Original Article

Economic Evaluation of Drug Treatment for Fracture Prevention in Thai Postmenopausal Women with Osteoporosis without Fracture History

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Objective: To evaluate the cost-utility of drug treatment for fracture prevention in Thai postmenopausal women with osteoporosis without fracture history, considering adverse events from drugs, and assess the budget impact over 5 years.

Materials and Methods: Cost-utility was assessed using a Markov model. Cycle length was set at 1 year and followed a lifetime horizon and societal perspective. The drug treatment to prevent osteoporotic fracture consisted of 4 alternatives: oral bisphosphonates, raloxifene, strontium ranelate, and denosumab for 5 years, compared with no treatment. The willingness to pay threshold was set at 160,000 Thai baht (THB) per quality-adjusted life year (QALY).

Results: Oral bisphosphonates was the only one cost-effective from the age of 65 years with a BMD T-score less than or equal –2.5. The incremental cost-effectiveness ratio (ICER) was 130,049 THB per QALY. The budget impact 15,964 million THB per annum if treated in target population about 1.43 million people per annum.

Conclusion: Bisphosphonates is cost-effective for osteoporotic fracture prevention in postmenopausal women without fracture history but have an enormous budget impact. Negotiated drug prices and clinical risk factors should be considered for the Subcommittee, Development of the National List of Essential Medicines (NLEM).

Keywords: Cost-utility, ICER, QALY, Osteoporosis, BMD T-score, Bisphosphonates

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Osteoporosis is a disease characterized by low bone mass and structural deterioration of tissue, leading to bone fragility and increases risk of fracture of hip, spine, and wrist[1-3].

Currently, it is estimated that over 200 million people worldwide suffer from osteoporosis[4]. Incidences of osteoporosis occur more in older people and in women, especially postmenopausal women. In Caucasians, osteoporosis is present in 15% of 50 to 59 years old, but this figure increases quickly to 70% of those over 80 years of age[1]. In Thailand, a study in Rajavithi Hospital between 2011 to 2012 showed a prevalence of osteoporosis of 21.6%, and a prevalence of osteopenia of 59.4% which could imply for possible increasing osteoporosis risks in the future[5]. The incidence of fractures from osteoporosis worldwide showed that they occurred 1 in 3 women aged over 50[6]. Hip fractures were associated with a 20% chance of mortality[1,7], 50% became disabilities and only 30% could return to normal[1]. Hip fractures and vertebral fracture were followed by a 2.5-fold and 5-fold increased risks of future fractures, respectively[8].

The NICE guideline 2014 recommendations are alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Denosumab is recommended only in high risk of fractures. Worldwide cost-effective treatments for osteoporotic fracture prevention include oral bisphosphonates[9-11], denosumab[12], strontium

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ranelate[10,13], and raloxifene[10,14] when compared with no treatment. In Thailand 2013[15], it was found that only alendronate was cost-effective compared with no treatment, but the adverse drug reaction was not taken into account. However, this policy results in a great impact on the budget. The objective of the present study was to evaluate the cost-utility of drug treatment for fracture prevention when adverse events were also considered and to assess the budget impacted for decision makers and reimbursement policies in Thailand.

Materials and Methods

The present study aimed to evaluate the cost-utility of drug treatment for prevention of fractures from osteoporosis by using an economic modeling system called the Markov model. The Markov model, based on previously models[15], was developed from probability of transitions of health state in Thai postmenopausal women to calculate costs and quality-adjusted life year (QALY) outcomes. Four drug alternatives were compared with no treatment. The duration of the drug treatment was 5 years. The populations in the Markov model were Thai postmenopausal women with osteoporosis without history of fractures from the age of 50 years. This model was simulated throughout the patients' lifetime with a 1-year cycle length and formed a societal perspective. The discount rate of cost and QALYs was 3%, as recommended by a guide to health technology evaluation for Thailand 2009[16]. The result produced the incremental cost-effectiveness ratio (ICER). A threshold value was set at 160,000 Thai baht (THB) per QALY which was equal to 1 GDP of Thailand. The ICER was calculated using the formula below.

$$\text{ICER} = \frac{\text{Total cost of drug treatment} - \text{Total cost of no treatment}}{\text{Total QALYs of drug treatment} - \text{Total QALYs of no treatment}}$$

Model structure

Figure 1, illustrated a schematic diagram of the Markov model consisting of 14 health states which were "well", "1st hip fracture", "1st vertebral fracture", "1st wrist fracture", "post 1st hip fracture", "post 1st vertebral fracture", "post 1st wrist fracture", "2nd hip fracture", "n vertebral fracture", "2nd wrist fracture", "post 2nd hip fracture", "post n vertebral fracture", "post wrist fracture", and death. Initially, all patients belonged in 'well' (osteoporosis without prior fracture). Patients could have their first fracture at hip, vertebral or wrist, or remain in 'well'. If patients incurred a fracture after 1 year, they could move to post fracture (hip, vertebral, or wrist fracture), or

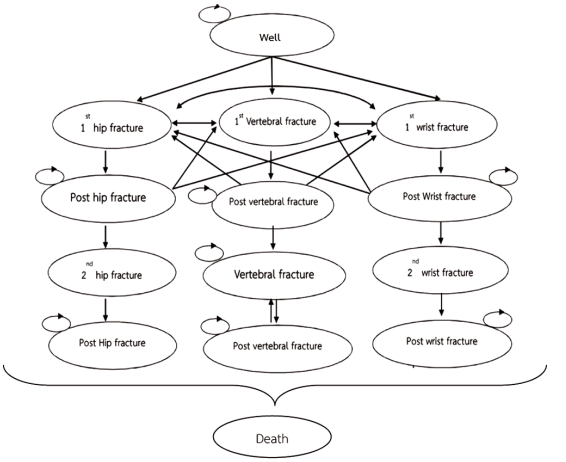

Figure 1. The schematic diagram of the Markov model.

experienced a new fracture health state. If the patients incurred post fracture they could move to 2nd fracture (the same as 1st fracture), or fracture in another site, or stayed in post fracture. All health states could lead to death. Assumptions of the Markov model were: 1) patients in the Markov model started from the age of 50 years, 2) no patient leaved the study, 3) hips and wrists could fracture a maximum of two times but vertebrae could fracture more than two times, and 4) assumed all patients were 100% complied with the treatment.

Clinical treatment alternatives compared

The comparator was no treatment. The drug treatments consisted of 4 alternatives comprising: 1) oral bisphosphonates (alendronate 70 mg weekly, risedronate 35 mg weekly), 2) raloxifene 60 mg oral daily, 3) strontium ranelate 2 g oral daily, and 4) denosumab 60 mg subcutaneously every 6 months. The alternative drug treatment was conducted for 5 years. Both two groups received 1,500 mg of calcium daily and vitamin D 0.2 M IU weekly.

Study parameters

Treatment efficacy and safety of drug: Results for the efficacy of the bisphosphonates, raloxifene and strontium ranelate, were taken from a systematic review and meta-analysis of Kingkeaw[15]. The efficacy of denosumab was taken from the systematic review. There was a paper from Fraser et al (2011)[17] which covered the inclusion criteria. The efficacy of each drug on reduced fracture risk is shown in Table 1. It was assumed that the efficacy of each drug was stable and disappeared after stopped the drug, excepted for

Table 1. Relative risk (RR) and 95% confidence interval (CI) of each drug

Drug	Efficacy of drug, RR (95% CI)			Reference No.
	Hip fracture	Vertebral fracture	Wrist fracture	
Bisphosphonates				15
1st	0.79 (0.44 to 1.44)	0.64 (0.39 to1.04)	1.19 (0.87 to 1.62)	
2nd	0.70 (0.56 to 0.87)	0.57 (0.49 to 0.68)	0.61 (0.45 to 0.83)	
Raloxifene				15
1st	-	0.53 (0.35 to 0.79)	-	
2nd		0.78 (0.44 to1.38)		
Strontium ranelate				15
1st	0.89 (0.67 to 1.18)	-	0.98 (0.73 to 1.31)	
2nd		0.73 (0.63 to 0.85)		
Denosumab				17
1st	0.71 (0.58 to 0.88)	0.29 (0.21 to 0.40)	0.71 (0.58 to 0.88)	
2nd	0.84 (0.65 to 1.09)	0.34 (0.24 to 0.48)	0.84 (0.65 to 1.09)	

the bisphosphonates which, after being taken for 5 years would maintain their efficacy for the next 5 years. Because of the randomized control trial (RCT), those taking bisphosphonates for 5 years were then divided into 2 groups: 1) those who stopped taking bisphosphonates after 5 years, and 2) those who continued taking bisphosphonates for a further 5 years. The results of the present study showed that clinical and morphometric vertebral fractures and non-vertebral fractures were not statistically significantly different[18,19]. Adverse events from the drugs were considered to be statistically significantly different from the placebo, or caused discontinuation of the drugs as recommended by the experts, included atypical femoral fracture (AFF) with 13.1/100,000 at year 5[20], and 1.0/10,000[21]; and osteonecrosis of the jaw (ONJ) with 3.47/100,000[22], and 4.2/10,000[21] from bisphosphonates and denosumab, respectively. Incidences of venous thromboembolism (VTE) from raloxifene and strontium ranelate were found at a rate of 0.00187[23] and 2.6/1,000[24], respectively (Table 2). It took only one patient with only one type of adverse event from a drug for the drug to be stopped and the efficacy of the drug to be ignored. Adverse events did not affect mortality rates.

Incidence of fractures: The probability of hip fractures and vertebral fractures were calculated using a chart from the World Health Organization (WHO) Fracture Risk Assessment tool (FRAX) based on the epidemiology of Thailand. The chart was based on the number of clinical risk factors (CRF), age range, bone mineral density (BMD) T-score and body mass index (BMI) set at 24 kg/m². The chart can be downloaded from https://www.shef.ac.uk/FRAX/charts.aspx. The FRAX® algorithms gave 10-year probabilities of fracture including 10-year probabilities of a hip fracture and of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture). The present study calculated the 10-year probabilities as rate per year and rate per year to probability per year, using the formulas r=[In(1–p)]/t and p=1–exp(–rt), respectively, where r=rate, p=probability and t=time (year). Clinical vertebral fractures were calculated from major osteoporotic fractures which were adjusted by multiplying them by the relative risk reduction of vertebral fractures from Ström et al (2010)[25], studied abroad, then adding morphometric vertebral fractures from Jitapunkul et al[26], studied in Thailand. The probability of wrist fractures had never been studied in Thailand before. This study used the incidence of distal radius fractures in Japan, Hagino et al (1999)[27].

Mortality: 'Well' and 'wrist fractures' were assigned a probability of death equal to that of general people, categorised by age group using data from the Ministry of Public Health, Health Information Group, Bureau of Policy and Strategy, Public Health Statistics, 2014[28]. The probabilities of death after hip and vertebral fractures were examined in Thailand in 2010[29] and South Korea[30], respectively. They were then adjusted according to the normal Thai death rate.

Health state utility values: The present study used general utility people from the age of 45 years in Thailand equal to 0.834[31]. The present research used a multiplier of the value utility of patients with fractures from abroad. A literature review of utility of hip and wrist fractures came from Peasgood et al (2009)[32], and vertebral fractures (morphometric and clinical fracture) from Hiligsman et al (2008)[33].

Table 2. Input parameters used in the model

Parameter	Mean	Distribution	Reference No.
Incidence of adverse event from drug			
AFF from bisphosphonates	13.1/100,000	0.00003	20
ONJ from bisphosphonates	3.47/100,000	0.00003	22
VTE from raloxifene	0.00187	0.00376	23
VTE from strontium ranelate	2.6/1,000	0.00259	24
AFF from denosumab	1.0/10,000	0.00010	21
ONJ from denosumab	4.2/10,000	0.00042	21
Utility			
Utility of 'well'	0.834	Beta	31
Reference case multipliers for hip fracture - year 1	0.700	Beta	33
Reference case multipliers for hip fracture - year 2	0.800	Beta	33
Reference case multipliers for all vertebral fracture - year 1	0.860	Beta	32
Reference case multipliers for all vertebral fracture - year 2	0.965	Beta	32
Reference case multipliers for wrist fracture - year 1	0.956	Beta	32
Utility of AFF decrease	0.200	Beta	34
Utility of ONJ decrease	0.196	Beta	35
Reference case multipliers for VTE decrease at 1 year	0.900	Beta	36, 37
Direct medical care cost			
Cost of drug per annum			
• Cost of bisphosphonate (alendronate) (70 mg/week)	10,510.18	Gamma	38
• Cost of raloxifene (60 mg/day)	20,252.68	Gamma	38
• Cost of strontium ranelate (2 g/day)	26,814.07	Gamma	38
• Cost of denosumab prefilled syringe (60 mg/6 month)	23,126.22	Gamma	38
• Cost of calcium carbonate tab (1,500 mg/day)	199.80	Gamma	38
• Cost of vitamin D2 (ergocalciferol) (0.02 M/week)	77.55	Gamma	38
Cost treatment of fracture			
• Cost of hip fracture treatment	27,987.51	Gamma	*
• Cost of vertebral fracture treatment	13,635.29	Gamma	*
• Cost of wrist fracture treatment	9,020.02	Gamma	*
• Cost per visit to OPD	299.37	Gamma	39
Cost of treatment of adverse event from drug			
• Cost of AFF treatment	26,827.27	Gamma	*
• Cost of ONJ treatment	12,657.52	Gamma	*
• Cost of VTE treatment	21,007.17	Gamma	*
Direct non-medical cost			
Medical device for hip/vertebral fracture - one off	3,906.66	Gamma	**
Home improvement for hip/vertebral fracture - one off	3,392.22	Gamma	**
Care per month for Hip fracture patient	6,024.81	Gamma	**
Care per month for Vertebral fracture patient	4,254.36	Gamma	**
Cost of transportation per visit	150.59	Gamma	40
Cost of food per visit	55.47	Gamma	40

AFF=atypical femoral fracture; ONJ=osteonecrosis of the jaw; VTE=venous thromboembolism; OPD=out-patient department

* Analysis of database from Central office for Healthcare Information 2015 and National Health Security Office (NHSO) 2015

** Data collection and analysis Bootstrapping from the study of Maleewong et al[42]

Adverse events from drug used which reduced the utility values were AFF and ONJ, which reduced the utility values from the start by 0.200[34] and 0.196[35], respectively. The VTE multiplier was 0.9[36,37] and showed a decrease of 10% (Table 2) if the fracture was greater than 1 time, the reference value multiplied

Table 3. Results of total costs, total QALYs and ICER

Treatment	Results (probabilistic) compliance 100%				
	Cost (baht)	LYs	QALYs	ICER per LY	ICER per QALY
No treatment	152,743	11.85	9.65		
Bisphosphonates	180,481	12.06	9.87	130,779	130,049
Raloxifene	231,792	11.97	9.77	38,161,032	705,679
Strontium ranelate	273,175	11.85	9.65	683,752	Dominated
Denosumab	235,635	12.04	9.85	438,069	430,829

LY=life year; QALY=quality-adjusted life year; ICER=incremental cost-effectiveness ratio

repeatedly.

Costs: The costs of treatment from a societal perspective were composed of direct medical costs and direct non-medical costs from a study in Thailand[15]. To avoid double counting for utility outcomes, indirect costs were excluded. In term of direct medical costs included cost of drug treatment[38], fracture and adverse event treatments and cost of out-patient department (OPD)[39]. On the other hand, direct non-medical costs included transportation[40], food[40], medical device, home improvements for hip or vertebral fractures[15], and costs of care per month for hip and vertebral fracture[15] (Table 2). All costs were converted to 2015 values using the consumer price index (CPI) and a discounted rate of 3%[41].

Sensitivity analysis

A one-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) were performed to determine the uncertainty of model parameters. For the one-way sensitivity analysis, each parameter at a time was varied across the possible range and shown as a tornado diagram. In addition, a PSA was carried out by varying all parameters randomly within the possible range. A Monte Carlo Simulation was generated in order to randomly select a value of each parameter 1,000 times and calculate expected costs and outcomes. The results of the PSA were presented as cost-effectiveness plans and acceptability curves.

Results

The cost-utility analysis of a baseline case from the age of 50 years and with a BMD T-score less than or equal to –2.5 showed that none of the alternative drugs were cost-effective. In addition, when varying the ranges of age and BMD T-score when starting the drugs, it appeared that from the age of 65 years, with a BMD T-score less than or equal to –2.5, bisphosphonates was the only cost-effective alternative, followed by denosumab, raloxifene, respectively. Strontium ranelate was dominated, higher cost and lower QALYs than comparator (Table 3). ICER of bisphosphonates was 130,049 THB per QALY when starting drug from the age of 65 years, with a BMD T-score less than or equal to –2.5. However, Denosumab was cost-effective from the age of 80 years and over, with a BMD T-score less than or equal to –2.5. Other drugs were not shown to be cost-effective at any range of age or BMD T-score.

The one-way sensitivity analysis was set at 65 years and over, and the BMD T-score less than or equal to –2.5. Greatest uncertainty model parameters were: 1) relative risk of bisphosphonates for prevention of 1° vertebral fractures, 2) cost of bisphosphonates, 3) relative risk of bisphosphonates for prevention of 1° hip fractures, 4) care per month for vertebral patients, 5) utility of general population, 6) proportion of morphometric vertebral fractures, and 7) hours of informal care for vertebral patients. Adverse events variables from the drugs had little effect on changing the results of the cost-effectiveness. Adverse event representing a percentage change of ICER between –0.016% to 0.145%, the ICER results were shown as a Tornado diagram in Figure 2.

The PSA results of drugs for osteoporosis treatment were illustrated using acceptability curves (Figure 3). The cost-effectiveness acceptability curves showed that starting bisphosphonates at the age of 65 years and over, with a BMD T-score less than or equal to –2.5, bisphosphonates had a cost-effectiveness of 61.2%. A probability to cost-effectiveness ratio of 50% means a willingness to pay about 130,000 THB per QALY.

The budget impact of bisphosphonates for prevention of osteoporosis fractures in postmenopausal women from the aged of 65 years, with a BMD T-score less than or equal to –2.5, being treated with the drug for five years from a third party perspective, was 15,964 million THB per annum (1,427,035 patients). If the drug price dropped 75% from 202 to 50.5 THB per

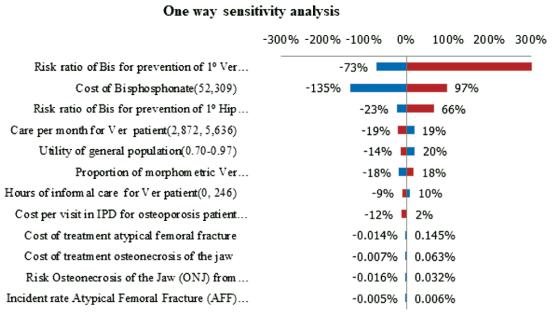

Figure 2. Tonado diagram.

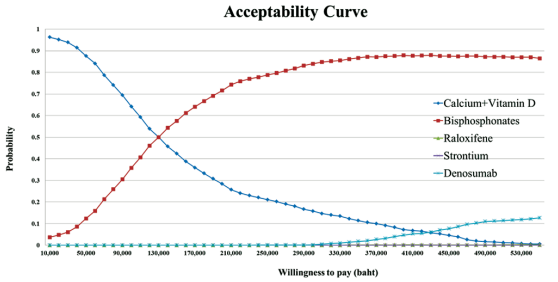

Figure 3. Acceptability curve.

tablet, which was the price that some hospitals could pay, the budget could be reduced to 5,713 million THB per annum. Furthermore, if the drug was given to people from the age of 70 years, the budget could be reduced to 4,230 million THB per annum. If we treated only those who had a 10-year probability of major osteoporotic fracture of 20% or a 10-year probabilistic of hip fracture of 3%, the budget could be reduced to 1,056 (262,578 patients) or 2,272 (564,722 patients) million THB per annum respectively.

Discussion

Oral bisphosphonates were the most cost-effective drugs for the prevention of osteoporotic fractures in Thai postmenopausal women with osteoporosis without fracture history compared to no treatment. Oral bisphosphonates were cost-effective from the age of 65 years, and with a BMD T-score less than or equal to –2.5. The present study assumed 100% compliance. If compliance decreased to 50%, the efficacy of the drug was reduced but still cost-effective. One way sensitivity analysis showed the greatest uncertainty in results including the relative risk (RR) of bisphosphonates for fracture prevention which was related to compliance. The lowest cost of bisphosphonates at 52 THB per tablet will create cost-savings, higher QALY and lower costs than no treatment showed in Tornado diagram. Adverse event had small impact on ICERs because of low incidence. Relative risk (RR) values were obtained from systematic review and meta-analysis. The results were obtained from probabilistic which random variables 1,000 times with Microsoft Excel this credible. However, the present study recommends using the information carefully.

The findings showed that all drug treatments had higher costs and higher outcomes than no treatment as found in the previous studies abroad[9-11,14], with the exception of strontium ranelate which had lower outcomes than no treatment, which was different from previous studies[10,13]. This is because the RR of prevention of hip fractures in the present study came from a systematic review and meta-analysis of Kingkeaw[15] which were higher than the previous studies[9,10]. These results were relevant to the study of Kingkeaw[15] which showed the cost-effectiveness of treatment with bisphosphonates had the highest cost-effectiveness, same as abroad[10,14]. The study abroad, adherence was highest with the 2 bisphosphonates, alendronate and risedronate at 60.7% and 58.4%, respectively[10,43], so if treatment with bisphosphonates calculated at 50% compliance in this study became cost-effective from the age of 65 years, and with a BMD T-score less than or equal to –2.5 and cost-effective with a probability of hip or major osteoporotic fracture at 10 years at above or equal to 2.4% and 7.4%, respectively. In the present study, there were 3 main points which differed from the previous studies in Thailand[15]. Firstly, the effects of stopping drug treatment due to adverse events (statistically significant different from no treatment, or due to recommendation from an expert) were included. Secondly, this study used updated inpatient department (IPD) costs of fracture treatment from the National Health Security Office (NHSO) and government officers and updated costs of drugs. Thirdly, the calculation of utility method in this study was calculated by reference case multipliers repeatedly if a fracture occurred more than once. These three different points affected the following results item by item. Firstly, adverse events had very little effect on the ICER because of their low incidence. Previous studies abroad suggested that gastrointestinal side effects had a small impact on cost-effectiveness[10]. The present study did not consider gastrointestinal (GI) side effects because serious GI side effects did not provide a statistically significant difference compared with no treatment. In addition, no previous study considered AFF and ONJ as the result

of taking bisphosphonates. Secondly, the cost per visit to an IPD for an osteoporotic fracture was less than previous studies as a result of an increase in the ICER. Thirdly, the quality of life became slightly lower as a result of osteoporotic patient had fracture history in more cost-effective models. In addition, the present study summarized the efficacy of both alendronate and risedronate as bisphosphonates. Cost of alendronate was represented bisphosphonate because it had lower cost than risedronate, if bisphosphonates was cost-effective in the present study, it would increase opportunity of patient to assess alendronate or risedronate as price competition among the companies. In the present study, denosumab is cost-effective from the age of 80 years. The age was higher than the previous studied[12] which cost-effective from the age of 70 years, because this study considered different RR of drug between with and without fracture history.

Limitations in the present study which need to be reported. Firstly, the lack of adverse events reported in Thailand, data from aboard were utilized. Secondary, the present study excluded costs of screening by using FRAX algorithm and costs for follow-up because both population in treatment and no treatment also utilize this cost. However, budget impact should consider this cost, if implement this policy. Finally, the present study lacked incidence data on hip fractures, vertebral fractures and wrist fractures in Thai women classified by age and BMD T-score, resulting in inaccurate budget estimation for this policy. In abroad, osteoporosis of women with fracture history had more cost-effectiveness than without fracture history[10] but in Thailand, only without fracture history was cost-effective[15]. In practical treatment, physicians will treat higher risk woman, who had fracture history, so studying in osteoporosis women with fracture history is recommend to confirm the result.

Conclusion

Oral bisphosphonate is cost-effective when treating Thai women from the age of 65, with a BMD T-score less than or equal to –2.5, but would cause enormous budget impact. The present study therefore recommends starting to use the drug in older patients with higher CRF, or negotiating the costs of the drug, which should be considered by the Subcommittee, Development of the National List of Essential Medicines (NLEM) to sustain the Thai healthcare system.

What is already known on this topic?

Firstly, AFF and ONJ had very little effect on the ICER because of their low incidence. Previous studies abroad suggested that gastrointestinal side effects had a small impact on cost-effectiveness. Secondly, this study summarized the efficacy of both alendronate and risedronate as bisphosphonates. Bisphosphonates is cost-effective in this study, it will increase opportunity of patient to assess alendronate or risedronate as price competition among the companies.

What this study adds?

In this study, there were 3 main points which differed from previous studies in Thailand[15]. Firstly, the effects of stopping drug treatment due to adverse events (statistically significant different from no treatment, or due to recommendation from an expert) were included. Secondly, this study used updated IPD costs of fracture treatment from the NHSO and the government officers and updated costs of drugs. Thirdly, the calculation of utility method in this study was calculated by reference case multipliers repeatedly, if a fracture occurred more than once.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. World Health Organization. Osteoporosis [Internet]. 2015 [cited 2015 Sep 17]. Available from: http://www.who.int/chp/topics/rheumatic/en/.
2. National Osteoporosis Foundation. 54 Million Americans affected by osteoporosis and low bone mass [Internet]. 2014 [cited 2015 Sep 22]. Available from: http://nof.org/news/2948.
3. International Osteoporosis Foundation. The Asia-Pacific regional audit [Internet]. 2013 [cited 2015 Sep 22]. Available from: http://www.iofbonehealth.org/sites/default/files/media/PDFs/Regional%20Audits/2013-Asia_Pacific.
4. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Washington, DC: National Osteoporosis Foundation; 2013.

5. International Osteoporosis Foundation. Epidemiology [Internet]. 2015 [cited 2016 Feb 13]. Available from: http://www.iofbonehealth.org/epidemiology.
6. Saengsuda S. Prevalence of osteoporosis and osteopenia in Thai female patients at Rajavithi Hospital. J Health Sci 2013;22:242-50.
7. International Osteoporosis Foundation. Osteoporotic fracture [Internet]. 2015 [cited 2015 Sep 17]. Available from: http://www.iofbonehealth.org/what-is-osteoporosis.
8. Chaysri R, Leerapun T, Klunklin K, Chiewchantanakit S, Luevitoonvechkij S, Rojanasthien S. Factors related to mortality after osteoporotic hip fracture treatment at Chiang Mai University Hospital, Thailand, during 2006 and 2007. J Med Assoc Thai 2015;98:59-64.
9. Borgström F, Strom O, Coelho J, Johansson H, Oden A, McCloskey EV, et al. The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX. Osteoporos Int 2010; 21:495-505.
10. Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, et al. The cost-effectiveness of alendronate in the management of osteoporosis. Bone 2008;42:4-15.
11. Pham AN, Datta SK, Weber TJ, Walter LC, Colon-Emeric CS. Cost-effectiveness of oral bisphosphonates for osteoporosis at different ages and levels of life expectancy. J Am Geriatr Soc 2011;59:1642-9.
12. Ström O, Jönsson B, Kanis JA. Intervention thresholds for denosumab in the UK using a FRAX(R)-based cost-effectiveness analysis. Osteoporos Int 2013;24: 1491-502.
13. Stevenson M, Davis S, Lloyd-Jones M, Beverley C. The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women. Health Technol Assess 2007;11:1-134.
14. Kanis JA, Borgstrom F, Johnell O, Oden A, Sykes D, Jonsson B. Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. Osteoporos Int 2005;16:15-25.
15. Kingkaew P. Cost-utility analysis of treatment for prevention of osteoporotic fractures [Internet]. 2013 [cited 2015 Jan 12]. Available from: http://www.hitap.net/en/research/17703.
16. Subcommittee on Development National List of Essential Medicines. Health technology assessment guide for Thailand. Bangkok: Chulalongkorn University Printing House; 2012.
17. Fraser LA, Vogt KN, Adachi JD, Thabane L. Fracture risk associated with continuation versus discontinuation of bisphosphonates after 5 years of therapy in patients with primary osteoporosis: a systematic review and meta-analysis. Ther Clin Risk Manag 2011;7:157-66.
18. McClung MR, Boonen S, Torring O, Roux C, Rizzoli R, Bone HG, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. J Bone Miner Res 2012;27:211-8.
19. Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006;296:2927-38.
20. Dell RM, Adams AL, Greene DF, Funahashi TT, Silverman SL, Eisemon EO, et al. Incidence of atypical nontraumatic diaphyseal fractures of the femur. J Bone Miner Res 2012;27:2544-50.
21. Papapoulos S, Lippuner K, Roux C, Lin CJ, Kendler DL, Lewiecki EM, et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. Osteoporos Int 2015;26:2773-83.
22. Fellows JL, Rindal DB, Barasch A, Gullion CM, Rush W, Pihlstrom DJ, et al. ONJ in two dental practice-based research network regions. J Dent Res 2011;90:433-8.
23. Adomaityte J, Farooq M, Qayyum R. Effect of raloxifene therapy on venous thromboembolism in postmenopausal women. A meta-analysis. Thromb Haemost 2008;99:338-42.
24. European Medicines Agency. Assessment report for Protelos and Osseor [Internet]. 25 May 2012 [cite 2015 Jan 10]. Available from: https://www.ema.europa.eu/documents/variation-report/osseor-h-c-561-a20-0030-epar-assessment-report-article-20_en.pdf.
25. Ström O, Borgström F, Kleman M, McCloskey E, Odén A, Johansson H, et al. FRAX and its applications in health economics--cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example. Bone 2010;47:430-7.
26. Jitapunkul S, Thamarpirat J, Chaiwanichsiri D, Boonhong J. Incidence of vertebral fractures in Thai women and men: a prospective population-based study. Geriatr Gerontol Int 2008;8:251-8.
27. Hagino H, Yamamoto K, Ohshiro H, Nakamura T, Kishimoto H, Nose T. Changing incidence of hip, distal radius, and proximal humerus fractures in Tottori Prefecture, Japan. Bone 1999;24:265-70.
28. Bureau of Policy and Strategy, Ministry of Public Health. Public health statistic 2011. Bangkok: The War Veterans Organization of Thailand Printing House; 2012.
29. Vaseenon T, Luevitoonvechkij S, Wongtriratanachai P, Rojanasthien S. Long-term mortality after osteoporotic hip fracture in Chiang Mai, Thailand. J Clin Densitom 2010;13:63-7.
30. Lee YK, Jang S, Jang S, Lee HJ, Park C, Ha YC, et al. Mortality after vertebral fracture in Korea: analysis of the National Claim Registry. Osteoporos Int 2012;23:1859-65.
31. Kimman M, Vathesatogkit P, Woodward M, Tai ES, Thumboo J, Yamwong S, et al. Validity of the Thai EQ-5D in an occupational population in Thailand. Qual Life Res 2013;22:1499-506.
32. Peasgood T, Herrmann K, Kanis JA, Brazier JE. An updated systematic review of Health State Utility

Values for osteoporosis related conditions. Osteoporos Int 2009;20:853-68.
33. Hiligsmann M, Ethgen O, Richy F, Reginster JY. Utility values associated with osteoporotic fracture: a systematic review of the literature. Calcif Tissue Int 2008;82:288-92.
34. Ekström W, Németh G, Samnegård E, Dalen N, Tidermark J. Quality of life after a subtrochanteric fracture: a prospective cohort study on 87 elderly patients. Injury 2009;40:371-6.
35. Miksad RA, Lai KC, Dodson TB, Woo SB, Treister NS, Akinyemi O, et al. Quality of life implications of bisphosphonate-associated osteonecrosis of the jaw. Oncologist 2011;16:121-32.
36. Hiligsmann M, Ben Sedrine W, Reginster JY. Cost-effectiveness of bazedoxifene compared with raloxifene in the treatment of postmenopausal osteoporotic women. J Bone Miner Res 2013;28:807-15.
37. Kim K, Svedbom A, Luo X, Sutradhar S, Kanis JA. Comparative cost-effectiveness of bazedoxifene and raloxifene in the treatment of postmenopausal osteoporosis in Europe, using the FRAX algorithm. Osteoporos Int 2014;25:325-37.
38. Drugs and Medical Supplies Information Center (DMSIC). Prices of drugs and medical devices. Nonthaburi, Thailand: DMSIC; 2001.
39. Riewpaiboon A. Standard cost lists for health technology assessment. Nonthaburi, Thailand: Health Intervention and Technology Assessment Program (HITAP); 2011.
40. Health Intervention and Technology Assessment: HITAP Ministry of Public Health. Standard cost list for health technology assessment [Internet]. 2010 [cited 2015 Jun 10]. Available from: http://costingmenu.hitap.net/.
41. Permsuwan U, Guntawongwan K, Buddhawongsa P. Handling time in economic evaluation studies. J Med Assoc Thai 2008;91 Suppl 2:S53-8.
42. Maleewong A, Kingkaew P, Teerawattananon Y. Economic evaluation on screening strategies and treatment options for postmenopausal osteoporosis [in Thai]. Nonthaburi, Thailand: Health Intervention and Technology Assessment Program (HITAP); 2007.
43. Gold DT, Silverman SL. Compliance with osteoporosis medications: Challenges for healthcare providers [Internet]. 2005 [cited 2017 Mar 8]. Available from: http://www.medscape.org/viewarticle/503214.