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ORIGINAL ARTICLE

Cost-effectiveness of FRAX®-based intervention thresholds for management of osteoporosis in Singaporean women

M. Chandran[1] · G. Ganesan[2] · K.B. Tan[2,3] · J.-Y. Reginster[4] · M. Hiligsmann[5]

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Abstract

Summary Cost-effectiveness analysis of FRAX® intervention thresholds (ITs) in Singaporean women > 50 years of age showed that generic alendronate was cost-effective at age-dependent major osteoporotic fracture (MOF) IT from the ages of 65 years for both full and real-world adherence whilst hip fracture (HF) ITs were cost-effective from the ages of 60 and 65 years. Alendronate was cost-effective irrespective of age only at fixed MOF IT of 14% and HF IT of 3.5%.

Introduction FRAX®-based intervention thresholds (ITs) were recently identified for osteoporosis management in Singapore. This study aimed to assess the cost-effectiveness of ITs in Singaporean women over the age of 50 years.

Methods A validated Markov microsimulation model was used to estimate the lifetime healthcare costs (SGD2019) per quality-adjusted life-years (QALY) of generic alendronate compared with no treatment. Cost-effectiveness of age-dependent FRAX® major osteoporotic fracture (MOF) and hip fracture (HF) ITs was explored. In addition, ITs that would lead to cost-effectiveness were computed. Fracture incidence and cost data were obtained from the Ministry of Health and a previously published Singaporean study. A cost-effectiveness threshold of SGD 62,500/QALY gained was used, based conservatively on 0.7 times the Singapore GDP per capita.

Results Generic alendronate was shown to be cost-effective at MOF ITs from the ages of 65 years, while HF ITs were cost-effective from the ages of 60 and 65 years, assuming full and real-world adherence, respectively. A 14% MOF and a 3.5% HF ITs were required for alendronate to be cost-effective above 50 years.

Conclusion This study suggests that the treatment of Singaporean women with alendronate is cost-effective at age-dependant FRAX® intervention thresholds at 65 years and older. Furthermore, identifying women at any age above 50 years with a 10-year risk of MOF or HF of 14% or 3.5% would lead to efficient use of resources. Cost-effective access to therapy for patients at high fracture probability based on FRAX® could contribute to reduce the growing burden of osteoporotic fractures in Singapore.

Keywords Alendronate · Cost-effectiveness analysis · FRAX · Intervention thresholds · Osteoporosis · Singapore

✉ M. Hiligsmann
m.hiligsmann@maastrichtuniversity.nl

M. Chandran
manju.chandran@singhealth.com.sg

[1] Osteoporosis and Bone Metabolism Unit, Department of Endocrinology, Singapore General Hospital, Singapore, Singapore

[2] Ministry of Health, Singapore, Singapore

[3] School of Public Health, National University of Singapore, Singapore, Singapore

[4] Center for Investigation in Bone and Articular Cartilage, University of Liege, Liège, Belgium

[5] Department of Health Services Research, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands

Introduction

The burden of osteoporosis and its dreaded consequence of fragility fractures is expected to increase worldwide as populations age. It is estimated that the number of individuals at risk for such fractures worldwide is going to increase two-fold from the 158 million it was in 2010 to 319 million in 2040 [1]. Nowhere is this grave projection going to hold more true than in Asia, which is home to 4.5 billion people. The population in Asia aged over 65 years is projected to more than quadruple by 2050, and to further grow by almost six-fold by the year 2100 [2]. It is predicted that by 2050, over half of the world's hip fractures will occur in Asia [3], and this will come at great cost; treating a single hip fracture represents approximately 19% of Asia

Pacific's regional per head gross domestic product (GDP) each year currently [4].

Singapore is an island nation in SE Asia. It is a developed economy with a total population of 5.4 million and a GDP per capita of SGD 89,000 (~USD62,900) [5]. Healthcare in Singapore is under the responsibility of the Singapore Government's Ministry of Health (MOH). Healthcare is kept affordable for Singaporeans through heavy government subsidies, supplemented by national insurance schemes and endowment funds such as Medisave, MediShield, Community Health Assist Scheme (CHAS), Medifund and ElderShield (https://www.moh.gov.sg/cost-financing/healthcare-schemes-subsidies).

Singapore too is facing the problem of increasing burden of osteoporosis and related fractures. In 2017, the incidence of osteoporotic fractures was estimated at 15,267 cases. By the year 2035, the number of incident fractures is projected to increase by 58% to 24,104 cases [6]. Increase in healthcare expenditure for osteoporosis in general is driven by the costs of treatment, making up 70% of the total costs [7]. In addition to the financial costs associated with the treatment of osteoporosis and osteoporotic fractures, the associated morbidity as well as the excess mortality associated with osteoporotic fractures have a major impact on quality of life, both immediately afterwards and in the long term [8, 9]. Singapore also has one of the most rapidly ageing populations in the Asia Pacific [10]. As a consequence, without targeted interventions, the economic burden of fragility fractures to the Singapore healthcare system is predicted to substantially increase in the coming decades [6]. The overall costs (including both direct and indirect) of incident fractures in Singapore were estimated at S$ 183.5 million in 2017, and it is forecasted to increase by 57.8% to S$ 289.6 million by 2035 [6].

Many regulatory agencies, governmental health bodies and osteoporosis societies worldwide have adopted intervention thresholds (ITs) based on densitometric T-scores. However, prospective epidemiological studies have shown that most osteoporotic fractures occur in individuals with a BMD T-score in the osteopenic or even normal range [11, 12]. Various fracture risk assessment tools that take into account a constellation of risk factors other than just BMD alone exist [13]. A strategy that incorporates clinical risk factors into the decision-making process may help identify patients who would have been otherwise missed and precluded from being offered treatment as well as serve to avoid treatment in low-risk individuals. The FRAX ® algorithm (http://www.shef.ac.uk/FRAX) is one such risk assessment tool. It was calibrated for Singapore-specific fracture risk and mortality rates in 2010. ITs based upon probabilities of major osteoporotic (MOF) and hip fractures (HF) using the FRAX® algorithm have been implemented in several countries [14]. Due to the vast heterogeneity in epidemiologic and economic characteristics between countries, intervention thresholds should be country specific. In the USA, a HF IT of 3% and a MOF IT of 20% were deemed as cost-effective [15], while MOF ITs of 7% and 15% were found to be cost-effective in the UK [16] and Switzerland, respectively [17]. Cost-effectiveness analyses can be especially useful to assess and guarantee the economic value of ITs in osteoporosis and have employed two different approaches. One way is to determine the cost-effectiveness of existing ITs derived by other methods; the other is to determine MOF or HF probabilities at which intervention becomes cost-effective [17].

FRAX ®-based age-dependent mean-weighted MOF and HF ITs for post-menopausal Singaporean women were identified in 2018 [18]. These ITs were derived using a translational approach which is similar to that employed by the National Osteoporosis Guideline Group (NOGG) in the UK [16, 19]. These intervention thresholds are age-specific and based on the principle that treatment is indicated for a woman if her probabilities for MOF and/or HF exceed that of a similar age woman with a history of a fragility fracture. However, economic evaluation of these thresholds and whether they are cost-effective have not been performed. Assessment of the economic value of such intervention thresholds is important for policymakers to know before recommendations for their implementation can be made.

Amongst the anti-osteoporosis agents currently available, the amino-bisphosphonates are the most widely used since they have demonstrated significant anti-fracture efficacy at vertebral, non-vertebral and hip sites [20]. Alendronate was the first commercially marketed amino-bisphosphonate for the treatment of osteoporosis and, consequently, the first to lose its patent and be provided to the market as a generic drug. After its introduction, generic alendronate was widely adopted by all payees in Singapore, owing to its lower price compared with branded alendronate and is the most frequently prescribed anti-osteoporosis agent in Singapore [6].

The purpose of our study was thus to explore the cost-effectiveness of using generic alendronate compared with no treatment at different age-dependent FRAX® MOF and HF ITs in Singaporean women older than 50 years of age. We also aimed to determine the FRAX® calculated fracture probabilities at which therapeutic intervention with generic alendronate would become cost-effective in this population.

Methods

Model structure

A previously validated Markov microsimulation model [21, 22] was adapted to the Singaporean healthcare context to estimate the cost-effectiveness of alendronate under different

ITs. Subjects initiate the model in the state "no fracture" and can transit between fracture health states (hip, vertebral, wrist and other fracture), their corresponding post-fracture states and death, along a 6-month cycle. Quality-adjusted life-years (QALY) that take into consideration quality of life as well as life-years was used to measure health effects. The Markov model captures both healthcare costs and QALY over a lifetime. The discount rates of 3% used for costs and QALY are in line with the Agency for Care Effectiveness (ACE) guidelines for economic evaluation in Singapore [23]. The model was built using TreeAge Pro 2020 (TreeAge Pro Inc., Williamston, MA, USA) and adheres to the recent recommendations for the conduct of economic evaluations in osteoporosis [24]. Figure 1 presents the model structure, and data used for the model are shown in Table 1.

Fracture risk

Baseline age-specific hip fracture, wrist fracture and other fracture (humerus, forearm and femur) incidences for the years 2015–2017 were obtained from the Singapore Ministry of Health (MOH) Central Claims Processing System that covers all admissions and emergency room visits to public and private acute and community hospitals in Singapore. For hip fractures, data on inpatient admissions of Singapore residents with a discharge diagnosis of fracture involving the neck or the intracapsular, upper epiphyseal, subcapital, cervical, trochanteric, or subtrochanteric areas were used. This data which had been retrieved using the following diagnostic codes from the International Classification of Disease, Tenth revision, Australian version (ICD-10-AM): S7200, S7201-S7211, S722-S723, was published in 2018 [25].

The MOH database captures only severe vertebral fractures that require hospitalization and/or emergency room visits and might not have captured less severe vertebral fractures. Therefore, the ratio between vertebral and hip fracture incidence obtained from a study by Chandran et al. was applied to derive vertebral fracture incidence [6].

Initial fracture probabilities were then adjusted to reflect the fracture risk in the target population in comparison with that of the general population. To determine 10-year MOF and HF probabilities, each age-specific fracture probability (i.e. hip, wrist, vertebral and other) was multiplied by a relative risk (RR). This method has been described previously by Tosteson et al. [15]. In the original FRAX® MOF probabilities derivation, only hip, clinical vertebral, wrist and humerus fracture are included. Since "other" fractures in our data set included fractures at other sites in addition to humerus fractures, when estimating the RR needed to get a

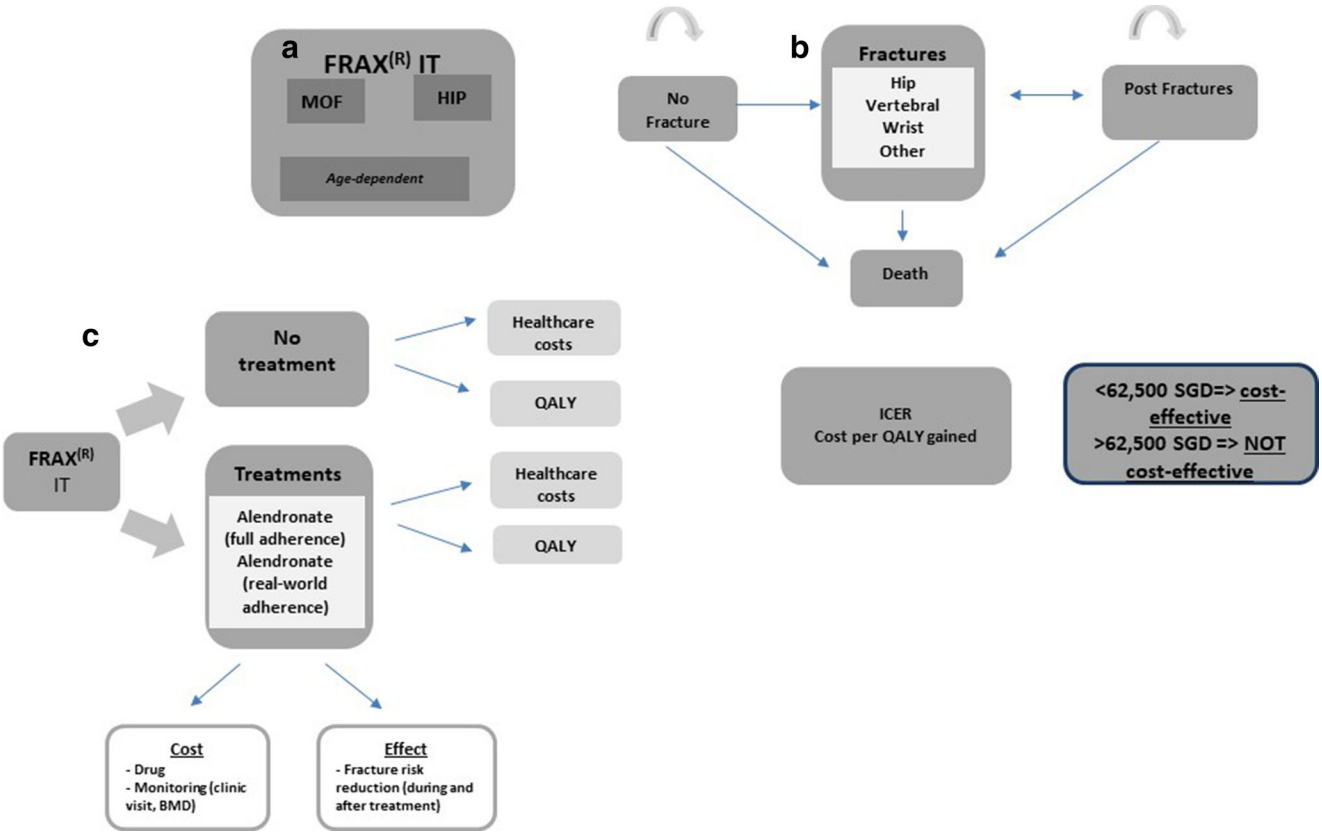

Fig. 1 **a** FRAX® intervention thresholds tested in the model. **b** Graphical representation of the model. **c** Results and interpretation

Table 1 Incidence of fractures, costs, utilities and treatment effects used in the model

Parameter	
Incidence of fracture (rate/100)	
Hip	0.011 (50–54 y), 0.027 (55–59 y), 0.070 (60–64 y), 0.157 (65–69 y), 0.334 (70–74 y), 0.694 (75–79 y), 1.116 (80–84 y), 1.973 (85+)
Vertebral	0.013 (50–54 y), 0.032 (55–59 y), 0.083 (60–64 y), 0.186 (65–69 y), 0.396 (70–74 y), 0.825 (75–79 y), 1.323 (80–84 y), 2.338 (85+)
Wrist	0.056 (50–54 y), 0.105 (55–59 y), 0.151 (60–64 y), 0.179 (65–69 y), 0.193 (70–74 y), 0.258 (75–79 y), 0.324 (80–84 y), 0.342 (85+), 0.072 (50–54 y), 0.137 (55–59 y), 0.171 (60–64 y), 0.240 (65–69 y), 0.366 (70–74 y), 0.520 (75–79 y), 0.670 (80–84 y), 0.913 (85+)
Other	0.072 (50–54 y), 0.137 (55–59 y), 0.171 (60–64 y), 0.240 (65–69 y), 0.366 (70–74 y), 0.520 (75–79 y), 0.670 (80–84 y), 0.913 (85+)
Fracture costs (SGD2019)	
Hip, first 6 months	28,823
Hip, yearly long term	2500
Vertebral, first 6 months	18,937
Wrist, first 6 months	15,718
Other, first 6 months	17,924
Health state utility values	
General population	0.837 (50–59 y), 0.811 (60–69 y), 0.771 (70–79 y), 0.724 (80+)
Hip (1st year/subsequent year)	0.55 (0.53–0.57)/0.86 (0.84–0.89)
Vertebral (1st year/subsequent year)	0.68 (0.65–0.70)/0.85 (0.82–0.87)
Wrist (1st year/subsequent year)	0.83 (0.82–0.84)/0.99 (0.97–1.00)
Other (1st year/subsequent year)	0.91 (0.88–0.94)/0.99 (0.97–1.00)
Treatment effects (RR)	Alendronate
Hip	0.67
Vertebral	0.45
Wrist	0.81
Other	0.81
Drug costs (per year)	
Clinic visit	SGD 200
BMD measurement	SGD 180

RR relative risk

pre-defined MOF IT, we only considered humerus fractures in the calculation; the latter constituted 29.5% of "other fractures" in our data set.

Fracture risk was also adjusted in the model when a new fracture occurred during the simulation process, as has been previously done [21]. The model incorporates, during the simulation process, an increased risk of subsequent fracture for individuals who have a prior fracture at the same location. These increased relative risks are 4.4 (3.6, 5.4), 2.3 (1.5, 3.7), 3.3 (2.0, 5.3) and 1.9 (1.7, 2.2) for vertebral, hip, wrist and other fractures, respectively [26]. As the underlying risk of fracture may contain prior fracture at other sites and a multiplicative hypothesis cannot be supported at this time, we conservatively did not model an increased risk of subsequent fractures at sites different from that of the prior fracture(s), except in the year following the fracture. However, an increased relative risk of 2.3 (2.0, 2.8) is modelled for a hip fracture after a vertebral fracture, because this effect is largely supported by the literature [26]. Since the increased risk after a fracture is shown to decrease with increasing age, we reduced the RR by 10% per each decade above the age of 70 years [27, 28]. Subsequent fractures of the same type are assumed to have no additional effect because of the absence of data providing an accurate relationship between the number of prior fractures and an increased risk.

Baseline mortality data for the general women population was derived from the Singapore's Department of Statistics [29]. An increased mortality after hip fracture and vertebral fracture was assumed in line with previous studies [22]. Because excess mortality may also be attributable to

comorbidities, we assumed that only 25% of the excess mortality following fractures was attributable to the fractures themselves [30].

Fracture cost

The healthcare payer perspective was used for the cost estimation in line with the ACE guidelines for health economic evaluation in Singapore [23]. All costs were obtained from administrative data of the Ministry of Health, were expressed in SGD 2019 and adjusted using the current inflation rates. Short-term fracture costs included that for admission for the index fracture, emergency department costs and 6-month post-fracture care such as post-operative follow-up and community hospital costs incurred after discharge. Long-term costs for hip fracture included outpatient visits and nursing home costs. Nursing home placement rates post-hip fracture are low in Singapore with only 2.7% of women aged 65 and older per year admitted to such long-term care. The direct cost of hip fracture was estimated to be SGD 28,823. The costs of wrist and other fractures were also derived from the same database and estimated at SGD 15,718 and SGD 17,924, respectively. The cost for vertebral fractures was derived from Chandran et al. [6], and was estimated to be SGD 5312. Hip fractures were further associated with yearly long-term costs of SGD 2,500.

Utility values

In the absence of utility data for osteoporosis and osteoporotic fractures in Singapore, the effects of fractures on utility were derived from the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS) study [31]. ICUROS is a large study that assessed the quality of life post-fracture of patients from 11 countries and included 2808 patients. Since fractures other than hip, clinical vertebral and wrist were not included in the ICUROS study, we used estimates from a previous systematic review [32]. Baseline utility data were assumed to be similar to that of US women [33]. Additional utility loss following multiple fractures was also modelled using previous studies [21].

Strategies

Three treatment strategies over a 5-year period were simulated in the model: (i) alendronate with full adherence, (ii) alendronate with real-world adherence levels and (iii) no treatment. To maintain comparability between the current analysis and other studies that have assumed full adherence [34] with oral bisphosphonates, an initial strategy assuming full adherence was conducted. An earlier published study of ours had demonstrated excellent compliance rates to oral bisphosphonate therapy at 2 years amongst patients recruited into the nationwide secondary fracture prevention program in Singapore- OPTIMAL [35]. However, the situation is quite different in ordinary clinical practice with adherence to these agents reported to be suboptimal. This can have substantial consequences on cost-effectiveness [36], and therefore, a strategy assuming real-world adherence with alendronate was also assessed.

To determine the effect of alendronate on fracture risk, a recent network meta-analysis of pooled data for oral bisphosphonates conducted by the National Institute for Clinical Excellence in the UK was used [37]. This study suggests that oral bisphosphonates have a RR of 0.45 for vertebral fracture, a RR of 0.67 for hip fracture and an RR of 0.81 for wrist fracture and other fractures. After stopping alendronate, a linear decrease of the effects for a duration similar to the duration of therapy was assumed, in line with previous economic analyses of oral bisphosphonates [38] and clinical data [39].

To model a real-life scenario with alendronate, we used a similar methodology as that has been used previously that focused on medication persistence. Persistence has been shown to have the most influence on cost-effectiveness [40]. Real-world persistence data with oral bisphosphonates were derived from a recent systematic review suggesting that the mean persistence was 53% at 6 months, 46% at 1 year, 37% at 2 years and 31% at 3 years [41]. For patients who stopped taking their therapy, the treatment cost immediately stopped and the offset (assumed as a period similar to duration on therapy) period started at the same time. For those who discontinued therapy within 6 months, no treatment effect was assumed, since at least 6 months of treatment is necessary to reduce the risk of fractures.

Treatment costs including medication costs, cost of follow-up visits at outpatient clinics, and bone density measurement were obtained from pre-subsidy charges at public healthcare institutions from the Ministry of Health. In accordance with the usual clinical practice in Singapore, it was assumed that there would be 2 clinic visits in the first 1 year followed by 1 visit annually in subsequent years. Each clinic visit costs SGD 200. The cost of one BMD measurement (SGD 180) using axial DXA scanning per year was also included. Gastrointestinal adverse events observed with oral bisphosphonates have been noted to be generally mild and transient in our patients. The cost and quality of life impact of these adverse events would thus only be minor and not affect the results and were therefore not included in the analysis.

Analyses

Under this microsimulation model, a total of 1,000,000 of individual patient simulations were run for each analysis. Total healthcare costs and accumulated QALYs were

estimated for each treatment strategy. The incremental cost-effectiveness ratio (ICER) was then calculated for alendronate considering both full and real-world adherence compared with no treatment. ICER was defined as the difference between the active treatment and the comparator treatment in terms of total costs (expressed in SGD2019) divided by the difference between them in terms of QALYs. If the ICER is above a cost-effectiveness threshold (representing the decision makers' willingness to pay), then the cost is too high for the benefits, and the intervention is not considered as cost-effective at the selected IT.

There is no agreed willingness-to-pay threshold for adopting health technologies in Singapore. While the threshold of one GDP per capita as recommended by the World Health Organization (WHO) is commonly used in publications [42], countries with explicit thresholds have adopted more stringent levels, with the thresholds of £20,000/QALY and £30,000/QALY used by UK's Health Technology Agency corresponding to 0.70 and 1.04 times of UK's GDP in 2015. For our base analysis, we used a stringent threshold with SGD 62,500 equivalent to 0.7 of Singapore's GDP per capita of SGD 89,000 in 2019.

FRAX®-based intervention thresholds

In this current economic study, the cost (SGD) per QALY gained of generic alendronate compared with no treatment at different FRAX®-based age-dependent mean-weighted MOF and HF ITs obtained through the translational approach described earlier [18] was assessed. At each age and at the corresponding FRAX® MOF and HF IT values, the ICER was derived. In addition, we also determined the MOF and HF ITs at which treatment with generic alendronate compared with no treatment became cost-effective using a cost-effectiveness threshold of SGD 62,500.

Sensitivity analysis

Two sensitivity analyses were conducted, one with a less stringent cost-effectiveness threshold (i.e. SGD 89,000 corresponding to 1× GDP) and one assuming reduced monitoring with only one BMD measurement every 2 years instead of annually and only one visit per year.

Results

The cost (SGD) per QALY gained of alendronate compared with no treatment at different age-dependent MOF intervention thresholds in Singapore is shown in Table 2. Alendronate was shown to be cost-effective (i.e. ICER < SGD62,500 per QALY gained) at MOF IT from the age of 65 years, at both full adherence and real-world adherence levels. The cost (SGD) per QALY gained of alendronate compared with no treatment at different age-dependent hip fracture intervention thresholds in Singapore is shown in Table 2. Alendronate was cost-effective at HF IT from the ages of 60 and 65 years, assuming full adherence and real-world adherence levels, respectively. Intervention with alendronate (in a scenario involving full adherence) was cost-saving at ages 80 years and above.

Assuming real-world adherence for alendronate (Fig. 2), a MOF IT of 14% resulted in a cost per QALY gained below cost-effectiveness threshold of SGD 62,500 at all ages.

Assuming real-world adherence for alendronate (Fig. 3), a HF IT of 3.5% resulted in a cost per QALY gained below cost-effectiveness threshold of SGD 62,500 at all ages.

On the sensitivity analysis, it was found that the cost per QALY gained decreased, with lesser frequency of clinic visits and DXA scanning. Under this scenario, alendronate was cost-effective (i.e. ICER < SGD 62,500 per QALY gained) at MOF ITs from the ages of 60 and 65 years, assuming full adherence and real-world adherence levels, respectively (Table 3). For HF IT, alendronate was cost-effective from the age of 60 years in both adherence scenarios. Cost-saving was seen for HF ITs under both full and real-world adherence scenarios from the age of 75 years and for full adherence for MOF ITs from the age of 80 years (Table 3). Under this sensitivity analysis, a MOF IT of 12% and a HF IT of 3% lead to cost-effectiveness results for generic alendronate for the entire age range.

Assuming a threshold of SGD 89,000 per QALY gained (i.e. 1× GDP), age-dependant MOF and HIP ITs were cost-effective from the age of 60 to 65 years, respectively, with both full and real-world adherence. Using this cost-effectiveness threshold, generic alendronate was cost-effective with at a MOF IT of 13% and a Hip fracture IT of 3% for the entire age range.

Discussion

Our study shows that interventions aimed at reducing fracture risk in osteoporotic patients can be implemented in a cost-effective manner in Singaporean women at high risk of fracture, at FRAX® MOF and HF ITs of 14% and 3.5% respectively; i.e. treating with generic alendronate can be considered as cost-effective in Singapore when the 10-year probability of a MOF equals or exceeds 14% or when the similar probability of a HF exceeds 3.5% and above. On the other hand, using the translational approach, it appears that prescription of generic alendronate for Singaporean women is cost-effective at age-dependent ITs from the age of 65 years for both MOF and HF assuming real-world adherence and from 65 years for MOF and 60 years for HF assuming full adherence.

Table 2 Incremental cost-effectiveness ratio (expressed in costs (SGD) per QALY gained) of alendronate compared with no treatment at different major osteoporotic fracture intervention thresholds (MOF ITs) and hip fracture intervention thresholds (HF ITs) in Singapore

2(a)Years -MOF ITs	**Alendronate Full Adherence Costs (SGD) per QALY gained**	**Alendronate Real World Adherence Costs (SGD) per QALY gained**
50 years-2.86%	307,248	392,553
55 years-4.84%	175,170	338,025
60 years-8.09%	63,960	113,431
65 years-13.01%	30,976	57,251
70 years-18.37%	13,231	27,396
75 years-23.98%	3,753	11,745
80 years-26.07%	1,679	10,117
2(b) Years -HF ITs	**Alendronate Full Adherence Costs (SGD) per QALY gained**	**Alendronate Real World Adherence Costs (SGD) per QALY gained**
50 years-0.61%	154,635	252,565
55 year-1.16%	92,689	162,051
60 years-2.32%	46,876	69,560
65 years-4.27%	23,910	43,911
70 years-6.79%	10,237	22,322
75 years-9.46%	957	8,456
80 years-12.65%	Cost-saving	3,858

Colour code: white, cost-saving (therapy costs lower than saved fracture costs due to drug effectiveness); light grey, below cost-effectiveness threshold (SD 62,500/QALY gained); dark grey: not cost-effective (i.e. above cost-effectiveness threshold)

The exchange rate between SGD and USD is 1 USD equals 0.71 SGD as of April 30, 2020

The MOF fixed IT of 14% in women over the age of 50, obtained from the cost-effectiveness approach in our study, was approximately the same as was seen in Switzerland [17] of 13.8%. Our IT for HF of 3.5% was lower than the 7% noted in a study from Taiwan [43] and slightly higher than the 3% denoted as cost-effective in the USA [15]. The reasons for these differences could include the variations in the risk of osteoporotic fractures between countries, the methodology used for epidemiological studies on fractures and for cost-effectiveness analyses and in WTP which varies with the GDP in different countries.

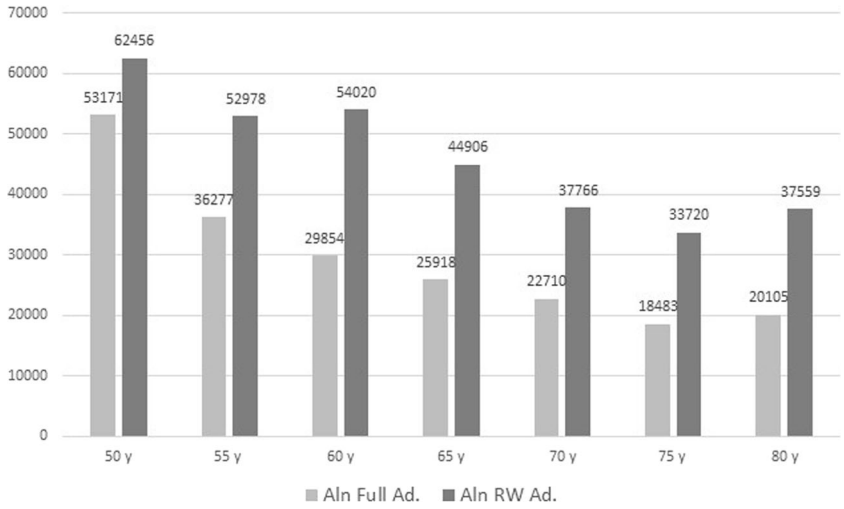

Fig. 2 Cost per QALY gained of full and real-world adherence with alendronate compared to no treatment in women with a 14% risk of MOF at all ages

Legend: Aln: Alendronate; Ad: Adherence; RW: Real World

The National Institute for Health and Care Excellence (NICE) of UK's updated multiple technology appraisal (MTA) on bisphosphonate use in osteoporosis concluded that generic oral bisphosphonates were cost-effective for people with even a 1% major osteoporotic fracture risk [37]. The recommendations made in this appraisal have been criticized for their clinical inappropriateness [44] and contradict that found in our study, in which cost-effectiveness was seen only at much higher intervention thresholds. This is not surprising given that the total costs of treatment including costs of clinic visits and DXA scanning are much higher in Singapore than in the UK.

Branded alendronate was used for the cost-effectiveness analysis study in Switzerland [17] unlike in ours where the cost-effectiveness of generic alendronate was explored. However, age-dependent intervention thresholds were cost-effective only at older ages in both countries with the threshold being cost-effective from the age of 60 in Swiss women and from the age of 65 in Singapore. This is likely because the *total* costs of treatment are likely similar in our countries with the cost of BMD monitoring and clinic visits being very high in Singapore. This likely outweighs the financial benefit of generic alendronate.

In the sensitivity analysis in our study, when less frequent clinic visits and DXA scanning were factored in, the MOF and HF ITs decreased, but only slightly to 12% and 3%. A less stringent cost-effectiveness threshold of SGD 89,000 (the GDP per capita of Singapore) also lowered the cost-effective MOF and HF ITs slightly to 13% and 3%, respectively.

Our findings pertain to the use of only generic alendronate. Generic alendronate was chosen for our study as it is the most frequently prescribed anti-osteoporosis agent in Singapore currently. It is possible that more effective, albeit costlier agents may prevent more fractures in higher risk people. This might result in more cost-savings and a net increase

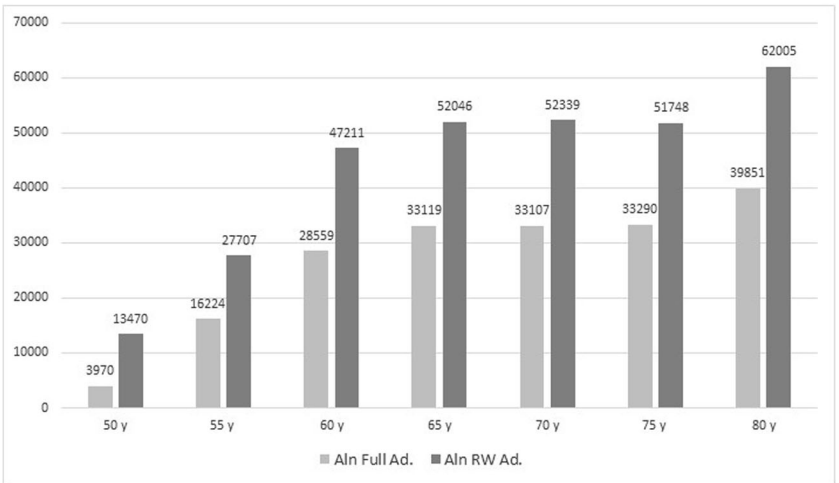

Fig. 3 Cost per QALLY gained of full and real-world adherence with alendronate compared to no treatment in women with a 3.5% risk of HFP at all ages

Legend: Aln: Alendronate; Ad: Adherence; RW: Real World

Table 3 Sensitivity analysis (lower monitoring costs) on the incremental cost-effectiveness ratio (expressed in costs (SGD) per QALY gained) of alendronate compared with no treatment at different major osteoporotic fracture (MOF) and hip fracture (HF) intervention thresholds (ITs) in Singapore

	MOF ITs		HF ITs	
Years	**Alendronate Full Adherence Costs (SGD) per QALY gained**	**Alendronate Real-World Adherence Costs (SGD) per QALY gained**	**Alendronate Full Adherence Costs (SGD) per QALY gained**	**Alendronate Real-World Adherence Costs (SGD) per QALY gained**
50 years	240,227	260,906	118,110	162,417
55 years	134,364	219,248	69,567	102,333
60 years	47, 324	70,263	33,819	42,207
65 years	20,677	31,881	15,571	23,918
70 years	6,771	12,145	4,468	9,039
75 years	3,753	11,745	Cost-saving	Cost-saving
80 years	Cost-saving	2,583	Cost-saving	Cost-saving

Colour code: white, cost-saving (therapy costs lower than saved fracture costs due to drug effectiveness); light grey, below cost-effectiveness threshold (SD 62,500/QALY gained); dark grey, not cost-effective (i.e. above cost-effectiveness threshold)

The exchange rate between SGD and USD is 1 USD equals 0.71 SGD as of April 30, 2020

in QALYs than what was seen with the current scenario with generic alendronate. Other antiosteoporosis medications, such as branded alendronate, risedronate, raloxifene, zoledronic acid (given as an annual intravenous infusion), teriparatide (given as a daily subcutaneous injection) and denosumab (administered as a subcutaneous injection once in 6 months), are also available in Singapore. Though direct head-to-head comparisons are lacking, there exists some data to suggest that agents such as Zoledronic acid and Denosumab may be more efficacious at reducing fracture risk than alendronate [37]. From a purely economic perspective, the cost-effectiveness of each treatment would differ, and each medication would have a different cost-effective threshold to intervene with at. However, to deprive a patient of a certain medication unless she attains the threshold that is needed for her to be on that medication would be ethically wrong, and deriving and implementing intervention thresholds for every single medication is impractical. It is to avoid this problem and because treatments with other medications were found to be cost-effective at their country's currently acceptable WTP thresholds that the National Osteoporosis Guideline Group in the UK has also recommended utilizing the same intervention thresholds for these other medications as is used for generic alendronate despite the formers' higher costs [19, 45].

Access to DXA is relatively easy in Singapore with 16.9 DXA machines available per 1 million population [46], and thresholds to identify who to send for bone densitometry using the Osteoporosis Self-Assessment tool for Asians (OSTA) and/or FRAX® have recently been suggested for Singapore [47]. The recently published Singapore Osteoporosis Guidance for primary care, recommends pharmacological intervention in patients with a BMD T-score at any axial site of ≤ -2.5 and/or a history of a fragility fracture [48]. FRAX®-based ITs can be considered as an *addition* to these already accepted intervention thresholds. If cost-effectiveness is the sole desired outcome, then fixed MOF and HF ITs of 14 and 3.5% should be recommended in all Singaporean women aged 50 and above. When these ITs were applied on a cohort of 1056 post-menopausal community dwelling Singaporean women recruited for an assessment threshold study [47], it was seen that 17% of women above the age of 50 would qualify for treatment. An alternative approach that would be still cost-effective would be to recommend age-dependent thresholds in women 65 years and above, and in those below the age of 65 years, MOF and HF ITs of 14% and 3.5%, respectively. With this latter strategy, approximately 27% of women 65 years and older and 6% of women below the age of 65 years would be eligible for treatment. This approach could

also potentially avoid unnecessary treatment of younger individuals who are likely to be at lower fracture risk while directing treatment to older individuals who are at higher risk.

Whether to employ a completely FRAX®-based intervention threshold approach or to consider them as an addition to existing intervention strategies in Singapore is a matter that should be gravely discussed at a healthcare policy decision-making level before implementation.

It should also be kept in mind that ITs based on cost-effectiveness analysis should not be the sole modality employed for decision-making in osteoporosis care. They should be used in conjunction with other clinical parameters to afford the best and most appropriate individualized care for patients.

Our study has some limitations. Some data such as mortality rates after hip and vertebral fractures, utility data for osteoporosis and osteoporotic fractures and data on persistence with oral bisphosphonate therapy were lacking in Singapore, and therefore, they had to be obtained from studies done elsewhere as described earlier. Another potential limitation of the study is that we did not adjust mortality according to baseline fracture probability and different combinations of risk factors of FRAX®. The risk factor combinations that yield the same fracture probability may yield different mortality effects.

Generic alendronate may be associated with poorer adherence [49] than the branded formulation. However, this is unlikely to be an issue with our study since we adopted a very cautious approach by estimating that only 53%, 46%, 37%, and 31% of patients would be persistent to the medication at 6 months, 1 year, 2 years, and 3 years, respectively [40], and by including this real-world adherence in our modelling strategy. While not including relatively common side effects of bisphosphonate therapy in our analysis might be considered as a limitation, it has to be noted that most economic evaluations of oral bisphosphonates have not included side effects, considering they are transient and do not affect quality of life and costs substantially. A few studies such as the NICE appraisal [37] have incorporated gastrointestinal disorders associated with oral bisphosphonates in cost-effective analysis by including additional general practitioner (GP) consultations and the use of a proton pump inhibitor and this was found to be connected with additional costs and a utility loss of 1 month. However, the inclusion of side effects has been shown to only have a very modest effect on cost-effectiveness using the lifetime horizon [50].

Our study has several advantages. It is the first such study from the only advanced economy in Southeast Asia [51]. We explored the cost-effectiveness of both age-dependent FRAX® ITs that have been previously obtained using a translational approach as well as derived fixed ITs that are cost-effective at all age ranges between 50 and 80 years. Our study considered real-world adherence with oral bisphosphonate therapy while determining the cost-effectiveness of ITs. Data on fracture incidences and osteoporosis and fracture care costs were obtained from the Singapore Ministry of Health's comprehensive databases. This ensured that the data used was nationally representative, credible and accurate. Ours is also the first such study on cost-effectiveness of osteoporosis care that had the close input of the Ministry of Health of a country. Such a collaboration between healthcare providers and policymakers enables the co-creation of solutions for problems in osteoporosis management. Having done the analysis using FRAX®-based fracture probabilities which is a very granular approach to estimate fracture risk incorporating several risk factors provides a more realistic reflection of everyday clinical practice.

Conclusion

Treatment of women with the most frequently prescribed anti-osteoporosis agent in Singapore, namely, generic alendronate, is cost-effective at age-dependant FRAX® intervention thresholds at 65 years and older. Furthermore, identifying women at any age above 50 years with a 10-year risk of MOF or HF of 14% or 3.5%, respectively, would lead to efficient use of healthcare resources. Cost-effective access to therapy for elderly patients at high fracture probability based on FRAX® could contribute to reduce the growing burden of osteoporotic fractures in Singapore.

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Compliance with ethical standards

Conflicts of interest None.

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