ACE agency for care effectiveness

ACE Clinical Guidance on "Osteoporosis: diagnosis and management"

Methodology used for economic evaluation of intervention thresholds for patients with osteopenia

Background

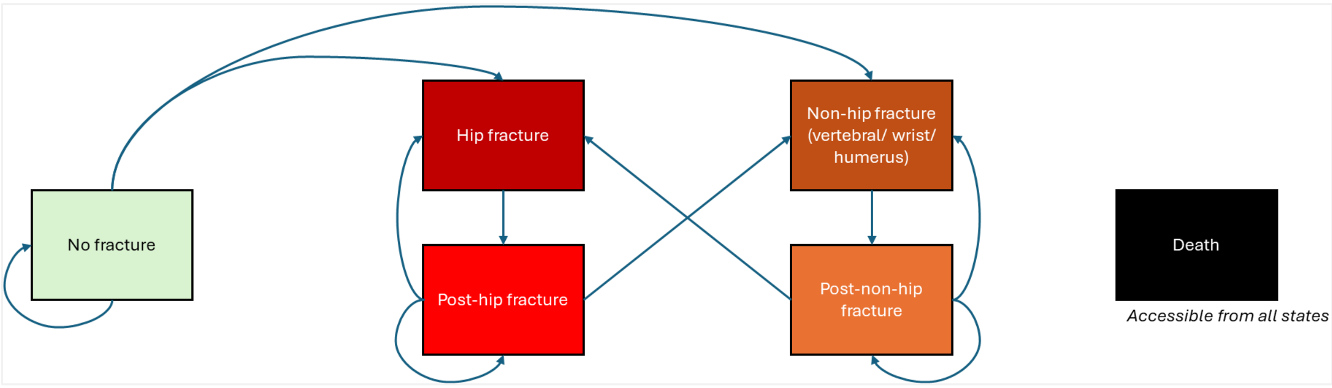
In Singapore, pharmacological treatment of osteopenia is currently initiated when the patient exceeds one of the following thresholds: 10-year probability of hip fracture of at least 3%, or 10-year probability of major osteoporotic fracture of at least 20%. However, these thresholds arose from a 2008 economic evaluation conducted by the United States (US) National Osteoporosis Foundation (NOF),[1] which was based on US data and do not reflect local epidemiology and current costs. Therefore, the Agency for Care Effectiveness (ACE) conducted an economic evaluation to identify cost-effective intervention thresholds for treatment-naïve patients with osteopenia that are contextualised to the local setting. ACE's method takes a tool-agnostic approach, not specific to any one fracture risk calculator. This serves to future proof the resulting thresholds.

Overview of cost-effectiveness approach

Model structure

A Markov model (**Figure 1**) was developed in Microsoft Excel to simulate fractures and mortality in age- and sex-specific groups: Males and females of ages 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥85 years old. Fractures included in our model were hip and non-hip (vertebral, wrist and humerus), corresponding to the fractures considered by the FRAX® calculator.[2] Re-fractures were permitted in the model. All patients begin at the "no fracture" state and transitions between states occurred at a 1-year cycle, over a 10-year time horizon.

Figure 1. Graphical representation of model



Each state was associated with an economic cost and quality-adjusted life year (QALY) value, which were both discounted at an annual rate of 3% in accordance with the ACE Drug and Vaccine Evaluation Methods and Process Guide.[3]

Overall approach

The analytical approach was based on the cost-effectiveness study methodology undertaken by the US NOF, from which the current commonly used thresholds (3% hip fracture probability/ 20% major osteoporotic fracture probability) arose.[1] The risk of fracture was artificially varied (using local incidence as the baseline), with total costs and QALY calculated for a treated and untreated individual. The incremental cost-effectiveness ratio of treatment as a function of fracture risk was analysed. This enabled identification of fracture risk at which treatment (compared to no treatment) became cost-effective. Cost-effectiveness was evaluated against commonly accepted willingness-to-pay thresholds. This analysis was repeated for each age-sex group.

Fracture and mortality risk

See **Table A1** for the list of model parameters derived from published literature.

Age- and sex-specific incidences of hip and non-hip fracture was obtained from Ministry of Health (MOH) Central Claims Processing system, which covers all hospitalisations in public and private acute hospitals, community hospitals, emergency department visits, and polyclinic encounters from 2015 to 2023. International Classification of Diseases (ICD)-10 codes used for database extraction can be found in **Table A2.** The annual fracture incidence rates were used to calculate the population-average 10-year fracture risk for each age-sex subgroup, which served as the baseline risk in the model.

For patients who underwent treatment, generic alendronate was assumed as the medication of choice as this is likely the most common pharmacological agent prescribed.[4] For patients prescribed alendronate, a fracture risk reduction was applied for 5 years of pharmacotherapy treatment. After 5 years, it was assumed that patients would begin a medication holiday for the remaining 5 years and treatment effectiveness was assumed to deteriorate linearly, as per previous local cost-effectiveness analysis.[5]

Age- and sex-specific baseline mortality risk was derived from the Department of Statistics Singapore 2024 report.[6] Fracture-specific mortality was derived from MOH internal data. After a fracture, patients entered a 'post-fracture' state for one year where re-fracture and mortality risks were elevated, before reverting to baseline fracture and mortality risks for subsequent years. A previous local osteoporosis cost-effectiveness study evaluating selective bone densitometry assessed that differences in cost-effectiveness across ethnicities were not large enough to warrant ethnic-specific bone densitometry screening strategies.[7] In line with this finding, ethnic-stratified analysis was not conducted in ACE's evaluation.

Costs associated with treatment and with incident fractures

Cost calculations were consolidated from the perspective of the Singapore healthcare system as recommended by the ACE Drug and Vaccine Evaluation Methods and Process Guide.[3] Patients on treatment were assumed to incur cost for medication, bone mineral density measurement once every two years, and primary care clinic consultation once a year. For patients who incur a fracture, cost incurred in the year of fracture include treatment for the fracture, community hospital admission (hip fracture), as well as follow-up specialist outpatient clinic (SOC) consultations eight times a year (hip fracture) or six times a year (non-hip fracture). In subsequent years, costs accrued for fracture patients included specialist outpatient clinic consultations, primary care consultations, and nursing home admission.

Health state utility values

Health state utility values were derived from a systematic review of 62 studies reporting osteoporotic fracture-related utility values.[8] As this meta-analysis pooled utility values from studies which used different measurement methods (ranging from Health Utilities Index to Standard Gamble), the results were re-analysed by meta-analysis of only EuroQol 5 Dimensions 3 Level (EQ-5D-3L™) data, with outliers removed. After a fracture, health state utility values were reduced for two years before reverting to baseline. As post-humerus fracture utility values were not reported by this systematic review,[8] non-hip fracture utilities were represented by wrist and vertebral fractures only. To address this potential limitation, the robustness of the model in response to variation in utility values were assessed using probabilistic sensitivity analysis (see section below).

Adverse events from treatment were not included in the model for the following reasons: Regarding atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ), the association with bisphosphonates is documented particularly in Asian populations,[9] though the evidence of association is limited to observational data (not detected in relevant RCTs).[10, 11] Given also the rarity of such adverse events, the likelihood of their inclusion changing the overall model findings is low. Nonetheless, the Expert Group took into account the potential for such side effects when interpreting and deliberating the model's results (see section *"Results and Expert Group deliberation underpinning recommended thresholds"* below). Gastrointestinal adverse effects were also excluded from the analysis, considering their minimal impact on cost and QALYs.

Probabilistic sensitivity analysis

To simultaneously include uncertainties in parameter estimates for treatment efficacy, cost of incident fractures, mortality rates, as well as utility values, probabilistic sensitivity analysis was conducted over 10,000 iterations. Uncertainties in utility values and mortality rates were modeled using a beta distribution, uncertainties in cost via a gamma distribution, and uncertainty in fracture relative risk under treatment via a lognormal distribution.

Given the considerable number of input parameters and their associated uncertainty, the probabilistic sensitivity analysis was presented as the main result of this evaluation. Cost-effective intervention thresholds were defined as the fracture risk at which treatment is at least 50% likely to be cost-effective or better. This is in line with decision-making patterns in the United Kingdom.[12]

Scenario analysis

The choice of medication was varied in scenario analysis. Besides alendronate, risedronate or intravenous (IV) zoledronate may be prescribed for patients in whom pharmacotherapy is indicated. Hence, the evaluation was rerun using costs associated with risedronate and IV zoledronate.

Results and Expert Group deliberation underpinning recommended thresholds

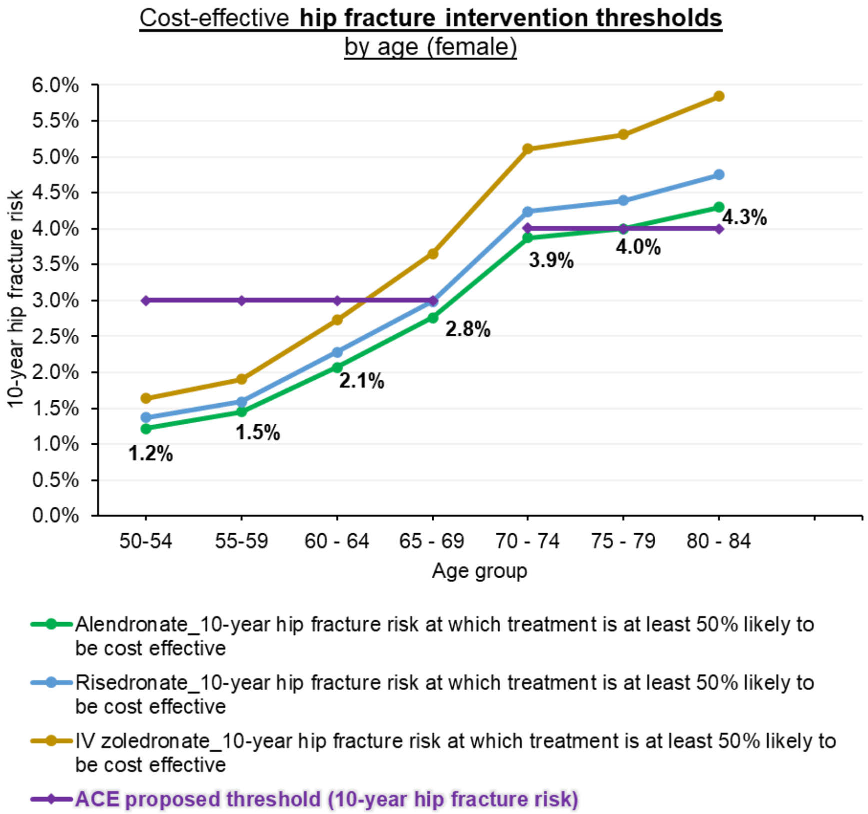
The results of the economic evaluation are summarised in **Figure 2** (female population) and **Figure 3** (male population). For both females and males, cost-effective hip fracture intervention thresholds increased with age and plateaued after 70 years of age. This could be due to greater baseline mortality with older age, as well as lower baseline QALY status. Men ≥70 years old had slightly lower hip fracture intervention thresholds than women of the same age. This is potentially due to the greater financial (due to higher nursing home admission rates) and mortality burden of hip fractures among older men. As the ratio between hip and non-hip fracture risks at baseline was locked in the Markov model based on real-world fracture incidence (see section *"Fracture and mortality risk"*), and hip fractures had greater financial and QALY impact compared to non-hip fractures, the model's outputs were likely driven by the former. This could be one reason why the major osteoporotic fracture intervention thresholds remained stable or seemed to decrease with increasing age.

The 2025 ACE Clinical Guidance (ACG) Expert Group discussed and adopted ACE's proposed age-stratified approach (**Figures 2 and 3**), establishing different thresholds for patients below and ≥70 years to enable more targeted treatment, particularly for older patients. However, the model's data interpretation had limitations, only extending reliably to ages 80-84. The agreed thresholds reflect a careful balance of clinical factors, including finding the balance between undertreatment and overtreatment of various age-sex groups. While treatment was cost-effective at thresholds lower than 3% risk of hip fracture for younger patients, the Expert Group agreed to retain a 3% treatment threshold, given concerns about prolonged bisphosphonate exposure if treatment is started too early. The higher hip fracture intervention thresholds for older patients (≥70 years old) should be considered in the context of local fracture epidemiology: the average hip fracture risk is considerably greater for patients ≥70 years old compared to younger patients. Therefore, even with a higher hip fracture intervention threshold, older patients would more commonly reach their intervention threshold compared to younger patients. Several options were considered when determining the appropriate hip fracture threshold for patients aged 70 and above. For example, among females, a 5% threshold would offer a more conservative treatment approach, while a 4% threshold would maintain treatment cost-effectiveness probability above 40%. The Expert Group deliberated over both options, ultimately deciding on the lower 4% threshold instead of 5%, noting that hip fractures predominantly occur in those aged 80 and above.[13]

As cost-effectiveness of alendronate and risedronate were similar, the Expert Group noted that the intervention thresholds are most applicable to these bisphosphonates compared to intravenous zoledronate. The Expert Group emphasised that these thresholds should serve as guidelines rather than strict cut-offs, with treatment decisions being individualised for each patient.

Figure 2. Cost-effectiveness analysis results for female population

Female population



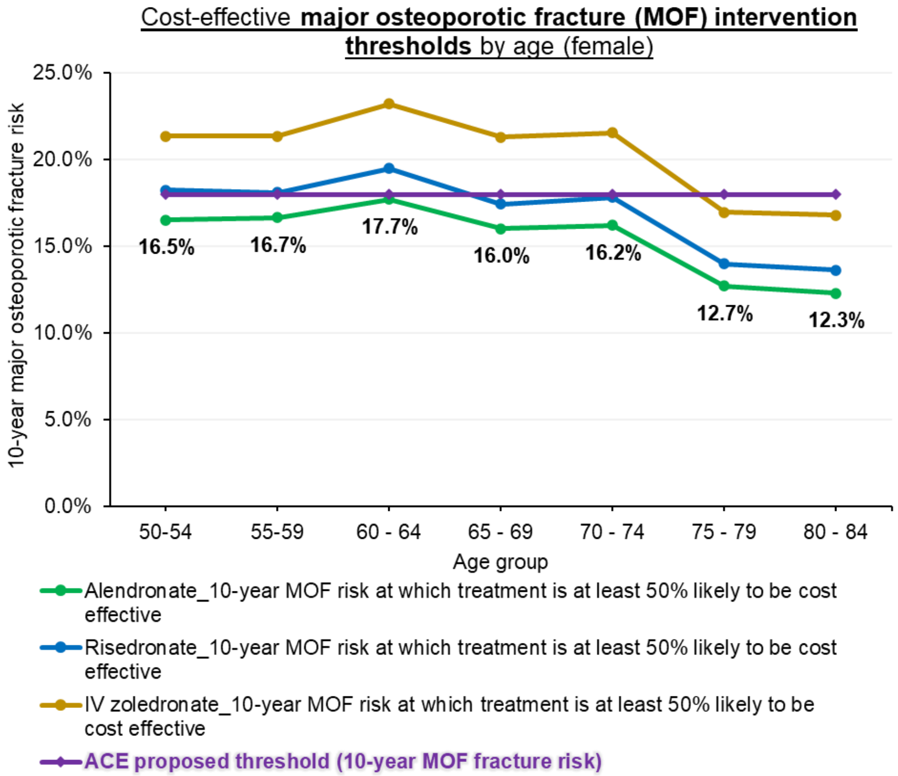
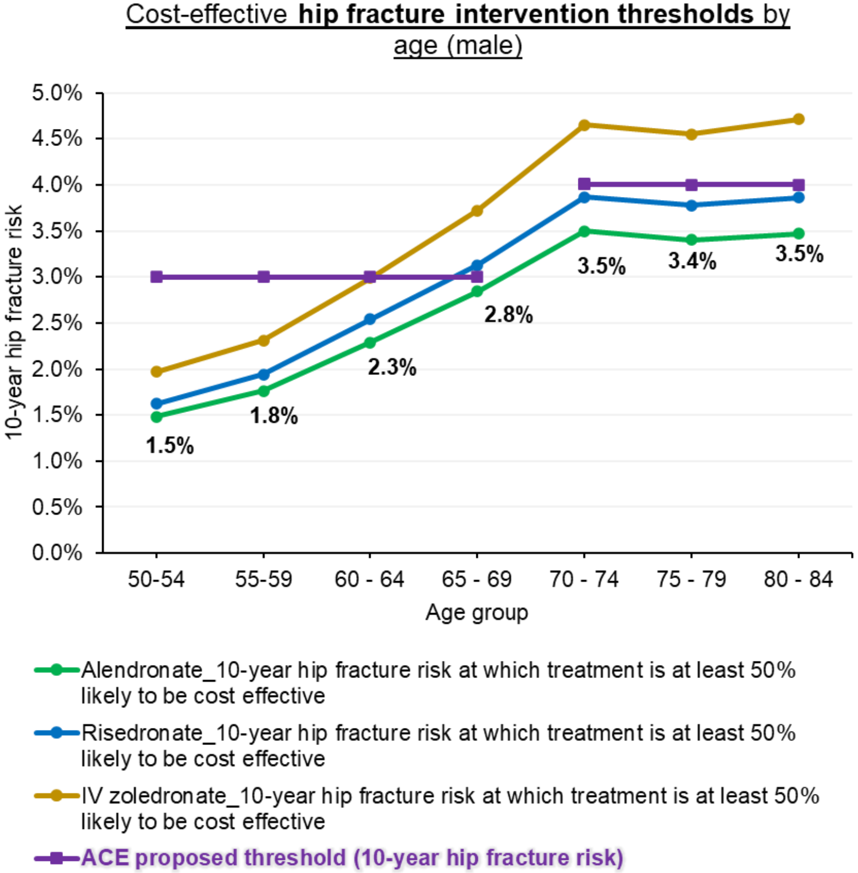
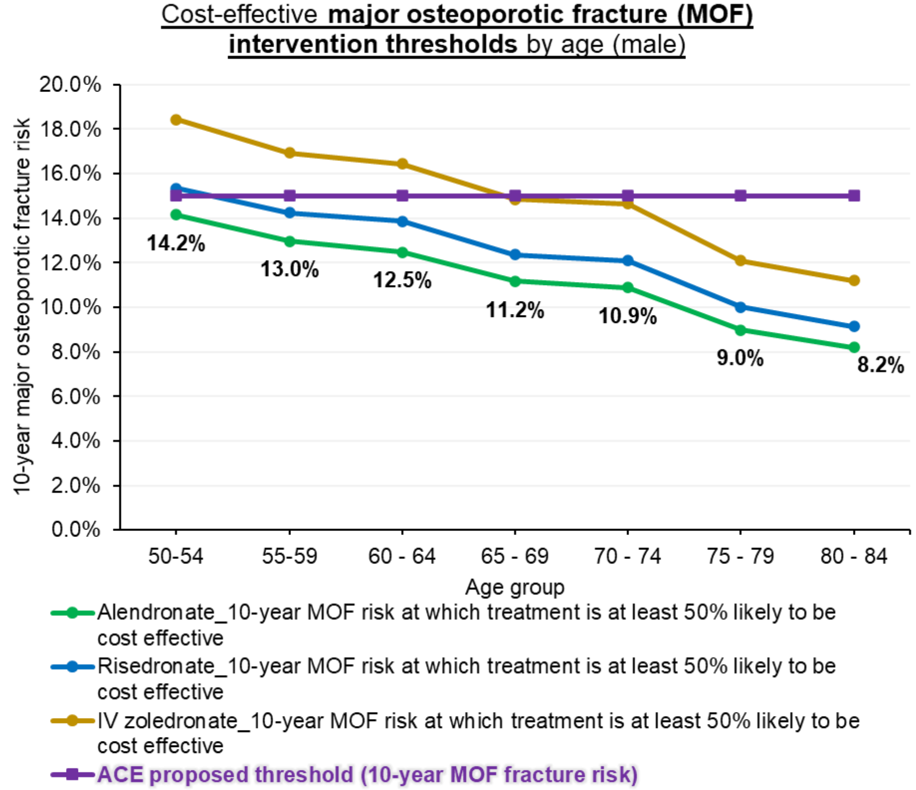


Figure 3. Cost-effectiveness analysis results for male population

Male population





Appendix

Table A1. Model input parameters derived from published literature and Expert Group discussions

<table>
<tr><th>Item</th><th>Unit</th><th>Value(s)</th><th>Reference</th></tr>
<tr><td>Treatment efficacy</td><td>Relative risk of fracture with treatment, compared to no treatment</td><td>
<table>
<tr><th>Time frame</th><th>Risk ratio for hip fracture (95% CI)</th><th>Risk ratio for non-hip fracture (95% CI)</th></tr>
<tr><td>Year 1 to 2</td><td>0.65 (0.43, 0.97)</td><td>0.68 (0.51, 0.92)</td></tr>
<tr><td>Year 3 to 5</td><td>0.64 (0.50, 0.82)</td><td>0.79 (0.68, 0.91)</td></tr>
<tr><td>Year 5 to 10 (drug holiday)</td><td colspan="2">Fracture risk returns to baseline linearly over years 5 to 10</td></tr>
</table>
Data derived from osteoporotic female population; there was a lack of hip fracture risk reduction data in male populations and only two trials among osteopenic-specific populations. Nonetheless, review of available treatment efficacy data among these three populations did not indicate large differences in effect size.[10] Hence, treatment efficacy was based on the female osteoporotic population. Estimates arise from intention-to-treat analysis so adherence effects are already factored in.
</td><td>Network meta-analysis[10]</td></tr>
<tr><td>Cost</td><td>Annual cost (SGD$ 2023-2024)</td><td>
<table>
<tr><th>Item</th><th>Cost components</th></tr>
<tr><td>Hip fracture</td><td>• 8 SOC visits
• Treatment for fracture
• Community hospital admission</td></tr>
<tr><td>Post-hip fracture state (1st year)</td><td>• 2 SOC visits
• Nursing home admission (applied to a subset of patients as estimated by national rates of nursing home admission by age and sex)</td></tr>
<tr><td>Post-hip fracture state (subsequent years)</td><td>• 2 clinic visits (average cost of SOC, GP, and polyclinic consultations)</td></tr>
</table>
</td><td>Internal MOH data</td></tr>
</table>

	• Nursing home admission (applied to a subset of patients as estimated by national rates of nursing home admission by age and gender)
Non-hip fracture	• 6 SOC visits • Treatment for fracture
Post-non-hip fracture state (1st year)	• 2 SOC visits
Post-non-hip fracture state (subsequent years)	• 2 clinic visits (average cost of SOC, GP, and polyclinic consultations)
Additional cost per year for patients on treatment	• 1 clinic visit (average cost of GP and polyclinic consultations) • Bisphosphonate medication • Bone densitometry screening cost (once every 2 years)

Item	Unit	Value(s)		Reference
Health state utility value	EQ-5D-3L	**State**	**Utility (95% CI)**	Values are derived from re-analysis of published meta-analysis, using EQ-5D-3L values alone[8]
		Pre-fracture		
		50–59 years old	0.820 (0.819, 0.822)	
		60–69 years old	0.820 (0.819, 0.822)	
		70–79 years old	0.745 (0.736, 0.754)	
		80–84 years old	0.671 (0.634, 0.709)	
		≥85 years old	0.671 (0.634, 0.709)	
		Hip fracture		
		50–59 years old	0.710 (0.690, 0.730)	
		60–69 years old	0.710 (0.690, 0.730)	
		70–74 years old	0.710 (0.690, 0.730)	
		75–79 years old	0.637 (0.551, 0.722)	
		80–84 years old	0.637 (0.551, 0.722)	
		≥85 years old	0.637 (0.551, 0.722)	

Non-hip fracture	
50–59 years old	0.761 (0.736, 0.787)
60–69 years old	0.761 (0.736, 0.787)
70–79 years old	0.761 (0.736, 0.787)
80–84 years old	0.761 (0.736, 0.787)
≥85 years old	0.761 (0.736, 0.787)

Table A2. List of ICD-10 codes utilised for identifying fracture cases from national healthcare databases

Type of fracture	**ICD-10 codes**
Hip fracture	S72, S7200, S7201, S7203, S7204, S7205, S7208, S721, S7210, S7211, S722
Non-hip fracture	S129, S2200, S3200, S321, T080, S2201, S2204, S422, S4220, S4221, S4222, S4223, S4224, S525, S5250, S5251, S5252, S5253, S526, S423, S424, S4240, S4241, S4242, S4243, S4244, S4245, S4249

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