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# Cost-effectiveness of treatment of women aged 70 years and older with both osteopenia and microstructural deterioration

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ABSTRACT

*Objective:* Treatment is usually withheld from women with osteopenia even though they are the source of over 70% of all women having fragility fractures. As microstructural deterioration increases fracture risk and zoledronate reduces it, we aimed to determine whether identifying and treating women with osteopenia and severe microstructural deterioration is cost-effective. We also compared the health economic outcomes of 'global' versus 'targeted' treatment using SFS of women aged ≥70 years with osteopenia.

*Design:* We assessed the cost-effectiveness from using a Markov model that simulated 10-year follow up of women with osteopenia. Decision analysis compared measurement of distal radial microstructure using high resolution peripheral computed tomography (at a cost of USD $210) to target women with severe microstructural deterioration for zoledronate treatment, compared to standard care defined as measurement of bone mineral density (BMD) with treatment recommended when femoral neck BMD T score is ≤ −2.5 SD with or without a prevalent fracture. In the 'global' treatment approach, high resolution peripheral quantitative tomography (HRpQCT) was not undertaken.

*Setting:* US healthcare system.

*Participants:* A hypothetical cohort of 1000 women aged ≥70 years with osteopenia and no previous fractures was studied.

*Measures:* Fractures, deaths, years of life lived, quality-adjusted life years (QALYs) lived and costs. Data inputs were obtained from published sources. A 3% annual discount rate was applied to future health benefits and costs.

*Results:* Women in the standard care group incurred 327 fractures during 7341.0 years and 4914.2 QALYs lived. Women in the intervention group incurred 300 fractures (number needed to treat 37) during 7359.2 years and 4928.8 QALYs lived. Net costs were USD $4,862,669 and $4,952,004, respectively, equating to 18.1 years of life saved and 14.6 QALYs saved, and incremental cost-effectiveness ratios of $4992 per year of life saved and $6135 per QALY saved. These ratios are well within the threshold considered to be cost-effective. Sensitivity analyses indicated the results were robust.

Relative to standard of care, 'global' and 'targeted' treatment respectively resulted in 0.0364 vs. 0.0181 years of life (YoLS) saved per person, and 0.0292 and 0.0146 QALYs saved per person. The net costs per person for the respective approaches were $US 359 and $US 89. The incremental cost-effectiveness ratios were $9864 per YoLS and $12,290 per QALY saved for the 'global' approach and $4992 per YoLS and $6135 per QALY saved for the 'targeted' approach.

*Conclusion:* Identifying and treating women ≥70 years of age with osteopenia and microstructural deterioration with zoledronate cost-effectively reduces the morbidity and mortality imposed by fragility fractures. This 'targeted' approach is more cost-effective than a 'global' approach and incurs only 25% of total costs.

*Implication:* Women with osteopenia with bone fragility due to microstructural deterioration should be identified and targeted for treatment.

*Summary:* Women with osteopenia have 70% of fractures. Treating those with microstructural deterioration conferred an incremental cost-effectiveness ratio of $4992/year of life saved and $6135 per QALY saved.

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## 1. Introduction

Advancing age is associated with bone fragility and an increased fracture risk [1]. The fracture burden is rising because longevity is increasing the number of older people in the community [2]. The term 'osteoporosis' is assigned to persons with bone mineral density (BMD) T-score of $\leq -2.5$ standardized deviations (SDs) below the premenopausal mean (1), but bone fragility is not confined to women with osteoporosis. Postmenopausal women with more modest deficits in BMD categorized as osteopenia, a BMD T-score between $-1$ and $-2.5$ SD, have a lower risk of fracture than women with osteoporosis, but they are not free of fracture risk [3].

Over 70% of all fragility fractures arise among the majority of postmenopausal women in the population with osteopenia [3–5]. This is similar to the burden of cardiovascular disease; most events arise from individuals with moderately hypertension or hyperlipidemia [6]. Thus, confining treatment to only women with osteoporosis fails to address the population burden of fractures.

Most fractures, particularly non-vertebral and hip fractures, which comprise over 70% of all fractures, occur in women over 70 years of age. Measurement of bone density forms part of the standard assessment of fracture risk in women presenting following a first fragility fracture or concerned about the possibility of a first fracture. However, uptake of therapy remains suboptimal, especially in women found to have osteopenia, even in the presence of a fragility fracture [7].

To curb this burden requires a strategy to identify and target postmenopausal women with osteopenia with bone fragility. Women with osteopenia at imminent risk (within 1–2 years) and intermediate risk (within 2–4 years) for fracture have bone fragility partly due to microstructural deterioration [7–11]. BMD does not capture this fragility because microstructural deterioration increases fragility disproportionately to the bone loss producing it and the modest BMD deficits of osteopenia [12].

These women can be identified by measuring microstructural deterioration using high resolution peripheral quantitative tomography (HRpQCT) and targeting them for therapy. We have quantified cortical and trabecular microstructural deterioration and expressed this deterioration as a structural fragility score. We reported using a threshold denoting severe structural deterioration captures a large proportion of women with osteopenia sustaining fractures before the event [3]. Treating women with osteopenia using zoledronate reduces fracture risk [13]. However, it is uncertain whether complementing a BMD measurement with additional measurement of the structural fragility score using HRpQCT to identify those at high risk with microstructural deterioration is cost-effective compared to current standard of care. We addressed this issue in the present study, adopting the perspective of the US healthcare system. We also evaluated and compared the economic outcomes of a 'global approach of treating all women $\geq 70$ years of age with osteopenia compared to current standard of care.

## 2. Methods

### 2.1. Model

A state-transition Markov model was developed in Microsoft Excel to simulate the progress of women aged $\geq 70$ years with osteopenia, no previous fractures and a SFS of $\geq 70$ at baseline [14]. The model comprised three health states: 'Alive, no prior fracture', 'Alive, post fracture' and 'Dead' (Fig. 1). 'Fracture' comprised major fragility fracture involving the hip, vertebra or wrist. All subjects began the simulation in the health state 'Alive, no fracture', and over yearly cycles, could develop a fracture (hip, vertebra or wrist) and survive or die within a year of that episode. If they survived, they transitioned to the health state 'Alive, post fracture'. Subjects in the health state 'Alive, post fracture' could experience recurrent fractures, but returned to the same health state if they survived. In all cycles, subjects were at risk of death from other (non-fracture related) causes. Decision analysis was used to compare the downstream health outcomes and costs of HRpQCT to screen fracture-free women aged $\geq 70$ years with osteopenia to identify and pre-emptively treat those with SFS $\geq 70$ with zoledronate 5 mg given every 18 months ('Intervention Group') versus no screening or treatment ('Standard Care Group') [15]. In a secondary analysis, we also evaluated and compared the economic outcomes of a 'global approach of treating all women $\geq 70$ years of age with osteopenia.

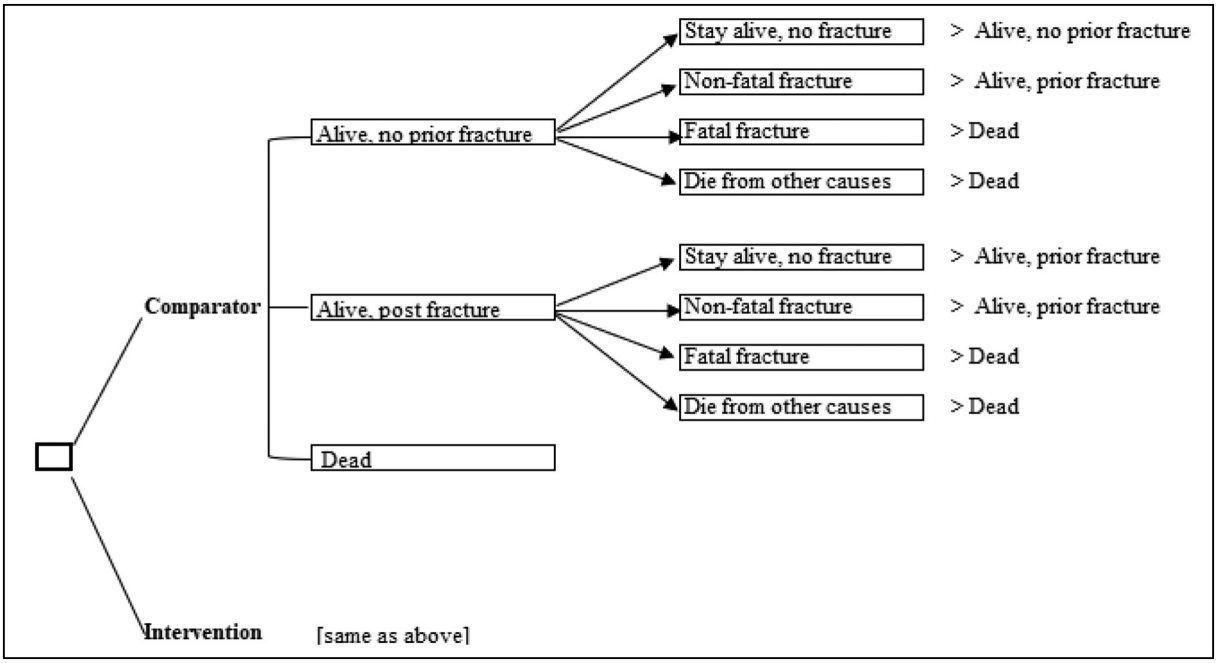


**Fig. 1.** Conceptualization of the model.
Model of comparator and intervention with three states, alive, no prior fracture, post fracture or dead. See text.

### 2.2. Model subjects

Model subjects comprised women initially aged ≥70 and < 85 years with osteopenia. Three cohorts were assembled comprising women aged 70–74, 75–79 and 80–84 years at baseline. Follow-up was simulated for 10 years. The ≥70 years age range was selected because the most o fractures arise from women aged ≥70 years with osteopenia [3,16], especially women having hip and other major fragility fractures which predispose to further fractures [17]. Subjects were profiled on participants in the Os des Femmes de Lyon (OFELY) and QUAlité Osseuse LYon Orleans (QUALYOR) cohorts of 566 women aged ≥70 years of age with BMD categorized as osteopenia followed prospectively following baseline assessment of microstructure [3,18,19]. The OFELY cohort of 1039 women mean age 68 years with a baseline measurement of microstructure have been followed for a median of 9.4 years. The QUALYOR cohort comprised 1539 women followed for 5 years; 1042 were recruited in Lyon and 497 in Orléans, France, based on having osteopenia with clinical risk factors for fracture, or T score −3.0 SD without clinical risk factor. Consent was obtained from all participants. These studies were approved by the CPP Sud-Est II institutional review board, Lyon, France. Images at the ultradistal radius were obtained and analysed using HRpQCT (XtremeCT, Scanco Medical AG, Switzerland) and StrAx1.0 (StraxCorp, Melbourne, Australia) [20,21,22].

### 2.3. Data inputs

Key data inputs, and their values used in the base case and sensitivity analyses, are summarized in Table 1. Data regarding the annual risks of first hip, vertebral or wrist fracture were obtained from the OFELY and QUAYLOR cohorts. At baseline, none of the 1539 women in the QUALYOR cohort had previous fractures, while 63 of the 295 women with osteopenia in the OFELY cohort had previous fractures. In these two cohorts, among women aged ≥70 years with osteopenia and a SFS of ≥70, the cumulative proportions with hip, vertebral and wrist fractures at two, four and eight years were 8.0%, 14.7% and 27.7%, respectively [3]. A polynomial function (with an excellent fit, $R^2$ = 0.999) was applied to these data points to derive one-year risks over a ten-year period (Supplementary Fig. S1). Among women aged ≥70 years with osteopenia and a SFS of < 70, the observed rates of fractures at 2, 4 and 8 years were 0.87%, 3.2% and 8.6%, respectively.

In the model, we assumed that compared to women without previous fractures, those who experienced major fragility fracture were 1.61 times more likely to incur another fracture, as reported by Morin et al. (relative risk [RR] 1.61 95% confidence interval [CI] 1.47–1.77) [23].

Brauer et al. estimated that 1-year mortality among US women who suffered hip fractures was 21.9% (95% CI 21.4% - 22.4%) [24]. There were no equivalent data for US women who suffered vertebral and wrist fractures and so we estimated these from Morin et al. [25], who followed 49,197 women from Manitoba, Canada. In 2006/2007, the 1-year mortality rates (per 1000) among women who suffered hip, vertebral or wrist fractures were 182.8, 125.0 and 18.3 respectively. We used the proportional differences in 1-year mortality reported by Morin et al. for hip versus vertebral and wrist fractures to estimate absolute 1-year mortality post-vertebral fracture (21.9%*[125.0/182.9] = 15.0%) and post-wrist fracture (21.9%*[18.3/182.9] = 2.2%). To derive a weighted-average 1-year mortality for all three fractures, we applied 1-year mortality estimates for hip (21.9%), vertebral (15.0%) and wrist (2.2%) fractures to data on the proportional distribution of these three types of fractures published by Burge et al. [26] These investigators estimated that in 2005, of all hip, vertebral and wrist fractures occurring in the US among women aged 65 to 84 years, 28.7%, 45.3% and 26.0% were in the hip, vertebra and wrist, respectively. Based on these data, the weighted-average 1-year mortality was 13.6%.

In the group having microstructure quantified using HRpQCT, we assumed in the base case analysis that 25% of subjects would have a SFS of ≥70 units based on published findings [3]. These subjects were all assumed to be given prophylactic zoledronate which is reported to produce a 36% relative fracture risk reduction based on combining efficacy data for each of hip (RR 1.0), vertebral (RR 0.45) and wrist (RR 0.56) fractures [13] and data on the proportional distribution of these three types of fractures [26]. Because Reid et al.[13] found that the

**Table 1**
Data inputs used in the model.

| Input parameter | Base-case value | Uncertainty range | Source |
|---|---|---|---|
| Cost of HRpQCT | USD $210 | USD $500 | |
| Underlying prevalence of SFS 70+ among women who undergo testing[a] | 25% | 15% - 35% | Base case value: Charpurlat 2020 [3]<br>Uncertainty range: assumption |
| Annual risk of hip, vertebral or wrist fracture[b] | Age-dependent | ± 20% | OFELY and QUAYLOR cohorts (personal communication) |
| Relative risk of fracture among people with previous fractures[b] | 1.61 | 1.47–1.77 | Morin 2014 [23] |
| 1-year mortality among people who have fractures Dominant | | | Brauer 2009 [24] and Morin 2011 [25] |
| Hip | 21.9% | 21.4% - 22.4% | |
| Vertebral | 15.0% | N/A | |
| Wrist | 2.2% | N/A | |
| > 1-year standardized mortality ratio among people who have fractures | | | Melton 2013 [29 (average of standardized mortality ratios for 1–5 years and > 5 ears.) |
| Hip | 1.4 | 1.1–1.7 | |
| Vertebral | 1.5 | 1.2–1.7 | |
| Wrist | 1.0 | 0.7–1.3 | |
| Utility: no prior fracture (multiplier)[b] | 1.00 | N/A | Nayak 2019 [30] |
| Utility: post fracture# (multiplier)[b] | 0.97 | N/A | Nayak 2019 [30] |
| Acute cost of fracture (USD)[b] | $5128 | ± 20% | Base case value: Burge 2007 [26]<br>Uncertainty range: assumption |
| Annual cost: no fracture (USD)[b] | $0 | N/A | Assumption |
| Annual cost: post fracture (USD)[b] | $1297 | ± 20% | Base case value: Burge 2007 [26]<br>Uncertainty range: assumption |
| Adherence to zoledronate | 100% | 80% | Assumption |
| Relative risk for fractures associated with zoledronate[b] | | | Reid 2018 [13] |
| Hip | 1.0 | N/A | |
| Vertebra | 0.45 | 0.27–0.75 | |
| Wrist | 0.56 | 0.37–0.85 | |
| Unit cost of zoledronate (USD) | $375 | N/A | Nayak 2019 [30] |

[a] All subjects identified as having osteopenia would undergo treatment with zoledronic acid every 18 months.
[b] Weighted-average values for hip, vertebral and wrist fractures.

benefit conferred by zoledronate for risk of hip fracture was not statistically significant, we assumed no benefit for this outcome in the model (RR 1.0). In the base-case analysis, we assumed that all women assigned to zoledronate treatment were fully adherent. In sensitivity analyses, we reduced adherence to 80%.

In the secondary evaluation of 'global treatment of all women, HRpQCT was not used. Instead, all women in the intervention group were given zoledronate. All other model parameters were the same as used in the primary evaluation.

Data on the distribution of the model subjects by age were drawn from the US Census Bureau [27] for the year 2017 and data on age-related probabilities of 'background' mortality from the Centres for Disease Control and Prevention [28] (Supplementary Table S1). Subjects in the health state 'Alive, post fracture' had a higher probability of 'background' mortality (standardized mortality ratio [SMR] of 1.22) based on mortality risks for people post fracture published by Melton et al. [29] The authors estimated SMRs 1–5 years post hip, vertebral and wrist fractures among women to be 1.2, 1.7 and 0.8, respectively, while equivalent SMRs > 5 years post fracture were 1.5, 1.2 and 1.0. For each fracture type, we took the average of the SMRs for the 1–5 and > 5-year periods and derived a weighted-average based on the proportional distribution of hip, vertebral and wrist fractures [26].

Costs were limited to direct costs from the perspective of the US healthcare system. The cost of HRpQCT was assumed to be USD $210 per person and increased in a sensitivity analysis to US $500. In the model, an arbitrary number of 1000 women had a HRpQCT measurement of whom 250 (25%) were assumed to have a SFS of ≥70 units and so were targeted for treatment with zoledronate 5 mg every 18 months. The cost per dose of zoledronate was USD $375 ($176 drug cost and $199 administration cost) (30). If given every 18 months, the annual cost was USD $250 ($375*[12/18]). In the Standard Care Group, no subjects received zoledronate. In both the targeted and Standard Care Groups, all subjects were assumed to be taking zoledronate *after* a major fragility fracture.

Weighted-average acute hospitalization costs occurring among US women aged 65–84 years published by Burge et al. were USD $24,043 for hip fractures, $788 for vertebral fractures and $551 for wrist fractures for the year 2005 (26). (Supplementary Table S2). These were updated to 2020 values using the personal consumption expenditures (PCE) health price index [31], and a weighted-average cost derived by applying the costs of each type of fracture to their proportional distribution estimated by Burge et al. [26] This was USD $10,111.

The distribution of fractures in the Burge et al. cohort from which costs were derived [26] and our cohort was similar; respectively (Burge versus the French cohorts): vertebral fractures (27% vs. 29%), hip fractures (14% vs.11%), non-vertebral non-hip fractures (59% vs. 60%). Long term annual costs published by Burge et al. were USD $3977 following hip fractures, $3237 following vertebral fractures and $0 following wrist fractures, relevant to the year 2005 [26]. The weighted-average cost updated to a 2020 value was $1762. For subjects remaining fracture free, we assumed that they did not incur any healthcare costs related to management of fragility fractures.

Data on utility (health-related quality of life) associated with fractures were drawn from Nayak et al. [30] As with costs, the weighted-

**Table 2**
Results of the sensitivity analyses.

| | ICER: USD per year of life saved | ICER: USD per QALY saved |
|---|---|---|
| Base case | $4922 | $6135 |
| Cost of HRpQCT (USD) | | |
| $500 | $20,901 | $26,049 |
| Proportion with SF ≥ 70 among population undergoing SFS testing | | |
| 15% | $12,636 | $15,749 |
| 35% | $1616 | $2014 |
| Annual risk of hip, vertebral or wrist fracture | | |
| −20% | $13,291 | $16,471 |
| +20% | Dominant[a] | Dominant[a] |
| Relative risk of fracture in people with previous fractures | | |
| 1.47 | $5089 | $6333 |
| 1.77 | $4735 | $5911 |
| 1-year mortality among people who have hip fractures | | |
| 21.4% | $4972 | $6173 |
| 22.4% | $4874 | $6098 |
| > 1-year standardized mortality ratio among people who have hip, vertebral and wrist fractures | | |
| Lower limits of 95% confidence intervals | $5359 | $6441 |
| Upper limits of 95% confidence intervals | $4589 | $5885 |
| Acute cost of fracture (USD) | | |
| $8089 (−20%) | $7587 | $9456 |
| $12,133 (+20%) | $2257 | $2813 |
| Acute cost of vertebral and wrist fractures (USD) | | |
| Five-fold increase to estimates by Burge et al. (25) | $1313 | $1636 |
| Ten-fold increase to estimates by Burge et al. (25) | Dominant[a] | Dominant[a] |
| Annual cost: post fracture (USD) | | |
| $1410 (−20%) | $6573 | $8192 |
| $2114 (+20%) | $3272 | $4078 |
| Adherence to zoledronate in the HRpQCT Group | | |
| 80% | $7897 | $9842 |
| Relative risk for vertebral fractures associated with zoledronate | | |
| 0.27 | $65 | $81 |
| 0.75 | $20,649 | $25,822 |
| Relative risk for wrist fractures associated with zoledronate | | |
| 0.37 | $1751 | $2179 |
| 0.87 | $12,449 | $15,546 |
| Time horizon | | |
| 15 years | $535 | $700 |
| Annual discount rate | | |
| 0% | $3033 | $3792 |

[a] Dominant: intervention associated with both improved health outcomes and lesser costs.

average utility of each fracture (0.96) was obtained by applying specific utilities for hip (0.90), vertebral (0.97) and wrist (1.00) fractures [30] to the proportional distribution of these three types of fractures (26). These utility values were factors by which age-related 'background' utilities [32] were multiplied (Supplementary Table S3).

### 2.4. Economic evaluation

The model compared outcomes between the HRpQCT and Standard Care Groups in terms of the number of fractures, years of life lived, quality-adjusted life years (QALYs) lived and costs over a 10-year time horizon. A 3% annual discount rate was applied to future health benefits and costs, in line with US guidelines [33]. For the economic evaluation, the outputs of interest were incremental cost-effectiveness ratio (ICERs) in terms of net costs (USD) per QALYs saved and per year of life saved.

### 2.5. Sensitivity analyses

In sensitivity analyses, we varied the key input parameters according to the limits of the uncertainty ranges described in Table 1. Annual discount rates were reduced to 0%. Furthermore, because the acute hospitalization costs estimated by Burge et al. for vertebral and wrist fractures were up to 10-fold less compared that reported [34,35], we multiplied their costs by factors of 5 and 10.

## 3. Results

The model predicted that in the Standard Care Group, 327 fractures (284 first and 43 recurrent) would have occurred over the 10-year time horizon among the 1000 subjects compared to 300 fractures (261 first and 39 recurrent) in the Intervention Group assessed using HRpQCT and treated based on finding SFS to be ≥70 units. Hence, targeting treatment based on the presence of severe microstructural deterioration prevented 27 fractures over the 10-year period, equating to a number needed to treat (number needed to screen) of 37.

The model predicted that in the Standard Care Group, subjects lived 7341.0 years (discounted) and 4914.2 QALYs (discounted) over the 10-year time horizon, compared to 7359.2 years (discounted) and 4928.8 QALYs (discounted) in the Intervention Group, equating to 18.1 years of life saved and 14.6 QALYs saved.

In terms of costs, subjects in the Standard Care Group were predicted to incur a total of USD $4,862,669 (discounted) in direct healthcare costs related to the prevention and management of fractures over the 10-year time horizon, compared to USD $4,742,004 (discounted) in the Intervention Group, representing a saving of USD $120,666. However, with the addition of USD $210,000 costs of HRpQCT at $210,000, the total costs of the Intervention Group was USD $4,952,004, representing a net difference of $89,334.

Thus, quantifying bone microstructure in women aged ≥70 years with osteopenia and treating the 25% found to have SFS of ≥70 led to 0.0181 years of life saved and 0.0146 QALYs saved per person over a 10-year time horizon, at a cost of USD $89 per person. These equated to ICERs of USD $4992 per year of life saved and USD $6135 per QALY saved. These ICERs fall well within the threshold considered to be cost-effective [36].

The results of the sensitivity analyses are presented in Table 2. Input parameters to which the cost-effectiveness results were most sensitive were the cost of HRpQCT, the underlying risk of hip, vertebral and wrist fractures and the efficacy of zoledronate in preventing these. Even the ICERs representing the most conservative assumptions (that is, the highest ICERs) fall within the threshold considered to be cost-effective [36].

The secondary evaluation of 'global treatment predicted that there would be 0.0364 years of life (discounted) and 0.0292 QALYs (discounted) saved per person, at a net cost per person of $US 359 (discounted). The incremental cost-effectiveness ratios were $9864 per YoLS and $12,290 per QALY saved.

## 4. Discussion

Measurement of severe microstructural deterioration identifies women aged ≥70 years with osteopenia at imminent risk for fracture [3]. Over 70% of the fracture burden in the community arises among women with osteopenia or normal BMD [3–5,10]. The preliminary health economic analyses in that report [3], provided an indicative measure of cost-effectiveness using a simplified model structure and key data inputs with a modelled time horizon to five years. The parameters of the present evaluation was more reflective of real world experience; namely, that the risks and case-fatality of fragility fractures were weighted by the different sites of their occurrence, women could experience recurrent fractures, there was not always 100% adherence to prophylactic treatment and the modelled time horizon was ten years.

We report here that the additional cost of measuring bone microstructure and targeting treatment to women over 70 years of age with osteopenia and severe microstructural deterioration is likely to be cost-effective. Targeting therapy in this way to 1000 women prevents 37 fractures over a 10-year period and saves 18.1 years of life and 14.6 QALYs, at a cost of USD $89.334. These equate to ICERs of USD $4992 per year of life saved and USD $6135 per QALY saved, which fall within the threshold considered to be cost-effective. According to the World Health Organization, the threshold ICER to determine cost-effectiveness should be referenced against a country's gross domestic product (GDP) per capita [36]. ICERs less than one times GDP per capita are considered 'high value', while ICERs 1 to 3 times GDP per capita are considered 'intermediate value'. The World Bank estimated that the GDP per capita in the US in 2018 was USD $62,795 [37].

Our base case analysis adopted highly conservative data inputs, especially pertaining to the benefit of zoledronate on hip fractures (zero benefit) and other non-vertebral and non-wrist fractures (zero benefit), as well as the acute hospitalization costs of vertebral and wrist fractures (less than USD $1000 each). This reinforces the conclusion that the intervention is cost-effective.

Most studies focus on women with osteoporosis. This will not reduce the *population* burden of fractures because these women contribute only 15–20% of all fractures in the community. Over 70–80% of fractures arises among the great many postmenopausal women with osteopenia [3–5,10]. Even in women aged 70–90 years, only 40% have osteoporosis; 60% have osteopenia or normal BMD [38]. These women usually remain untreated because this *diagnostic* threshold for 'osteoporosis' is often used as a *treatment* threshold. Even in the presence of a fracture, treatment is often withheld when BMD is less severely reduced than – 2.5 SD [7].

Women aged over 70 years account for 45–60% of all major fragility fractures [3]. This age group is also responsible for over 75% of the costs of fragility fractures [38], reflecting the frequency of fractures in older women and the higher cost of managing fractures. This highlights the need to identify and treat women aged ≥70 years with osteopenia [3]. Measuring microstructural deterioration identifies these women. This study suggests that a targeted preventive strategy would be cost-effective, and constitute a 'high value' intervention, according to World Health Organization definitions.

Relative to current standard of care, targeted treatment using SFS would be more cost-effective than 'global treatment, and only comprise 25% of the total costs. Assuming that there are 8.5 million women in the US aged ≥70 years with osteopenia [39], the net costs of the 'global' treatment approach would amount to $US 3.05 billion over 10 years.

This study has several limitations. The input data were based on cohorts of French women with osteopenia and cannot be assumed to be representative of the US population. However, many multinational studies confirm that microstructural deterioration increases fracture

risk in all persons [3,8–11], and multinational studies support the consistency of antifracture efficacy of drugs in different populations [49–42]. Modelled analyses contain assumptions but we selected conservative values for the base-case input parameters and tested a reasonable range of values in sensitivity analyses. Input parameters with the greatest uncertainty concerned costs of managing fragility fractures and the short- and long-term mortality associated with fragility fractures. However, the cost-effectiveness results were not sensitive to these inputs (Table 2).

The efficacy of zoledronate influenced cost-effectiveness, but even assuming that hip fracture risk was not reduced and conservative margins of efficacy (upper limits of the 95%CIs for relative risk) for vertebral and wrist fractures, testing and treating the targeted women over 70 years of age with osteopenia and microstructural deterioration remained cost-effective. Furthermore, only fractures of the wrists, spine and hips were considered. Zoledronate may also reduce the incidence of fractures at other sites, and so the cost-effectiveness of the intervention is likely to have been under-estimated. Only zoledronate treatment was modelled [13]. Less costly medications are also efficacious in women with osteopenia [43,44]. HR-pQCT is not widely available. However, a new smaller HR-pQCT device has been developed which is FDA cleared and CE marked (conforming with health, safety, and environmental protection standards within European Economic Area) and is becoming available for clinical use. It improves access to assessment at similar costs to DXA and provides a visual assessment of the deterioration with 3–5 microsievert radiation exposure per scan.

### 4.1. Conclusion and implications

The population burden of fractures will not be addressed by treatment to women with osteoporosis alone. Women with osteopenia at risk of fracture can be cost-effectively identified by measuring microstructural deterioration and promptly treated [13,40–45]. This approach is likely to curtail the growth morbidity, mortality, and economic burden of fractures accompanying longevity.

## CRediT authorship contribution statement

D Liew: conceptualization, methology, software formal analysis, writing.

RD Chapurlat: investigation, resources, supervision, project administration, funding.

E Sornay-Rendu: investigation, resources, supervision, project administration.

Eric Lespessailles: investigation, resources, supervision, project administration.

Yu Peng: methodology, software, resources.

E Seeman: conceptualization, writing.

## Declaration of competing interest

ES is a board member and shareholder in Straxcorp. YP is employee of Straxcorp.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2020.115682.

## References


[1] J.A. Kanis, Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report, WHO Study Group. Osteoporos Int. 4 (1994) 368–381.

[2] K. Christensen, G. Doblhammer, R. Rau, W. James, J.W. Vaupel, Ageing populations: the challenges ahead, Lancet. 373 (9696) (2009) 1196–1208.

[3] Chapurlat R, Bui M, Sornay-Rendu S, Zebaze R, Delmas PD, Liew D, Lespessailles E, Seeman E. Deterioration of cortical and trabecular microstructure identifies women with osteopenia or normal bone mineral density at imminent and long-term risk for fragility fracture: a prospective study. J Bone Miner Research. In press. DOI: https://doi.org/10.1002/jbmr.3924.

[4] E.S. Siris, Y.T. Chen, T.A. Abbott, et al., Bone mineral density thresholds for pharmacological intervention to prevent fractures, Arch. Intern. Med. 164 (2004) 1108–1112.

[5] J.A. Pasco, E. Seeman, M.J. Henry, et al., The population burden of fractures originates in women with osteopenia, not osteoporosis, Osteoporos. Int. 17 (2006) 1404–1409.

[6] G. Rose, Sick individuals and sick populations, Int. J. Epidemiol. 30 (3) (2001) 427–432.

[7] W.D. Leslie, E. Seeman, S.N. Morin, L.M. Lix, S.R. Majumdar, The diagnostic threshold for osteoporosis impedes fracture prevention: a registry-based cohort study, Bone 114 (2018) 298–303.

[8] Y. Bala, R. Zebaze, A. Ghasem-Zadeh, et al., Cortical porosity identifies women with osteopenia at increased risk for forearm fractures, J. Bone Miner. Res. 2 (2014) 1356–1362.

[9] Ahmed LA, Ghasem-Zadeh A, Y. Bala Y, Zebaze R, Seeman E, Bjørnerem Å. Measurement of cortical porosity of the proximal femur improves identification of women with nonvertebral fragility fractures. Osteop Intern. 2015;26: 2137–46.

[10] Samelson EJ, Broe KE, Xu H et al. Cortical and trabecular bone microarchitecture as anindependent predictor of incident fracture risk in older women and men in the Bone Microarchitecture International Consortium (BoMIC): a prospective study. November 28, 2018 https://doi.org/10.1016/S2213-8587(18)30308-5.

[11] E. Biver, C. Durosier-Izart, B. van Rietbergen, R. Rizzoli, S. Ferrari, Evaluation of radius microstructure and areal bone mineral density improves fracture prediction in postmenopausal women, J. Bone Miner. Res. (2017), https://doi.org/10.1002/jbmr.3299.

[12] M.B. Schaffler, D.B. Burr, Stiffness of compact bone: effects of porosity and density, J. Biomech. 21 (1988) 13–16.

[13] I.R. Reid, A.M. Horne, B. Mihov, et al., Fracture prevention with zoledronate in older women with osteopenia, N. Engl. J. Med. 379 (2018) 2407–2416.

[14] A. Briggs, M. Sculpher, An introduction to Markov modelling for economic evaluation, Pharmacoeconomics. 13 (4) (1998) 397–409.

[15] R.J. Lilford, S.G. Pauker, D.A. Braunholtz, J. Chard, Decision analysis and the implementation of research findings, BMJ. 317 (7155) (1998) 405–409.

[16] Zebaze R, Atkinson EJ, Peng Y, Bui M, Ghasem-Zadeh A, Kholsa S, Seeman E. Increased Cortical Porosity and Reduced Trabecular Density are Not Necessarily Synonymous With Bone Loss and Microstructural Deterioration https://doi.org/10.1002/jbm4.10078.

[17] H. Johansson, K. Siggeirsdóttir, N.C. Harvey, A. Odén, V. Gudnason, E. McCloskey, G. Sigurdsson, J.A. Kanis, Imminent risk of fracture after fracture, Osteoporos. Int. 28 (2017) 775–777.

[18] M. Arlot, E. Sornay-Rendu, P. Garnero, B. Vey-Marty, P.D. Delmas, Apparent pre- and postmenopausal bone loss evaluated by DXA at different skeletal sites in women: the OFELY cohort, J. Bone Miner. Res. 12 (1997) 883–890.

[19] Chapurlat R, Pialat JB, Merle B, et al. The QUALYOR (QUalité Osseuse LYon Orléans) Study: a new cohort for non-invasive evaluation of bone quality in postmenopausal osteoporosis. Rationale and study design. Arch Osteoporos. 2017;13(1):2.

[20] A. Laib, H.J. Hauselmann, P. Ruegsegger, In vivo high resolution 3D-QCT of the human forearm, Technol. Health Care 6 (5–6) (1998) 329–337.

[21] Zebaze RM, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet;375:1729–36.

[22] R. Zebaze, A. Ghasem-Zadeh, A. Mbala, E. Seeman, A new method of segmentation of compact-appearing, transitional and trabecular compartments and quantification of cortical porosity from high resolution peripheral quantitative computed tomographic images, Bone 54 (2013) 8–20.

[23] S. Morin, M. Lix, W.D. Leslie, The importance of previous fracture site on osteoporosis diagnosis and incident fractures in women, J. Bone Miner. Res. 29 (7) (2014 Jul) 1675–1680.

[24] C.A. Brauer, M. Coca-Perralillon, D.M. Cutler, et al., Incidence and mortality of hip fractures in the United States, JAMA 302 (14) (2009) 1573–1579.

[25] S. Morin, L.M. Lix, M. Azimaee, C. Metge, P. Caetano, W.D. Leslie, Mortality rates after incident non-traumatic fractures in older men and women, Osteoporos. Int. 22 (2011) 2439–2448.

[26] Burge R, Dawson- Hughes, Solomon DH, Wong JB et al. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. J. Bone Miner. Res. 2007; 22:465–75.

[27] US Census Bureau. Anerican Fact Finder. Available at: https://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml.

[28] Centers for Disease Control and Prevention. National Center for Health Statistics. Available at: https://www.cdc.gov/nchs/products/life_tables.htm.

[29] L.J. Melton III, S.J. Achenbach, E.J. Atkinson, et al., Long-term mortality following fractures at different skeletal sites: a population-based cohort study, Osteoporosis Intern 24 (2013) 1689–1696.

[30] Nayak S and Greenspan SL. Cost-effectiveness of 5 versus 10 years of alendronate treatment prior to drug holiday for women with osteoporosis. Osteoporosis Intern https://doi.org/10.1007/s00198-05258-2.

[31] Federal Reserve Bank of St Louis Economic Data. Personal consumption expenditures: Services: Health care (chain-type price index). Available at: https://fred.stlouisfed.org/series/DHLCRG3Q086SBEA#0.

[32] B. Janssen, A. Szende, Population norms for the EQ-5D, in: A. Szende, B. Janssen,

J. Cabases (Eds.), Self-Reported Population Health: An International Perspective Based on EQ-5D, Springer, Dordrecht, 2014.
[33] G.D. Sanders, P.J. Neumann, A. Basu, et al., Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine, JAMA 316 (2016) 1093–1103.
[34] Budgu S, Mikyas Y, Tang M, Badamgarav E. Osteoporotic frsctures: a systemic review of the U.S. healthcare costs and resource utilization. Pharmacoeconomics 2012; 30:147–70.
[35] C. Pike, H.G. Dirnbaum, M. Schiller, H. Sharms, R. Burge, E.T. Edgell, Direct and indirect costs of non-vertebra;l fracture patients with osteoporosis in the US, Pharmacoeconomics. 28 (2010) 395–409.
[36] R.W. Dubois, Cost-effectiveness thresholds in the USA: are they coming? Are they already here? J Comp Eff Res. 5 (1) (2016) 9–11.
[37] World Bank. at: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=US.
[38] Trajanoska K, Schoufour JD, de Jonge EAL et al. Fracture incidence and secular trends between 1989 and 2013 in a population based cohort: The Rotterdam Study Bone 2018; 114; 116–124.
[39] N.C. Wright, A.C. Looker, K.G. Saag, J.R. Curtis, E.S. Delzell, S. Randall, B. Dawson-Hughes, The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine, J. Bone Miner. Res. 29 (11) (2014) 2520–2526.
[40] S.R. Cummings, J. San Martin, M.R. McClung, et al., Denosumab for prevention of fractures in postmenopausal women with osteoporosis, N. Engl. J. Med. 361 (2009) 756–765.
[41] Saag KG, Petersen J, Brandi ML et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. New Engl J Med https://doi.org/10.1056/NEJMMoa1708322.
[42] P.D. Delmas, Treatment of postmenopausal osteoporosis, Lancet. 359 (2002) 2018–2026.
[43] S.A. Quandt, D.E. Thompson, D.L. Schneider, M.C. Nevitt, D.M. Black, Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of-1.6 to −2.5 at the femoral neck: the Fracture Intervention Trial, Mayo Clin. Proc. 80 (3) (2005) 343–349.
[44] J.A. Kanis, O. Johnell, D.M. Black, et al., Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: a reanalysis of the multiple outcomes of raloxifene evaluation trial, Bone 33 (3) (2003) 293–300.
[45] R. Zebaze, C. Libanati, M.R. McClung, J.R. Zanchetta, D.L. Kendler, A. Hoiseth, A. Wang, A. Ghasem-Zadeh, E. Seeman, Denosumab reduces cortical porosity of the proximal femoral shaft in postmenopausal women with osteoporosis, J. Bone Miner. Res. 31 (2016) 1827–1834.