/day)	203	164-502	gamma	(Drug Medical Supply Information Center (DMSIC), 2001)
Vitamin D (ergocalciferol) (0.02 mU/week)	68	-	gamma	(Drug Medical Supply Information Center (DMSIC), 2001)
Treatment cost (Baht/visit)				
Out-patient department visit	305	365-366	gamma	*
In-patient visit for OS patient with hip fracture	63,401	1,206-610,720	gamma	*
In-patient visit for OS patient with vertebral fracture	25,254	0-306,570	gamma	*

Table 1. (continued)

Parameters	Point estimate	Range	Distribution	Source
In-patient visit for OS patient with wrist fracture	12,847	0-138,370	gamma	*
Treatment cost of drug's side effects (Baht/visit)				
Atypical femoral fracture treatment	90,893	1,207-306,570	gamma	*
Osteonecrosis of the jaw treatment	16,983	3,742-97,776	gamma	*
Venous thromboembolism treatment	19,246	1,207-313,561	gamma	*
Direct non-medical care cost				
Transportation cost per visit	154	138-169	gamma	(standard cost lists for health technology assessment 2009)
Food cost per visit	56	50-62	gamma	(standard cost lists for health technology assessment 2009)
Medical device for hip fracture patient (one off)	3,982	3,902-4,769	gamma	(Kingkeaw et al., 2013)
Home improvement for hip fracture patient (one off)	3,457	3,111-3,802	gamma	(Kingkeaw et al., 2013)
Caregiver expenses per month for hip fracture patient	6,140	4,279-8,001	gamma	(Kingkeaw et al., 2013)
Caregiver expenses per month for vertebral fracture patient	4,335	2,972-5,744	gamma	(Kingkeaw et al., 2013)
Utility data				
Utility of osteoporosis	0.83	-	beta	(Kimman et al., 2013)
Atypical femoral fracture decrement	0.20	0.143-0.248	beta	(Ektrom et al., 2009)
Osteonecrosis of the jaw decrement	0.20	0.17-0.22	beta	(Miksad et al., 2011)
Reference case multipliers for fracture				
Vertebral fractures-1st year	0.86	0.83-0.89	beta	(Hiligsmann et al., 2008)
Vertebral fractures-subsequent year	0.96	0.95-0.97	beta	(Hiligsmann et al., 2008)
Hip fractures-1st year	0.70	0.64-0.77	beta	(Peasgood et al., 2009)
Hip fractures - subsequent year	0.80	0.68-0.96	beta	(Peasgood et al., 2009)
Wrist fractures-1st year (distal forearm fracture)	0.95	0.86-1	beta	(Peasgood et al., 2009)
Wrist fractures-subsequent year	1	-	beta	(Peasgood et al., 2009)
Venous thromboembolism decrement at 1 year	0.1	0.01-0.16	beta	(Hiligsmann et al., 2013; Kim et al., 2014)

Note: * = Analysis of Central Office of Healthcare Information and National Health Security Office databases
sc = subcutaneous injection
mU = million unit

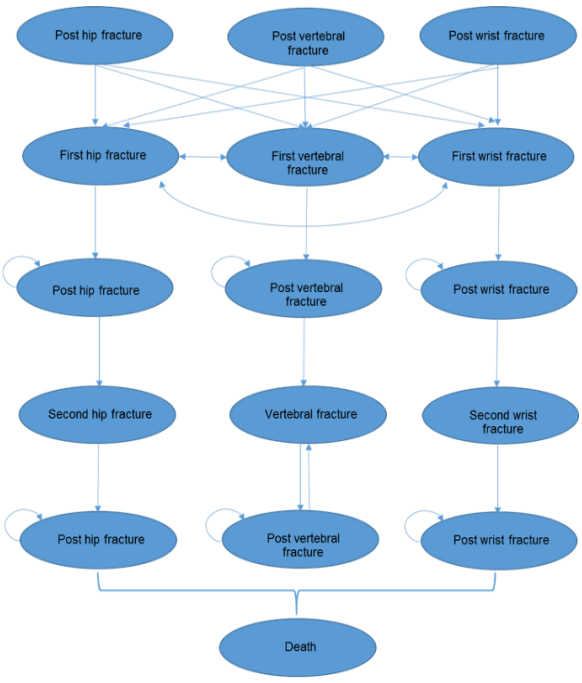

Figure 1. Model diagram of bone fracture cascades

2.2 Input parameters

Most model input parameters were obtained from Thai literature and databases. However, data were gathered from studies outside Thailand in cases where there were no equivalent domestic sources. Four stakeholder groups-health economists, healthcare providers (internal medicine specialists), third-party payers and representatives from the pharmaceutical industry-participated in two consultation meetings to define the study population, interventions, model structure, outcomes, comparator, assumptions and valid data input as well as provide comments on interim findings.

2.2.1 Epidemiology, intervention effectiveness and side effects

According to a health survey of 255 post-menopausal osteoporotic Thai women, 19.3% had a history of hip fractures, 24.7% spine/vertebral fractures, and 22.5% wrist fractures (Pongchaiyakul et al., 2002). Transitional probability of hip and vertebral fractures (Table 1) were calculated using charts of the Fracture Risk Assessment (FRAX®) tool based on the epidemiology of Thailand (Strom et al., 2010). The charts provide 10-year fracture probabilities according to BMD T-score, the number of clinical risk factors (CRF) and body mass index (BMI) set at 24 kg/m^2. The chart can be downloaded from

https://www.shef.ac.uk/FRAX/charts.aspx. However, as there were not any studies of the probability of wrist fractures in Thailand, this study used data on the incidence of distal radius fractures in Japan (Hagino et al., 1999). The risk of sequential bone fractures is higher among patients with preceding fractures (Table 1). A meta-analysis reported a significantly higher risk of recurrence among patients with a history of fractures than among those without a history (relative risk=1.86, 95% confidence interval: 1.75-1.98) (Kanis et al., 2004). As for mortality rates, the probability of death after a hip fracture and vertebral fracture were retrieved from domestic study (Vaseenon et al., 2010) and South Korean studies, respectively (Lee et al., 2012).

For this recurrent group, recommended adjunct interventions based on systematic reviews and meta-analyses include bisphosphonates, raloxifene, strontium ranelate, teriparatide, and denosumab (National Institute for Health and Care Excellence, 2014; Thai Osteoporosis Foundation, 2000). In the bisphosphonates, the effectiveness of alendronate and risedonate were systematically reviewed and pooled with meta-analysis (Kingkeaw et al., 2013) since the experts agreed that their efficacy was not significantly different. The effects of drug treatment were for the duration of drug use except for bisphosphonates which contained preventive effects 5 years after they were discontinued (Black et al., 2006; Fraser, 2011). Based on Thai clinical practice guidelines of osteoporosis (Thai Osteoporosis Foundation, 2000), all interventions were applied for 5 years, whereas teriparatide was applied for only 2 years because of the uncertainty of potential long-term side effects. Adverse effects from drugs recommended for discontinuation on advice arising from the expert meeting included atypical femur fracture (AFF), osteonecrosis of the jaw (ONJ), and venous thromboembolism (VTE). The incidence rates of these adverse events were retrieved from pertinent literature (Adomaityte et al., 2008; Dell et al., 2012; European Medicines Agency, 2013; Fellow et al., 2011; Papapoulos et al., 2015).

2.2.2 Costs

Cost estimation adopted a societal perspective where both direct medical and non-medical costs were estimated. Previous cost data were adjusted according to the consumer price index of the medical service category. All cost values are for 2019 and were converted to US dollars ($) using an exchange rate of THB 31.03=$1 for international comparison (Exchange rate of Bank of Thailand in 2019). The average national prices of adjunct and comparator drugs considered in this study were obtained from the Ministry of Public Health database (Drug Medical Supply Information Center (DMSIC), and used to calculate the cost per treatment course for each drug and then incorporated into the model. Alendronate cost was applied as acquisition cost of bisphosphonate for the base case analysis. All cost input data are shown in Table 1.

Direct medical costs for hospitalized episodes of hip, wrist, and vertebral fractures were obtained from Central Office of Healthcare Information and National Health Security Office (NHSO) databases. These third-parties responsible for collecting nationwide medical service data provided cost estimates for bone fractures in Thailand. In addition, according to ICD10, treatment costs for adverse effects per visit of the evaluated drugs were derived from the same databases and applied with the incidence rate of each adverse event. The analysis was specific to post-menopausal women with bone fracture diseases using the International Classification of Diseases code (World Health Organization, 2010). Direct non-medical costs, including housing improvements, mobility aids, and informal care provided by caregivers were derived from a previous domestic study (Kingkeaw et al., 2013).

2.2.3 Utility

Healthy osteoporotic patients have the highest utility weight. However, no direct utility weights have been reported in Thailand. Therefore, the utility weights of hip, wrist, and vertebral fractures were obtained from foreign studies, and these values were adjusted to the normal utility weight of 0.83 among healthy Thai women aged ≥45 years (Kingkeaw et al., 2013). The utility value of each fracture was adjusted by using the normal utility weight of healthy women multiplied by the reference case multiplier. Utility weights of drug side effect in those in a healthy state were also derived from previous international studies (Table 1) (Ektrom et al., 2009; Hiligsmann et al., 2008; Hiligsmann et al., 2013; Kim et al., 2014; Kimman et al., 2013; Miksad et al., 2011; Peasgood et al., 2009).

2.3 Cost-utility analysis

Primary outcomes were differences in the incidence of fractures, incremental costs, life years gained, QALYs gained and ICER (calculated as the total cost of the adjunct intervention minus that of the comparator, divided by the total QALY of the intervention minus that of the comparator). For base case analysis, the expected lifetime costs and outcomes for each intervention were calculated using a discount rate of 3% for both costs and outcomes. Results are presented as ICER of the intervention versus that of the comparator. An official willingness-to-pay (WTP) of the Thai Health Economic Working Group threshold (160,000 Baht or US$4,600/QALY gained) for inclusion in the NLEM for 2012 was used as the cost-effectiveness threshold (Thavorncharoensap et al., 2013).

2.4 Sensitivity analysis

One-way sensitivity analyses were conducted to evaluate uncertainties surrounding each input within plausible ranges, such as drug prices, risk ratios, and medication adherence and are presented using a tornado diagram. In cases with no existing cost-effective intervention against the threshold, threshold analysis for a cost-effective intervention price was conducted. Probabilistic sensitivity analysis (PSA) was conducted to simultaneously examine the effects of all parameter uncertainties using a Monte Carlo simulation (Microsoft Excel 2013, Microsoft Corp., Redmond, WA). Various probability distributions were applied to describe the uncertainties as follows, (a) probability and utility took values from 0 to 1 and then applied beta-distribution, (b) costs were positively skewed and then gamma-distribution was applied and (c) relative risk parameters presented a ratio scale and then applied log-normal distribution. The probability distributions are revealed in Table 1. One thousand Monte Carlo simulations were run with results presented as a cost-effectiveness acceptability curve (Teerawattananon and Chaikledkaew, 2008). The expected net monetary

benefit was calculated against WTP ranges to report the probability that the intervention is cost-effective.

3. RESULTS

Cost-utility analysis results with ICERs are shown in Table 2. Compared to calcium plus vitamin D alone, all alternative drugs in addition to calcium plus vitamin D were more expensive with slightly increased QALY. Bisphosphonates added to calcium plus vitamin D was cost-effective, yielding an ICER of 92,995 Baht (US$2,997) per QALY gained. Denosumab added to calcium plus vitamin D yielded a greater ICER of 1,701,932 Baht (US$54,848) per QALY gained, whereas teriparatide added to calcium plus vitamin D was more expensive with slightly improved QALY and yielded an ICER of 10,354,673 Baht (US$333,699) per QALY gained (Table 2). Based on starting age and BMD of the cohort population, bisphosphonates are cost-effective for fracture prevention in post-menopausal Thai women with osteoporosis and a history of bone fractures in all age ranges and BMD groups (Table 3).

One-way sensitivity analysis showed that the input parameter with the most influence was the cost of bisphosphonate drugs (Figure 2). PSA from 1,000 Monte Carlo simulations revealed that bisphosphonate drugs are 50% more likely to be cost-effective at the WTP threshold of 92,000 Baht (US$2,960) (Figure 3). In addition, only bisphosphonates are cost-effective against the aforementioned threshold, whereas the other drugs are cost prohibitive (Figure 3).

Table 2. Outcome estimation from model-based cost utility analysis

Drug	Lifetime cost (Baht)	Life years (years)	QALY (years)	ICER
Calcium plus vitamin D	1,000,236	16.293	12.8300	Based case
Bisphosphonates in addition	1,006,845	16.311	12.9010	92,995
Raloxifene in addition	1,094,370	16.297	12.8558	3,648,595
Denosumab in addition	1,105,580	16.308	12.8919	1,701,932
Strontium ranelate in addition	1,124,666	16.302	12.8632	3,744,709
Teriparatide in addition	1,467,409	16.303	12.8751	10,354,673

Table 3. Incremental Cost-effectiveness Ratio (ICER) of patients taking bisphosphonates based on age and BMD

BMD	Age							
T-Score	50	55	60	65	70	75	80	85
-2.5	92,995	51,034	75,262	74,631	80,266	72,303	79,265	88,559
-3	68,514	36,011	60,047	65,406	71,461	60,320	70,719	81,917
-3.5	41,009	17,246	40,568	51,460	61,645	51,722	64,056	74,272
-4	13,595	-875	23,879	37,795	52,336	44,387	58,887	67,011

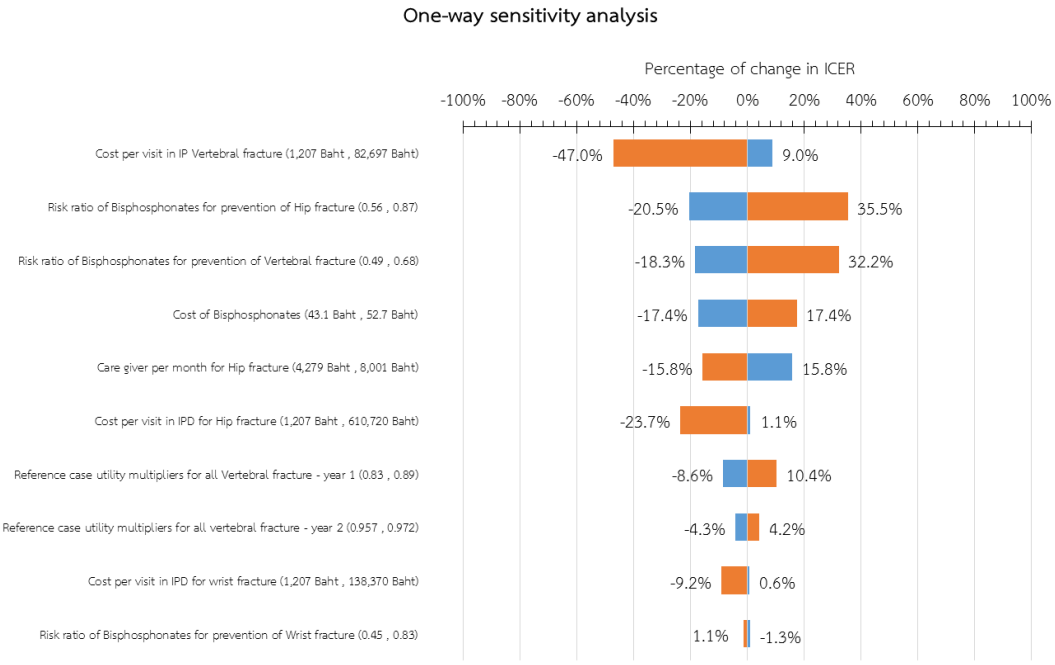

Figure 2. Tornado diagram of the one-way sensitivity analysis

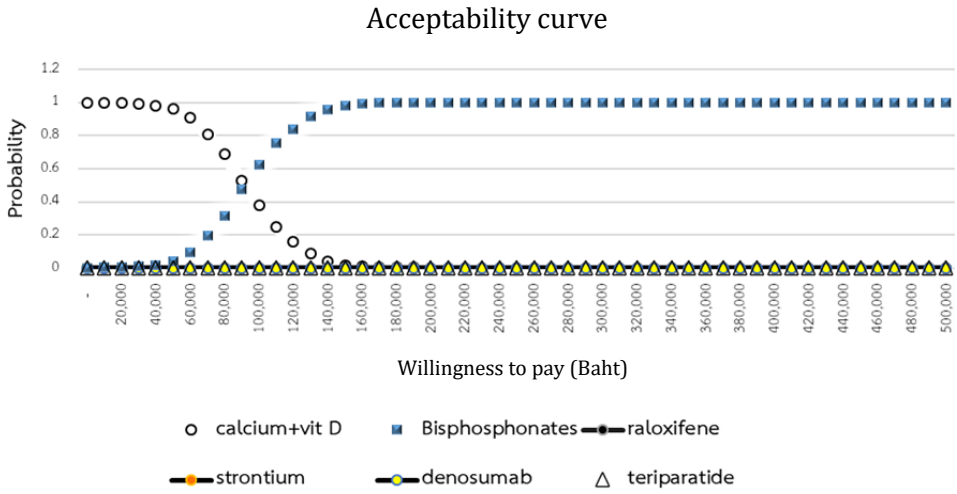

Figure 3. Cost-effectiveness acceptability curve

4. DISCUSSION

This cost-utility analysis revealed that only adjunct intervention with bisphosphonate drugs offers a cost-effective alternative to the standard intervention alone for post-menopausal osteoporotic Thai women aged ≥50 years with a BMD T-score of ≤-2.5 SD and a history of bone fractures as indicated by ICERs below the current WTP threshold. In addition, adjunct teriparatide provides a slightly better health benefit than calcium plus vitamin D alone but at a much higher cost, resulting in a much greater ICER. Thus, teriparatide is not cost effective. However, teriparatide is recommended for patients age 65 and older and do not respond to other drugs (National Institute for Health and Care Excellence, 2014). These findings differ from those of a previous Thai study that reported that bisphosphonate was only cost-effective in patients aged ≥65 years (Kingkeaw et al., 2013). In addition, Bisphosphonate costs in previous study were higher than this study. Although this study considered side effects of the intervention, which account for a substantial fraction of the total treatment cost, they were of a relatively low incidence. Moreover, the present analysis took into account patients' utility weights from their preceding health state before entering into a new health state group at each successive cycle. In contrast, the previous study applied a constant utility weight to each health state and ignored the site of prior fractures (hip, wrist, or spine) before the subsequent fracture. These exclusions likely underestimated the preventive efficacy of bisphosphonate. For instance, consider patients starting without a history of fractures and then experiencing a hip fracture followed by a spinal fracture. If it is assumed that in the absence of a fracture the utility weight is 1.00, whereas a hip fracture has a utility weight of 0.85. Then the utility weight of the next health state (spinal fracture) is 0.60 (yielding a 30% reduction from the preceding health state). If the drug completely prevents both fractures, then the utility score gains are 0.15 and 0.25, respectively, whereas if the preceding utility score is ignored, then the spinal fracture's utility weight will be 0.70, which is a 30% reduction from the naïve state (1.00), and the prevention of both fractures yields a lifetime savings of only 0.15 and 0.15, respectively. The results from this article are in accordance with those of Kanis et al. (2008) that the bisphosphonate alendronate is indeed a cost-effective treatment for secondary bone fracture prevention among osteoporotic women, though there was a reduction of ICER from risk factors such as age and BMD. This study pooled the effectiveness of alendronate and risedronate and selected the more cost-effective drug according to expert consensus as the two drugs did not significantly differ in their usefulness. The researchers assumed that bisphosphonates retained preventive efficacy for 5 years after the last administration, whereas the other drugs had no therapeutic effects immediately after termination. This assumption is based on current evidence that supports residual effects of bisphosphonates only (Black et al., 2006; Fraser et al., 2011). Although several studies evaluated teriparatide discontinuation, Murphy et al (2018) found that the majority of teriparatide patients were receiving bisphosphonate therapy, and the true effect of discontinuing teriparatide remains unknown. However, the researchers conducted a sensitivity analysis to determine the maintenance effect of teriparatide at 2 and 5 years. The results revealed that the ICER decreased to 7,234,820 Baht (US$233,150) and 5,284,690 (US$170,300) per QALY gained, respectively, but it was still not cost-effective compared to calcium plus vitamin D.

Results from this study were presented to the NLEM committee to negotiate drug prices from pharmaceutical companies, and it was concluded that any drug in the bisphosphonate group can be included in the NLEM if it is less expensive than the base case. Moreover, drug price can be reduced by >80% if included in the NLEM. Therefore, ICERs of bisphosphonates for policy implementation will be even lower than those presented in the present study.

This study has made every attempt to adhere to the guidelines to conduct economic evaluation in osteoporosis (Hiligsmann et al., 2019). However, there is one recommendation

that cannot be completely followed. The guideline suggests avoiding a restriction of number of fractures after a fracture, and this study did not limit the number of vertebral fractures as per guidelines but placed the limit at two for hip and wrist fractures. Based on the model's assumptions, this study attempted to simulate patients' fracture histories. Hip and wrist fractures were limited to two per person on the advice of experts, whereas many spine fractures were allowed because there are many vertebrae with fragile components. However, results indicate that there are some limitations that need to be considered prior to implementing policies regarding these protective drugs. First, utility weights used in the model were gathered from foreign studies because of the unavailability of data for Thailand. Second, some data on the incidence of wrist fractures came from Japan (Hagino et al., 1999). Third, although osteopenia leads to increased risks for bone fractures (Tomasevic et al., 2018), this study focused on analyzing women with both osteoporosis and a history of fractures and, thus, were at greater need for medications because of the higher risk. Finally, model-based estimations cannot account for all relevant variables. However, unlike previous investigations, severe side effects, which are important contributors to drug costs, were incorporated in this cost-utility analysis.

5. CONCLUSION

Bisphosphonate drugs are the most cost-effective adjuncts to calcium plus vitamin D for the secondary prevention of bone fractures among post-menopausal osteoporotic Thai women, whereas all other adjunct interventions examined were cost-ineffective. In fact, the addition of strontium ranelate and raloxifene had deleterious health effects but incurred higher incremental costs than calcium plus vitamin D alone. Bisphosphonate drugs are recommended for NLEM inclusion.

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