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ORIGINAL ARTICLE

Establishing and evaluating FRAX® probability thresholds in Taiwan

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KEYWORDS
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Background/purpose: The Taiwanese FRAX® calculator was launched in 2010. However, cost-effectiveness thresholds for the prescription of antiosteoporosis medications were not established. This study aims to establish and evaluate FRAX®-based probability thresholds in Taiwan.
Methods: Using previous data from Taiwan and literature, we determined cost-effectiveness thresholds for prevention of osteoporotic fractures by alendronate with a Markov model, as well as using two other translational approaches. Sensitivity analysis was applied using different alendronate prices. A clinical sample was used to test these Taiwan-specific thresholds by determining the percentages of high-risk patients who would be qualified for current National Health Insurance reimbursement.
Results: With the Markov model, the intervention threshold for hip fracture was 7% for women and 6% for men; for major osteoporotic fracture, it was 15% for women and 12.5% for men. Both translational approach models were cost effective only for certain age groups. However, if branded alendronate was reimbursed at 60% of the current price, they became cost effective in almost all age groups. This clinical screening study showed that the National Health Insurance Administration model identified the highest proportion (44%) of patients qualified for National Health Insurance reimbursements, followed by the Markov model (30%), and the United States model (22%).

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: Three FRAX®-based models of alendronate use were established in Taiwan to help optimize treatment strategies. The government is encouraged to incorporate FRAX®-based approaches into the reimbursement policy for antiosteoporosis medicines.

Introduction

The National Nutrition and Health Survey in Taiwan reported that 41.2% of women and 22.6% of men over 50 years of age have osteoporosis, based on the bone mineral density (BMD) data.[1] The hip fracture (HF) incidence in Taiwan was among the highest in the world.[2] However, a study showed that only 25% of female HF sufferers in Taiwan underwent a BMD test, 33% received antiosteoporosis medications (AOMs), and 60% had a diagnosis of osteoporosis.[3]

To reduce the osteoporosis care gap, efforts were made to improve awareness among patients and healthcare providers, including making osteoporosis a national priority,[4] publishing the Taiwan Osteoporosis Practice guideline[5] with nationwide educational courses for six types of healthcare professionals,[4] training courses for osteoporosis nursing specialists,[6] a nationwide osteoporosis education and screening program covering approximately 5000 adults,[7] press conferences on osteoporosis issues, etc.

In Taiwan, a gap exists between comprehensive osteoporosis care and the current payment standards from National Health Insurance Administration (NHIA) on BMD tests and AOMs. To be reimbursed for dual-energy X-ray absorptiometry, patients must have a fragility fracture or be a woman receiving AOMs. NHI does not reimburse strontium ranelate, and teriparatide is considered a second-line agent. For all other AOMs, reimbursement is granted if the patient experiences a fragility fracture of the hip or spine area and has a BMD T-score of ≤ -2.5, or experiences at least two fragility fractures of the hip or spine area and has a BMD T-score of < -1.[8] The rules are stricter than those suggested by domestic or international professional societies,[5,9,10] which emphasize treating patients with fragility fractures independent of BMD and considering the incorporation of algorithms based on the World Health Organization FRAX® fracture risk assessment tool.

The current NHI payment standards for AOMs were not based on cost-effectiveness analysis. Even though the Taiwanese FRAX® calculator was launched in 2010,[5,11] cost-effectiveness probability thresholds, against which AOM treatment has to be assessed, have not been established. The Taiwan Osteoporosis Practice guideline suggested adopting United States of America thresholds [3% for HF, and 20% for major osteoporotic fracture (MOF)], drawing on expert advice.[5] Empirical data showed that the 3% HF cutoff point may be very low in Taiwan, because nearly 90% of older adults ($\geq$65 years) were screened as being at high risk in one cohort, compared with 33% using the 20% MOF cutoff point.[12]

The objective of this study is therefore two-fold:

(1) To establish practical Taiwanese FRAX®-based intervention thresholds in Taiwan using the Markov model and translational approach

(2) To test Taiwan-specific FRAX® cutoff points in clinical samples and determine the optimal one, which can identify more high-risk patients for medication reimbursement

Materials and methods

The Markov model used epidemiological, cost, and quality of life data to estimate the fracture probability at which alendronate treatment became cost effective compared with no treatment. Two translational approach models were developed based on prior guidelines.[5,9,10] The "fracture model" adopted the assumption that individuals with a fracture probability equal to or greater than that of patients with a prior fragility fracture should be considered for treatment. From the Taiwanese NHI AOM payment standards, we developed the "NHIA model" assuming that patients with a fracture probability equal to or greater than that of patients with a prior fragility fracture and BMD T-score $= -2.5$ should be treated.[8]

Markov model approach

We constructed a Markov model to estimate the cost-effective MOF and HF intervention thresholds.[13] There are four health states in the model: well, fracture, post-fracture, and death. The cycle was set at 1 year and every patient was followed through the model until death.[14] When the parameters in the model were not available from Taiwan data, we applied estimates from other countries, indexing the data source, a method applied in a previous European osteoporosis burden report.[15]

HF Markov model

We used a mathematical formula to derive the 1-year probability of HF from the 10-year probabilities estimated from the Taiwanese FRAX® calculator. This number would vary in many simulations until cost-effectiveness cut points were found. All other parameters in Table 1 were obtained from Taiwan data,[5,16] except that transition probability from postfracture to death was derived from a Korean study.[17]

MOF Markov model

Fracture incidences were obtained from the Malmo study,[18] and the 2010 Taiwan population figures were used to estimate the proportion of each component of MOF (vertebra, hip, humerus, and forearm) in Taiwan. Taiwanese NHI data were used for calculating the probability of refracture.[19] However, the probability of transition from "fracture" to "death" was estimated from a US study.[20] As there were no

Table 1 Transition probabilities and input value for interventions in osteoporosis (hip fracture model).

From	To	Transition probabilities				Utility
(↓)	(→)	Well (*A*)	Fracture (*B*)	Postfracture (*C*)	Death (*D*)	
Well (*A*)		1 − *B* − D	0.0072	—	0.0063	1
Fracture (*B*)		—	0.0250	1 − *B* − *D*	0.1500$^{(F)}$/0.2200$^{(M)}$	0.66
Postfracture (*C*)		—	—	1 − *D*	0.0700	0.8
Death (*D*)		—	—	—	1	0

All parameters were used in accordance with the literature; sex-specific parameters are indicated as follows: F = female; M = male.

data on the transition from "postfracture" to "death," we assumed that these probabilities were 33% of those from fracture to death, based on group consensus (Table 2).

Utility value of HF

We used a formula to convert the Taiwanese HF Short-Form Health Survey (SF-36) scores[21] to EuroQoL group EQ-5D utility scores and calculated the utility of HF status as 0.66.[22] Utility of subsequent years after HF was estimated to be 0.8, based on a systematic review (Table 1).[23]

Utilities of MOF

Based on the utility data from previous studies,[23,24] and the proportion of each fracture type estimated earlier, we calculated the utility of different statuses (Table 3).

Efficacy of treatment

The efficacy of alendronate, after 5 years of use, in reducing fracture risk was derived from a systematic review as 0.62 (0.40–0.96).[25]

Cost assumptions

The cost was based on 2010 values, converted into US dollars (USD). Both effect and cost were discounted at an annual rate of 1.36%. The currency exchange rate between USD and new Taiwan dollar was set at 1:30.

Hip fracture

From a Taiwanese retrospective study, the cost of hospitalization following HF, including inpatient rehabilitation, was estimated to be $3243/year.[14] Our orthopedic ward data showed that nearly 25% of HF patients needed long-term care (LTC) after hospital discharge. Specifically, 11% were transferred to nursing homes (cost $1760/month), 13% of them lived at home with care provided by foreign-paid caregivers ($480/month), and 2% of them lived at home with domestic-paid care givers ($1242/month). The average annual outpatient costs (clinic visits and outpatient rehabilitation) of HF were $173, according to 2010 NHI statistics.

Major osteoporotic fracture

From an NHI database study, the cost of hospitalization for MOF were estimated to be $1533.[26] We assumed that only patients suffering from HF would require LTC. The annual cost of LTC for men and women after LTC was obtained from the proportion of each type of fracture in Table 3 and LTC costs for HF. The average annual outpatient costs for men and women were estimated to be $214 and $200, respectively, from NHI statistics.

Treatment with branded alendronate cost USD 450/year. The cost of BMD measurement by dual-energy X-ray absorptiometry at two sites was USD 40/year.

Willingness to pay

We set the willingness to pay thresholds for each additional Quality Adjusted Life Year (QALY) gained as twice the Taiwan gross domestic product, which was USD 42,628 in 2010.

Translational approach

To derive the intervention threshold from the two translational models, we fixed the body mass index as 25 kg/m^2 for men and 23 kg/m^2 for women. The 10-year probability of MOF and HF at 5-year intervals was derived from the Taiwan FRAX® calculators[5] and plotted as figures. In the

Table 2 Transition probabilities and input values for intervention in osteoporosis (major osteoporotic fracture model).

From	To	Transition probabilities				Utility
(↓)	(→)	Well (*A*)	Fracture (*B*)	Postfracture (*C*)	Death (*D*)	
Well (*A*)		1 − *B* − *D*	0.0152$^{(F)}$/0.0127$^{(M)}$	—	0.0063	1
Fracture (*B*)		—	0.0515	1 − *B* − *D*	0.0780$^{(F)}$/0.1130$^{(M)}$	0.75$^{(F)}$/0.7$^{(M)}$
Postfracture (*C*)		—	—	1 − *D*	0.0260$^{(F)}$/0.0380$^{(M)}$	0.91$^{(F)}$/0.93$^{(M)}$
Death (*D*)		—	—	—	1	0

All parameters were used in accordance with the literature; sex-specific parameters are indicated as follows: F = female; M = male.

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Table 3 Age-specific estimated number of the major osteoporotic fractures at different sites in male and female.

Type of fractures	Age (y)								Total (N, %)		Utility (fracture)	Fracture[a]	Utility (postfracture)	Postfracture[b]
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–89						
Male														
Vertebra	1723	921	1132	851	1491	1452	1759	1015	10,343	37	0.59	0.22	0.93	0.34
Proximal humerus	574	240	300	323	618	420	443	429	3349	12	0.65	0.08	1	0.12
Hip	769	658	356	710	890	1471	2865	1437	9156	33	0.7	0.23	0.8	0.26
Distal forearm	893	1168	701	991	266	411	488	119	5037	18	0.956	0.17	1	0.18
Total									27,885	100		0.70		0.91
Female														
Vertebra	1444	1262	1595	1691	2724	2917	2042	1448	15,125	24	0.59	0.14	0.93	0.23
Proximal humerus	1112	1015	663	1356	1344	1652	1027	989	9158	15	0.65	0.10	1	0.15
Hip	547	439	1021	1198	1933	3435	3788	3265	15,626	25	0.7	0.18	0.8	0.20
Distal forearm	3739	3643	2991	2662	3165	2710	2121	1224	22,256	36	0.956	0.34	1	0.36
Total									62,164	1.00		0.76		0.93

[a] The utility value for major osteoporotic fractures is calculated as percentages of type of fractures multiplied by utility for fracture.
[b] The utility value for major osteoporotic fractures is calculated as percentages of type of fractures multiplied by utility for postfracture.

fracture model, all patients were assumed to have a prior fragility fracture while other risk factors were negative, and BMD data were not available. In the NHIA model, all patients were assumed to have a prior fragility fracture and a BMD T-score of −2.5, while other risk factors were negative.

Sensitivity analysis

Sensitivity analysis was applied to determine whether different medication costs would affect the cost-effective intervention thresholds.

Empirical applications of three intervention thresholds

The cutoff points of FRAX®, determined by three different approaches, were used to recruit high-risk patients in clinics for osteoporosis assessment. This study was approved by the Board of Ethics of National Taiwan University, Taipei. Groups A, B, and C applied the US threshold, NHIA model threshold, and Markov model threshold, respectively. After enrollment, participating physicians confirmed the presence of hip or spine fractures using radiological tests, and prescribed BMD measurement according to NHI regulations and the Taiwan Osteoporosis Practice guideline.[5]

Results

Figure 1 shows the Markov model threshold at which alendronate treatment becomes cost effective. The HF intervention threshold was 7% for women and 6% for men, and the threshold for MOF was 15% for women and 12.5% for men.

Figure 2 shows a plot of the two translational approach models (fracture model and NHIA model) by sex, age, and fracture type (HF or MOF). In general, thresholds from the NHIA model were higher for younger people and lower for older ones, compared with those derived from the fracture model. With a price of USD 450, intervention became cost effective for women aged at least 60 years (NHIA model, MOF) and at least 65 years (fracture model, MOF). For men, the interventions were cost effective only between ages 55 years and 85 years (NHIA model, MOF), and between ages 75 years and 90 years (fracture model, MOF). For HF, treatment was cost effective for women aged over 65 years (NHIA model) and between 65 years and 85 years (fracture model), and for men aged between 55 years and 85 years (NHIA model) and over 75 years (fracture model).

In the sensitivity analysis, the intervention threshold did not decrease very much when the cost decreased from USD 450 to 390 (the current generic price in Taiwan). However, if the cost reduced to 60% of the current price (USD 270), the intervention threshold decreased to <5% for MOF and to about 2% for HF. Under these conditions, almost any FRAX®-based age-specific intervention thresholds from the two translational approaches was considered cost effective (see Figure 2).

In this clinic screening study, each group enrolled 75 patients. However, only 57 (Group A), 54 (Group B), and 58 (Group C) patients completed radiological tests and BMD measurements, which were required to determine whether they were eligible for NHI reimbursements. Overall, 33% of

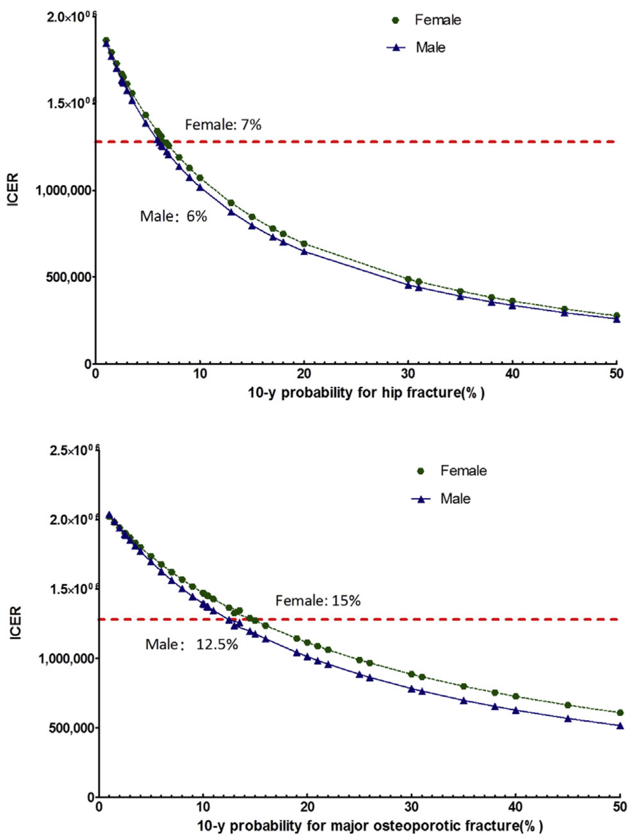

Figure 1 Ten-year probability of major osteoporotic and hip fracture by sex. The cost-effectiveness threshold was set at willingness to pay that is twice the Taiwan gross domestic product per capita. Cost effectiveness of alendronate was compared with no treatment as a function of 10-year probability of hip fracture and major osteoporotic fracture in Taiwan. The dashed lines show the fracture probabilities (hip fracture: 6% for men, 7% for women; major osteoporotic fracture: 12.5% for men, 15% for women) are cost effective in Taiwan for willingness to pay set at twice the gross domestic product per capita of Taiwan. ICER = incremental cost-effectiveness ratio.

the participants ($N = 57$) qualified for NHI reimbursement, 12% ($N = 20$) had fractures with a BMD T-score of >-2.5, 15% ($N = 26$) did not have fractures but were osteoporotic, and the rest (39%, $N = 66$) did not have fractures and were not osteoporotic. The thresholds determined by the NHIA model (Group B) identified the largest percentage of patients (44%) who were eligible for government-funded medications (Table 4).

Discussion

This study has shown that treatment of osteoporosis can be delivered with a FRAX®-based strategy, which incorporates sex- and fracture-specific thresholds. Among the three proposed models, the intervention thresholds derived from the current NHIA payment standards would detect most patients eligible for government-reimbursed AOMs. However, the cost-effectiveness threshold was very sensitive to drug price changes. If generic alendronate was reimbursed at 60% of the current price of branded drugs, it would be cost effective for nearly all age-specific thresholds derived by both models with a translational approach.

When applying the Markov model using Taiwanese data, our intervention threshold based on MOF was higher than that in Spain or Hong Kong,[27,28] but lower than that in Japan,[29] Switzerland,[30] or the USA.[10] Similarly, our intervention threshold for HF is lower than that in France but higher than the US threshold.[10,31] There may be several reasons for these differences. First, the risk of fracture varies in different countries and depends on the methodology used for epidemiological studies. Second, we included some indirect costs, including those for post-fracture care delivered by a nursing home or in the community. Third, the willingness to pay for healthcare also varies with the gross domestic product in different countries.

Several structural issues in the modeling analysis should be addressed. Length of treatment and adherence to drug therapy can be important determinants for prevention of osteoporotic fractures, but are usually omitted from published models. Similarly, adverse drug events will cause discontinuation of drug therapy and may increase the cost. Osteonecrosis of the jaw, gastrointestinal problems, and atypical subtrochanteric and diaphyseal femoral fractures should be considered in future modeling analyses.

Experts in Taiwan previously recommended drug therapy for those with a 10-year probability of MOF higher than 20% and HF higher than 3% in Taiwan, adopting from the US threshold, but no domestic cost-effectiveness analysis and data were available.[5] Our intervention thresholds from the Markov model were higher for HF but lower for MOF than the US models. When applying both thresholds to a community sample of close to 2000 people, our new threshold identified only about 67% of high-risk individuals who required referral for further evaluation.[32] Previous concerns about the oversensitivity of the 3% cutoff point can be partially prevented.[12] It also highlighted the importance of developing country-specific FRAX® thresholds.

We established age-specific thresholds using a translational approach. This approach was developed based on the guideline of the National Osteoporosis Guideline Group in the UK, with the assumption that individuals who have a higher probability of fracture than those who already had a fragility fracture should be eligible for drug therapy.[9] It has also been adopted by Ireland,[33] Turkey,[34] Switzerland,[30] and Belgium.[12,35] Besides the National Osteoporosis Guideline Group fracture model, we also derived a stricter NHIA model based on our reimbursement rules (previous fragility fracture and T-score $= -2.5$). The threshold of the NHIA model was higher than that of the fracture model for younger patients. However, it became lower with increasing age (roughly after the age of 70–80 years). As older adults tended to have a T-score of <-2.5, fixing BMD at that T-score reduced the risk of future fragility fractures.

In our clinical screening study, patients who were classified to be at high risk using the NHIA model were most likely to qualify for government-funded medication, followed by the threshold derived from the Markov model and then the US threshold. In Taiwan, payment standards of AOMs from the NHI are based only on the history of fragility

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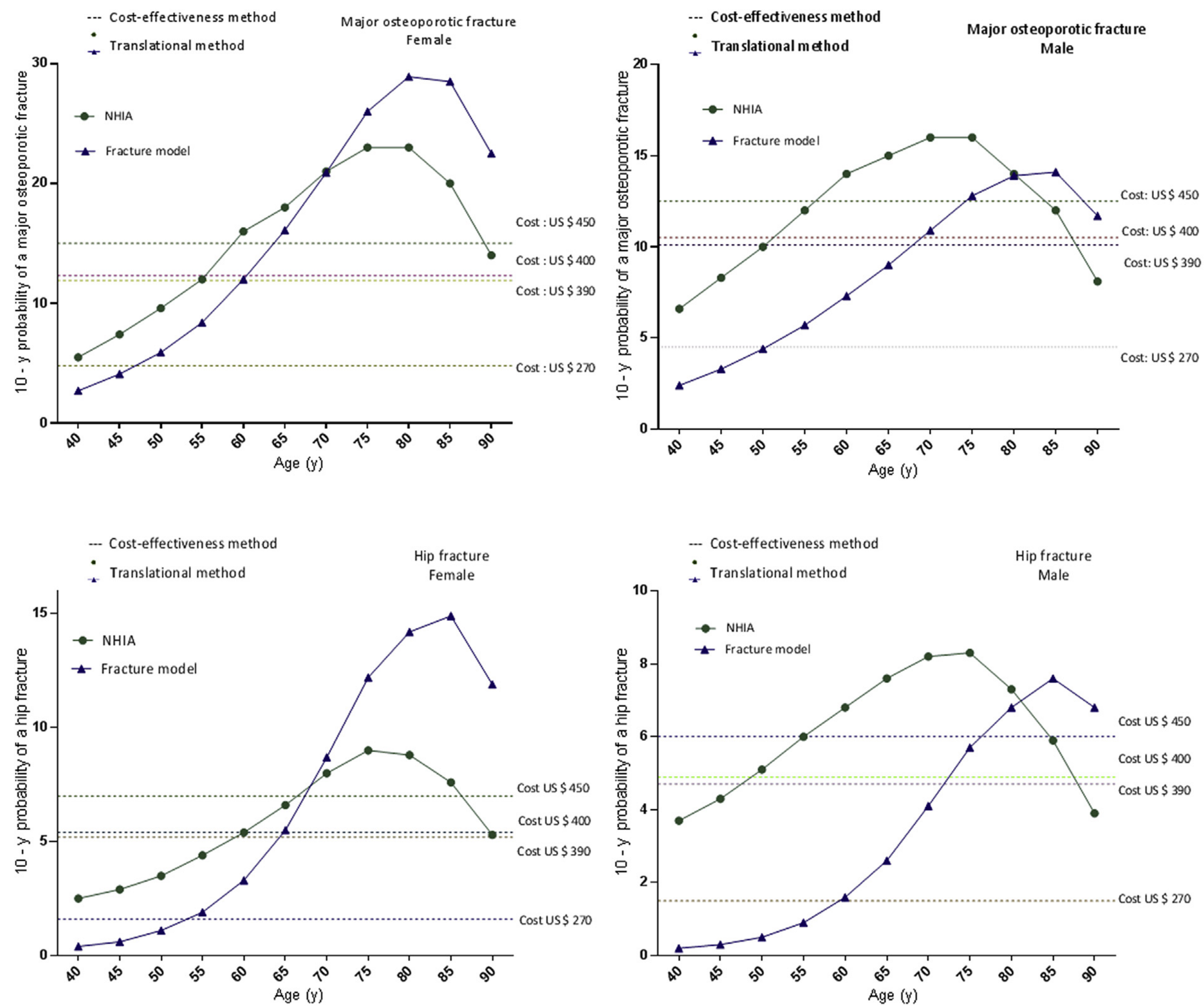

Figure 2 Ten-year probability of major osteoporotic and hip fracture by sex, age, and fracture type. Cost-effectiveness method and translational method are shown. Sex-specific and fracture-type-specific intervention thresholds for alendronate therapy were used to reduce fractures derived from translation approach. Fracture model: age-dependent risk derived from positive history of fragility fracture; NHIA model: age-dependent risk derived from a positive history of fragility fracture and the BMD T-score as −2.5. The dashed lines show the intervention thresholds with four levels of price of alendronate in the sensitivity analysis. BMD = bone mineral density; NHIA = National Health Insurance Administration.

Table 4 Clinical sample screening results from three FRAX®-based intervention thresholds.

	A		B		C		Total	
	N (%)							
	57	33.7%	54	32.0%	58	34.3%	169	100.0%
NHI reimbursable	13	22.8%	24	44.4%	20	34.5%	57	33.7%
fracture (+) & T > −2.5	5	8.8%	8	14.8%	7	12.1%	20	11.8%
fracture (−) & T ≤ −2.5	11	19.3%	8	14.8%	7	12.1%	26	15.4%
fracture (−) & T ≥ 2.5	28	49.1%	14	25.9%	24	41.4%	66	39.1%

Group A: United States of America intervention thresholds (20% for major osteoporotic fracture and 3% for hip fracture).
Group B: One-part fracture with T-score < −2.5 with translational approach.
Group C: Cost-effectiveness Taiwanese thresholds (major osteoporotic fracture: 12.5% for male and 15% for female; hip fracture: 6% for male and 7% for female).
NHI = National Health Insurance.

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fracture and BMD data, and do not consider FRAX® data. However, many rural areas may not have easy access to BMD assessments, and many fragility fracture cases are therefore ineligible for funding. The NHIA model-derived FRAX® threshold fitted most closely with the current NHI reimbursement rules and was also relatively difficult to reach. If future reimbursement policy incorporates this model, more high-risk patients can be treated. However, whether treating such patients can reduce fracture rates and improve patient outcomes should be examined in further research.

There are several limitations to our study. First, in the Markov model, some domestic fracture-related data are lacking; further research is needed to obtain such data to provide more accurate estimations. Second, extraskeletal effects of alendronate treatment, such as adverse drug events, were not considered in our analysis because their definite risk and cost were uncertain in Taiwan. Third, complex interactions between the effectiveness of continuous adherence to medication programs and the impact of this on cost were not included in the model. Fourth, we applied a fixed value of body mass index to the transitional model, but the probability of fracture will also vary with different body mass indexes. Lastly, new generic medications and revised payment standards may also influence the real situations in clinical practice.

The risk of HF in the Taiwanese population is the highest in the Asia-Pacific region. This FRAX®-based analysis has established fixed and age-specific intervention thresholds to improve the performance of FRAX®-based screening and clinical managements. Adaption of FRAX®-based medication reimbursements by NHI may allow treatment for more high-fracture-risk patients and improve osteoporosis care in Taiwan.

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