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ORIGINAL RESEARCH

Cost-effectiveness of pulse-echo ultrasonometry in osteoporosis management

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Purpose: Osteoporosis is asymptomatic morbidity of the elderly which develops slowly over several years. Osteoporosis diagnosis has typically involved Fracture Risk Assessment (FRAX) followed by dual energy X-ray absorptiometry (DXA) in specialist care. Point-of-care pulse-echo ultrasound (PEUS) was developed to overcome DXA-related access issues and to enable faster fracture prevention treatment (FPT) initiation. The objective of this study was to evaluate the cost-effectiveness of two proposed osteoporosis management (POMs: FRAX→PEUS-if-needed→DXA-if-needed→FPT-if-needed) pathways including PEUS compared with the current osteoporosis management (FRAX→DXA-if-needed→FPT-if-needed).

Materials and methods: Event-based probabilistic cost–utility model with 10-year duration for osteoporosis management was developed. The model consists of a decision tree for the screening, testing, and diagnosis phase and is followed by a Markov model for the estimation of incidence of four fracture types and mortality. Five clinically relevant patient cohorts (potential primary FPT in women aged 75 or 85 years, secondary FPT in women aged 65, 75, or 85 years) were modeled in the Finnish setting. Generic alendronate FPT was used for those diagnosed with osteoporosis, including persistence overtime. Discounted (3%/year) incremental cost-effectiveness ratio was the primary outcome. Discounted quality-adjusted life-years (QALYs), payer costs (year 2016 value) at per patient and population level, and cost-effectiveness acceptability frontiers were modeled as secondary outcomes.

Results: POMs were cost-effective in all patient subgroups with noteworthy mean per patient cost savings of €121/76 (ranges €107–132/52–96) depending on the scope of PEUS result interpretation (test and diagnose/test only, respectively) and negligible differences in QALYs gained in comparison with current osteoporosis management. In the cost-effectiveness acceptability frontiers, POMs had 95%–100% probability of cost-effectiveness with willingness to pay €24,406/QALY gained. The results were robust in sensitivity analyses. Even when assuming a high cost of PEUS (up to €110/test), POMs were cost-effective in all cohorts.

Conclusion: The inclusion of PEUS to osteoporosis management pathway was cost-effective.

Keywords: diagnostics, dual-energy X-ray absorptiometry, economic evaluation, Fracture Risk Assessment tool, PICOSTEPS, screening

Introduction

Osteoporosis is a typically asymptomatic morbidity of the elderly which develops slowly over several years.[1–3] Osteoporosis weakens the bones through bone loss after the age of 40 years and increases bone loss after menopause and during the final years of life, making them fragile and more likely to break. Osteoporosis diagnosis often occurs only after a minor fall or sudden impact causes a bone fracture.[4–6] Clinically,

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the World Health Organization defines osteoporosis with reference to bone mineral density. Bone mineral density in adults is usually denoted by its T-score relative to the peak bone mass distribution in healthy women aged 20–40 years, and a T-score ≤–2.5 indicates osteoporosis.[7]

Osteoporosis is a common illness with a prevalence estimate of 400,000 (around 7.3% of the population in the year 2016)[8] in Finland. Each year, ~6,000 first and 1,000 repeat hip fractures and a total of 30,000–40,000 osteoporosis-related fractures occur[5] mostly in patients without osteoporosis diagnosis.[6] Although the incidences of some fractures have decreased in Finland (potentially due to improved functional ability, osteoporosis management, and other measures),[9–12] there is an increase in incidence of some fractures.[13–15] The fracture peak may be just emerging in countries such as Finland that had a high birth rate after the second world war, because the incidence of fractures increases exponentially with age.[5] Globally, osteoporosis management is a concern in postmenopausal women. Approximately 40% of women and about 14% of men over 50 years of age will have a hip, vertebral or wrist fracture in their remaining lifetime.[16–18]

Besides the recommendation of adequate dietary calcium and vitamin D intake[5] (211,833 and 6,050 Finns with reimbursement for calcium and vitamin D in the year 2016, respectively), reimbursed fracture prevention treatments (FPTs) in Finland can include hormone replacement therapy (190,194 estrogen, 15,925 testosterone), bisphosphonates (31,549: alendronate [22,028], risedronate [6,310], ibandronate [3,139], clodronate [229], zoledronic acid [54]), denosumab (15,610), strontium ranelate (530), teriparatide (457), and calcitonin (22).[19] In osteoporosis management, two types of osteoporotic fracture prevention are distinguished: primary osteoporotic fracture prevention, which aims to prevent any osteoporosis-related fracture, and secondary osteoporotic fracture prevention, which aims to prevent subsequent osteoporosis-related fracture in osteoporotic individuals who have already suffered a fracture.

Osteoporosis testing of high-risk populations is effective. The high-risk populations for the testing include women aged >65 years with other risk factors such as heavy smoking or parental osteoporosis-related fracture; or individuals with fracture due to low-energy impact; comorbidities or pharmacologic therapies increasing osteoporosis risk; incidental observations on X-rays; or unexplained body height loss.[5] However, identifying the high risk is difficult, and testing bone mineral density in all is not indicated.[7] Recent guidelines[4,5,20,21] and Finnish practice[22] recommend that the 10-year fracture risk, estimated using the proprietary Fracture Risk Assessment (FRAX) tool,[23] should be used to screen potential osteoporosis for testing bone mineral density.

The medical need for effective on-site diagnostics is high, because around three-quarters of osteoporosis cases remain undiagnosed[24] and many osteoporotic individuals are not identified until they experience fracture. Thus, potentially more than three-quarters of osteoporotic individuals do not receive any FPT. This is no surprise, as osteoporosis testing with the current methods alone is challenging.[6]

To overcome the limitations of using mostly radiographic, large diagnostic tools which are rarely available in primary care facilities, a novel handheld device based on the pulse-echo ultrasound technology (pulse-echo ultrasonometry or ultrasonography [PEUS], Bindex®; Bone Index Finland, Kuopio, Finland) was developed.[25–29] PEUS is used as a point-of-care osteoporosis testing-diagnosis tool after FRAX screening and it can help avoid dual-energy X-ray absorptiometry (DXA) for most postmenopausal women.[25,26,29] The bone mineral density estimates obtained using PEUS have correlated very well with those obtained with the DXA method[26,28] and are associated with clinically confirmed fractures in the previous 5 years.[25] The DXA has been the gold standard of choice in the bone mineral density-based diagnostics.[5,20,21,30]

The cost-effectiveness of current care-based conventional osteoporosis management (COM)[4,5,7,20–22] and two proposed osteoporosis managements (POM) including FRAX screening, testing, diagnosis, and FPT if needed was modeled. Based on a literature search in the PubMed database, no assessments have been published on the subject matter. Overall, evidence-based health economic evaluations including the screening, testing, diagnosing, and FPT have been rarely conducted.

Materials and methods

The Patients-Intervention-Comparator-Outcome-Setting-Time-Effects-Perspective-Sensitivity analysis (PICOSTEPS) principle was applied.[31,32] PICOSTEPS is in line with a health technology assessment guideline prepared by the Finnish Medicines Agency,[33] and Finnish official guidance for the cost-effectiveness analyses attached with pharmaceuticals reimbursement applications submitted to the Finnish Pharmaceuticals Pricing Board.[34] Furthermore, PICOSTEPS describes the essential components of evidence-based health economic and outcomes research analytical framework in the order of importance.[31]

Patients

Five risk cohorts of postmenopausal women were modeled based on clinical rationale: women aged 65 years with

secondary osteoporotic fracture prevention, and women aged 75 or 85 years with primary or secondary osteoporotic fracture prevention.[5] The other characteristics were: T-score −2.8 (normal distribution, 95% CI −3.1 to −2.5) for osteoporotic and −0.25 (95% CI −1.00 to 0.50) for non-osteoporotic,[23] and no parental hip fracture, oral glucocorticoid therapy, rheumatoid arthritis, or alcoholism. The potential events included hip (institutionalized to long-term care after the hip fracture or not institutionalized), vertebral, wrist, and other fractures.

Intervention and comparator

The cost-effectiveness of osteoporosis management pathways (Figure 1) was simulated in the osteoporosis screening–testing–diagnosis model, namely, the POM (FRAX followed by (→) PEUS-if-needed→DXA-if-needed→FPT-if-needed) and

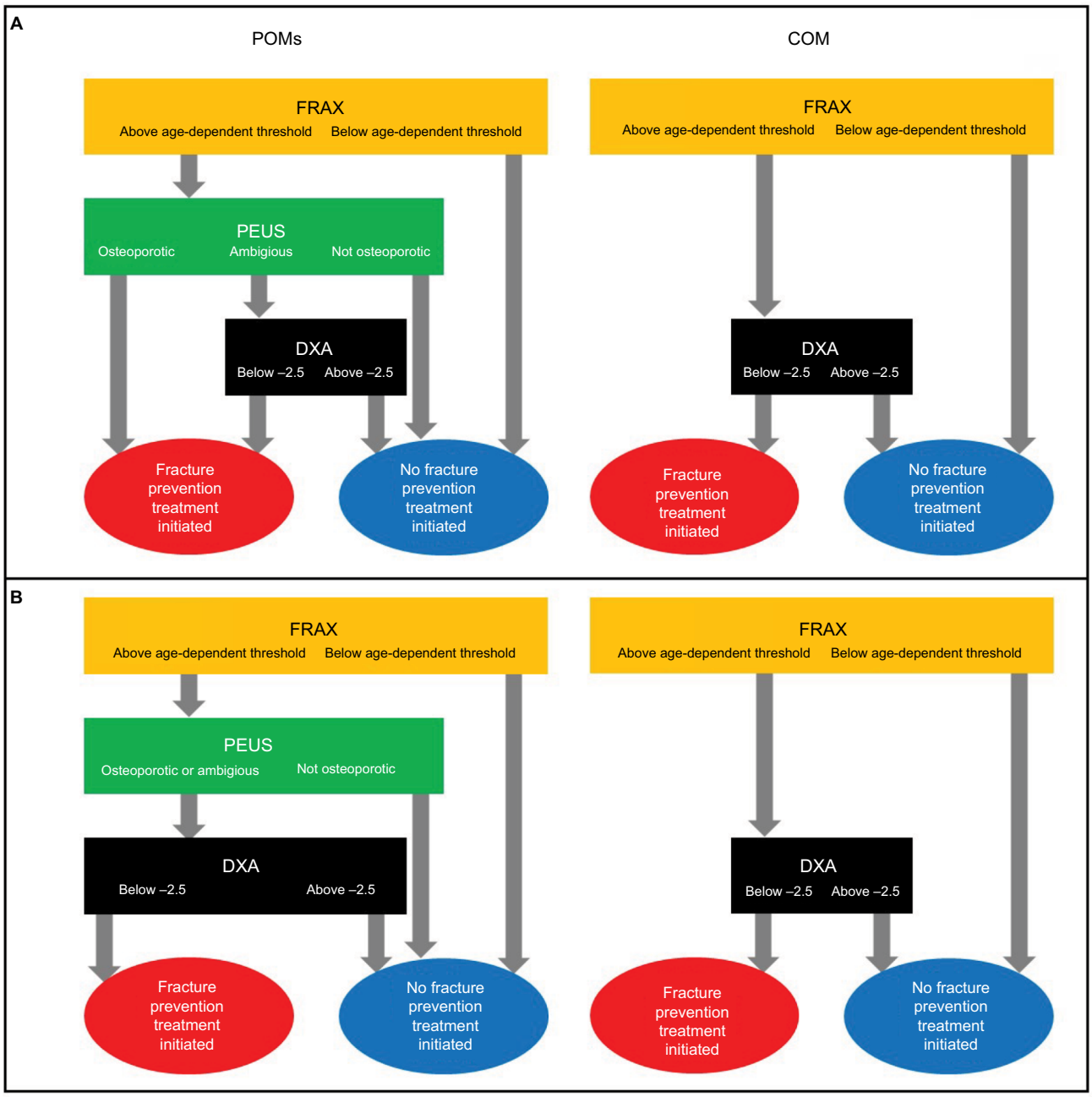

Figure 1 Decision tree: POM pathways are on the left-hand side and the COM pathway is on the right-hand side.
Notes: The upper part of (**A**) presents the POMA strategy, where PEUS is used for osteoporosis testing and diagnosis.[25–29] The lower part of (**B**) presents the alternative, POMB strategy, where PEUS is used for osteoporosis testing only and a positive diagnosis is confirmed with DXA.
Abbreviations: COM, conventional osteoporosis management; DXA, dual-energy X-ray absorptiometry; FRAX, Fracture Risk Assessment; PEUS, pulse-echo ultrasound technology; POM, proposed osteoporosis management; POMA, proposed osteoporosis management pathway A; POMB, proposed osteoporosis management pathway B.

COM (FRAX→DXA-if-needed→FPT-if-needed). COM as a comparator was based on its clinical rationale and recommendation in Finland[5] and elsewhere.[4,7,20–22,30] POM was included as the intervention based on its results[25–29] and potential affordability.

The need for PEUS and/or DXA in the model is based on the age-dependent FRAX,[23] which predicts the 10-year fracture risk to help the clinical decision making.[5,23] If the 10-year fracture risk exceeded the age-dependent threshold values of 5.9% (age 65–74 years), 11.7% (75–84), or 19.8% (85–) in the FRAX screening, intermediate fracture risk was present and bone mineral density was assessed (i.e., the individual underwent PEUS and/or DXA). If the 10-year fracture risk was below the age-dependent threshold values in the FRAX screening, low fracture risk was present and lifestyle advice and reassurance were given.

Outcome

The key outcome of the analysis was an incremental cost-effectiveness ratio: the difference in simulated costs divided by the difference in simulated effectiveness. Also, the mean costs and effectiveness were presented as secondary outcomes.

Setting

The event-based modeling approach with a clinical decision tree and a Markov extrapolation model[35,36] was selected to capture all relevant data and to simulate (5,000 iterations) the comprehensive osteoporosis management in Finland using Microsoft Excel 2016 with Visual Basic for Applications. A decision tree analysis was done to model the screening–testing–diagnosis process preceding the potential initiation of FPT (Figure 1). A Markov modeling followed to assess the fractures and FPT (Figure 2). The event-based modeling strategy was carried out as follows: specify diagnosis and determine initial cohort distribution, define the natural history of the disease (i.e., events and their risks), apply relative risk modifiers (i.e., patient characteristics and treatments), compute costs and effectiveness, and run the simulation model.

Testing and diagnosis: decision tree model

The osteoporosis screening–testing–diagnosis decision tree model (Figure 1) included COM and POM, and their sensitivity and specificity. FRAX constituted the initial screening tool common to both pathways,[23] with a mean accuracy rate of 1.000 (assumed normal 0.975–1.025 95% CI).

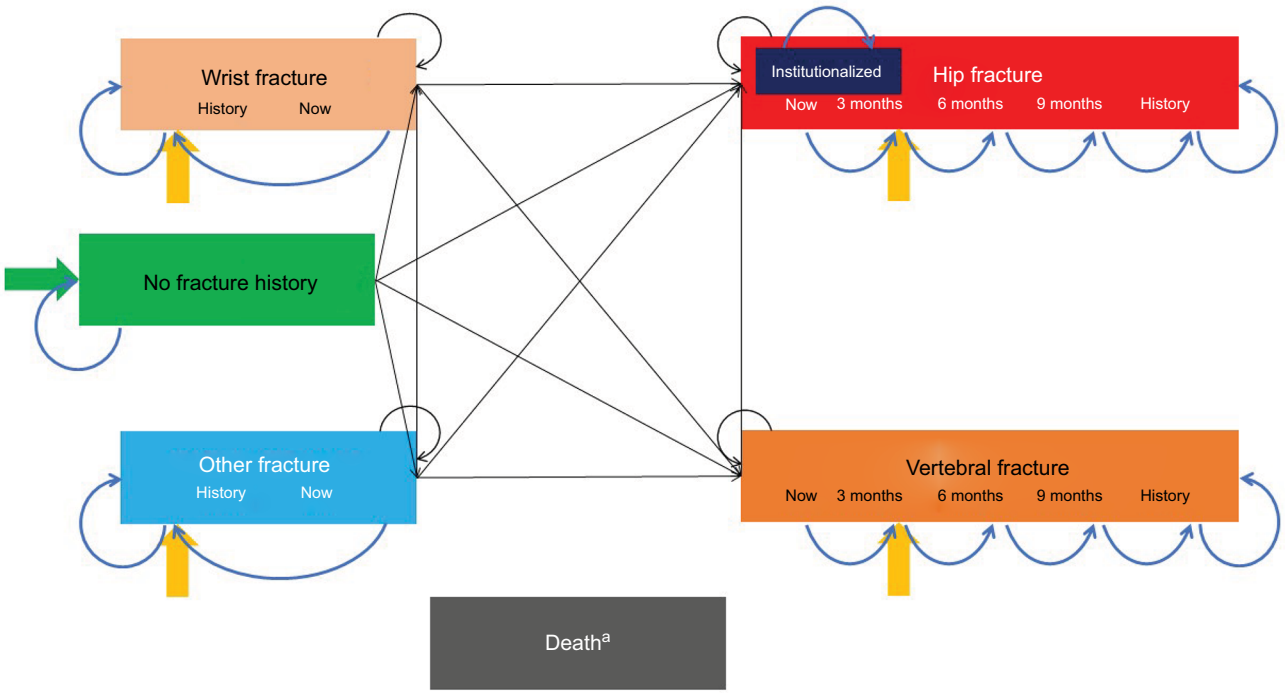

Figure 2 Markov model.
Notes: The bold green arrow points to the starting state of primary prevention of osteoporotic fractures, and the bold yellow arrows point to the starting state of secondary prevention. The black arrows correspond to fracture events, and the blue arrows indicate health-state transitions without new fractures. [a]Transitions to the absorbing dead state are possible from any state.

In the decision tree, PEUS was calibrated to the 90% sensitivity–specificity threshold in accordance with the International Society for Clinical Densitometry guidelines[37,38] and modeled using Dirichlet distribution (i.e., altogether 10% of PEUS results are false negatives or false positives and have incorrect osteoporosis management). Thus, cost-effectiveness analysis with correct and incorrect treatment pathways was needed to evaluate how much effectiveness is potentially lost when using the POM.

In the POM pathway A (POMA, Figure 1) of the decision tree, 32.6% of individuals have ambiguous PEUS results (between the 90% sensitivity–specificity calibration thresholds).[26] These individuals require and are provided a DXA measurement to verify the diagnosis. A recent real-world study confirmed the proportion of ambiguous PEUS results with the need of sending 32.5% of individuals to DXA investigation after PEUS measurement.[29] In POMA, both false positives and negatives occur up to 10% of the patients in total and are modeled accordingly. These results constituted initial cohort distribution for the Markov model in the case of POMA. Thus, in the POMA strategy, PEUS is used for osteoporosis testing and diagnosis,[25–29] which is a potentially common strategy in the Finnish public sector based on the clinical and economic rationale.

In the POM pathway B (POMB, Figure 1) of the decision tree, both ambiguous and osteoporotic PEUS results require and receive a DXA measurement, which eliminates the false positives. These results constituted the initial cohort distribution for the Markov model in the case of POMB. Thus, in the POMB strategy, PEUS is used for osteoporosis testing only and a positive diagnosis is confirmed with DXA, which can be a potentially common strategy in, for example, the USA.

Bone fractures and prevention: Markov model

The fractures and FPT were modeled with a Markov state transition model. The transitions were determined by clinical outcomes and a hierarchy of fractures was assumed, with hip fractures being more serious than vertebral fractures, which were in turn more serious than wrist and other fractures (Figure 2). Due to the duration of the fractures and available data, the Markov model had a 3-month cycle. Hip and vertebral fractures were represented as tunnel states because their costs and mortality depended on the time since the fracture. A state was used to model the proportion of individuals who were permanently institutionalized after a hip fracture.

In osteoporosis, the fracture risk can be reduced through FPT. A review of postmenopausal osteoporosis FPTs has been recently published,[39] and alendronate once weekly is recommended as the first-line FPT in Finland.[5] In addition, generic alendronate is the most affordable FPT[40] with a high number of reimbursements in Finland[19] and it is also likely to be a cost-effective FPT.

Time

The modeling was limited to 10 years due to the age of most individuals, potential changes in the FPTs, and limited knowledge regarding the extrapolated effects beyond 10 years (FRAX represents 10-year risk).[7,23] Conversions between rates and probabilities were performed using the common transformation methodology.[41] The annual discounting rate of effectiveness and costs was 3%.[33,34]

Effects

The long-term Markov fracture and FPT modeling included hip, vertebra, wrist, and other fractures. Finnish FRAX collaboration data demonstrated the 10-year risk of hip or any fracture in Finland per individual's age, bone mineral density (T-score), and number of risk factors.[7,23] To find osteoporotic fractures, US-based data on the age- and sex-specific relative risk of fracture attributable to osteoporosis were used.[42] Relative risk for fracture was increased in individuals with a prior fracture, which could be accounted for by using the FRAX risk lookup, where prior fracture is one of the risk factors.[23] The age-dependent results on the fracture rates in the USA were then used to split the Finnish 10-year risk estimate of any fracture into component types of vertebra, wrist, or other fracture and modelled in the Markov model.[42] The fracture prevention Markov model concurred with the health states used in earlier evaluations.[43] Furthermore, institutionalization risk to long-term facility after hip fracture was modeled based on the Finnish real-world evidence.[44]

Alendronate 70 mg/week FPT was modeled for osteoporotic individuals. For them, the fracture occurrence was adjusted downward based on the distributional efficacy estimated from a published meta-analysis of FPT.[45,46] Suboptimal FPT uptake (adherence) based on 20% adherence at 5 years modified the efficacy through persistence to mimic the real-world situation.[47,46] In line with this modeling study, the study included postmenopausal women, naive to bisphosphonates, who received a first prescription of alendronate.[47] No rebound was assumed (i.e., FPT effect stops at the time of FPT discontinuation; Table 1).

The individuals can die from any health state. The background mortality was modeled based on the year 2016 official Finnish mortality statistics,[48] excluding deaths due to osteoporosis (10th revision of the International Statistical

Table 1 Effect estimates, CI or SEs, and distributions applied

Estimated decrease in fracture risk due to alendronate therapy in women				
Primary/secondary prevention	*Relative risk*	*95% CI*		*Distribution*
Hip fracture[45,46]	0.66/0.49	0.30/0.24	1.54/1.01	Lognormal from 95% CI
Vertebral fracture[45,46]	0.60[a]/0.53[a]	0.43/0.41	0.80/0.68	Lognormal from 95% CI
Wrist fracture[45,46]	0.67/0.52[a]	0.19/0.33	2.32/0.92	Lognormal from 95% CI
Other fracture[45,46]	0.80[a]/0.99	0.67/0.76	0.97/1.29	Lognormal from 95% CI
Institutionalized	*Probability*	*SE*		*Distribution*
After hip fracture[44]	0.148	0.100		Uniform±P2%
FPT	*Probability*	*SE*		*Distribution*
Start FPT if osteoporosis (assumption)	1.000	0.000		Uniform±P2%
Continue FPT per year[47,46]	0.725	0.100		Uniform±P2%
HRQoL without fracture[51]	*Mean*	*SE*		*Distribution*
65–74 years	0.842	0.010		Normal with SE
75–84 years	0.808	0.013		Normal with SE
85+ years	0.685	0.030		Normal with SE
Disutility to HRQoL	*Mean*	*SE*		*Distribution*
Alendronate use (assumption)	–0.010	0.010		Uniform±P2
Multiplicative HRQoL decrement[52]	*Relative risk*	α	β	*Distribution*
Hip fracture, first/subsequent year	0.797/0.899	655/2,007	167/225	Beta
Vertebral fracture, first/subsequent year	0.720/0.931	169/1,021	66/76	Beta
Wrist or other fracture, first 3 months	0.940/0.910	326/318	21/31	Beta

Note: [a]Statistically credible effect as the FPT was based on the 95% CI.
Abbreviations: FPT, fracture prevention treatment (alendronate); HRQoL, health-related quality of life; SE, standard error; CI, confidence interval.

Classification of Diseases codes M80 or M81).[48,49] The FPT had an indirect effect through fractures to mortality. An elevated mortality relative risk of 4.53 during the first 6 months after the hip or vertebral fracture (1.75 in the subsequent 6 months and 1.78 thereafter) was modeled.[50,42] Wrist or other fractures were not considered to increase mortality.

Finally, health-related quality of life was modeled using nationally representative age-, income-, education-, marital status-, and morbidity-adjusted Finnish EuroQol 5-dimensional 3-level scores for women based on a Tobit model,[51] and multiplicative health-related quality of life losses associated with the fractures.[46,52] The EuroQol 5-dimensional 3-level scores used represent the most suitable health-related quality of life for a postmenopausal woman available for the Finnish modeling purposes. Alendronate use was conservatively assumed to be associated with reduction in health-related quality of life (Table 1).

Perspective

The analysis included direct costs based on the Finnish guidance,[33,34] and applied third-party payer perspective common in the guidance of many European countries.[53–62] The analysis included direct health-related costs (e.g., patient co-payments, FPTs, treatments, visits, hospitalizations, traveling)[33,34] and excluded taxes, productivity losses (e.g., absenteeism, presenteeism, sickness allowances, pensions), other income transfers, and time costs.

Costs

The Finnish weekly cost of the most affordable generic alendronate 70 mg was €1.70, excluding value-added tax.[40] Fracture-associated costs were estimated based on the Finnish resource use in a representative national register study,[44] which was valued with the national Finnish unit costs[63] according to real values in the year 2016 (Table 2).[64] The national health care costs[63] were converted to year 2016 values using the latest official Finnish Communal Expenses Index for health care.[64] Traveling costs[65] were converted to 2016 real values using the transportation section of the latest official Finnish Consumer Price Index.[66] Due to lack of data, a recursive fracture was considered to have the same costs and consequences as the first fracture.

Proprietary FRAX was available free of charge.[23] Finnish year 2016 price lists of hospital districts were searched to find the prices of DXA measurements. A price of €268 (incl. visit price) could be a representative input value (i.e., average of most affordable prices per district incl. visit was €297.50), with the lowest (€124.00, probably not feasible) and highest (€476.00) costs. The mean cost of specialist visit and the mean cost of DXA measurement alone would be €313.76 and €67.50, respectively, that is, a total of €381.26. However,

Table 2 Fracture costs (€, in the year 2016 real value)

State, unit	Resource	Weighting basis[63]	Weighted cost[63,a]	Cost/event[b]
Hip fracture, months 1–3	44.0% artificial joint[44]	DRG 209B–C	8,150.73	7,760.47
	49.3% other surgery[44]	DRG 210–211	7,436.07	
	6.7% without surgery: index hospitalization 7.1 days[44]	996.20/day	7,584.58	
Institutionalized, per 3 months	91.31 days	115.00/day	123.32	11,260.66
Hip fracture history, months 4–6, 7–9, 10–12[c]	8.2 days of specialist hospitalization, index hospitalization excluded,[44] 33.3% based on clinical experience	996.20/day	8,759.65	5,511.27
	60.4 primary care days,[44] 33.3% based on clinical experience	115.00/day	7,448.53	
	2.9 primary care visits[44] 33.3% based on clinical experience	110.00/visit	342.08	
Vertebral fracture, months 1–3		DRG 214A–C, 215A–C	7,038.51	7,038.51
Vertebral fracture, months 4–6, 7–9, 10–12[c]	Derived proportionally: hip fracture costs in months 4–6 vs. 1–3	DRG 214A–C, 215A–C	Proportionally 4,998.55	4,998.55
Wrist or other fracture, months 1–3[c]		DRG 218–219, 223, 225A–B DRG 235–236, 250–251, 253–254	3,157.59	3,157.59

Notes: All state costs were assumed to vary by ±10%. [a]Weighted,[63] and converted to 2016 value.[64] [b]Excluding travel to the secondary (€39.09) or primary (€7.65) care location that was included in the modeling.[65,66] [c]No additional costs were included for the subsequent years after hip or vertebral fracture or for the subsequent months after wrist or other fracture.
Abbreviation: DRG, diagnosis-related group.

for conservative results, €87.00 was used as the base case input for DXA cost. Thus, the total cost of DXA included one primary care doctor visit and travel (€133.26), the DXA test (€87.00, excluding visit) on the official Finnish price lists for communal invoicing, travels (€78.18),[65,66] call (€27.88), and statement (€21.45).[63,64]

The total cost of the PEUS single-site test included primary care nurse visit and travel (€66.77),[63–66] call (€27.88) and statement (€21.45),[63,64] and PEUS test (€50.00), and the total cost of the DXA specified above for the proportion of individuals undergoing the DXA in POM. The assumed cost of PEUS may overestimate the true PEUS cost to Finnish health care.

Willingness to pay

A complicating factor when interpreting the results of cost-effectiveness analysis in the Finnish setting is the lack of an official willingness-to-pay threshold,[67–69] a specific limit for additional investment to an additional quality-adjusted life year (QALY) gained.

In the UK, the most plausible willingness-to-pay threshold in non-end-of-life situations is £20,000[60] (€24,406, mean exchange rate €1=£0.81948 in the year 2016),[70] or maybe, in some cases, up to £30,000 (€36,609) per QALY gained.[60,70] These willingness-to-pay thresholds may also be valid for the screening–testing–diagnosing–osteoporotic fracture prevention if needed process in Finland.[67–69]

Sensitivity

The robustness of results was tested using one-way and multiway sensitivity analysis scenarios. These included Patient, Setting, and Effects.

The sensitivity of probabilistic analysis was implemented based on distributions, and results were depicted in terms of a cost-effectiveness acceptability frontier.[71] The frontier showed the optimal strategies with the highest expected monetary net benefit (pay-off) as a function of willingness to pay.

Results

The average absolute costs saved with POMA vs. COM were €121/patient (1.3%), ranging from €107/patient (75 years old, primary or secondary osteoporotic fracture prevention) to €132/patient (85 years old, secondary osteoporotic fracture prevention). The relative savings with POMA ranged from 1.0%/patient (75 years old, secondary osteoporotic fracture prevention) to 1.7%/patient (65 years old, secondary osteoporotic fracture prevention). The average absolute costs saved with POMB vs. COM were €76/patient (0.8%), ranging from €52/patient (0.5%; 75 years old, secondary osteoporotic fracture prevention) to €96/patient (1.1%; 85 years old, primary osteoporotic fracture prevention), as shown in Table 3.

In a setting of 40,000 tested women per year, POMA could result in potential annual cost savings of around €4.8 million (range €4.3–5.3 million depending on the

Table 3 Ten-year base case results with 3% per annum discounting: COM pathway vs. POM pathways

Age (years), cohort	POMA: PEUS used for testing and diagnosis			POMB: PEUS used for testing only		
65, SOFPT	*Costs (€)*	*QALYs*	*CE verdict*	*Costs (€)*	*QALYs*	*CE verdict*
COM	7,581	6.802	ICER 307,527[a]	7,565	6.805	Dominated[b]
POM	7,451	6.802	Most affordable	7,502	6.806	Most affordable
75, POFPT	*Costs (€)*	*QALYs*	*CE verdict*	*Costs (€)*	*QALYs*	*CE verdict*
COM	9,638	5.701	ICER 60,478[a]	9,748	5.697	Dominated[b]
POM	9,531	5.699	Most affordable	9,668	5.697	Most affordable
75, SOFPT	*Costs (€)*	*QALYs*	*CE verdict*	*Costs (€)*	*QALYs*	*CE verdict*
COM	10,280	5.684	ICER 87,808[a]	10,147	5.698	Dominated[b]
POM	10,173	5.683	Most affordable	10,094	5.699	Most affordable
85, POFPT	*Costs (€)*	*QALYs*	*CE verdict*	*Costs (€)*	*QALYs*	*CE verdict*
COM	8,753	3.096	ICER 90,387[a]	8,930	3.084	Dominated[b]
POM	8,622	3.095	Most affordable	8,834	3.084	Most affordable
85, SOFPT	*Costs (€)*	*QALYs*	*CE verdict*	*Costs (€)*	*QALYs*	*CE verdict*
COM	9,107	3.065	ICER 101,120[a]	9,084	3.072	Dominated[b]
POM	8,975	3.064	Most affordable	8,993	3.072	Most affordable

Notes: [a]COM probably not cost-effective in comparison to POMA in Finland. [b]Dominated, POMB is more or as effective and less costly than COM.
Abbreviations: CE, cost-effectiveness; COM, conventional osteoporosis management; ICER, incremental cost-effectiveness ratio; PEUS, pulse-echo ultrasonography; POFPT, primary osteoporotic fracture prevention treatment; POM, proposed osteoporosis management; POMA, proposed osteoporosis management pathway A; POMB, proposed osteoporosis management pathway B; QALY, quality-adjusted life year; SOFPT, secondary osteoporotic fracture prevention treatment.

patient group). The respective potential annual cost savings with POMB could be €3.0 (€2.1–3.8) million.

Cost-effectiveness

COM resulted in a marginal average QALY gain of 0.001 in comparison with POMA. Due to the negligible QALY gain and additional costs, COM was not cost-effective (the incremental cost-effectiveness ratios range from €60,000 to 308,000/QALY gained) vs. POMA with the common willingness-to-pay threshold values. However, POMB dominated COM, as it resulted in negligible or similar QALY gain with lower costs (Table 3).

Sensitivity analyses

Multiple one-way and multiway sensitivity analysis scenarios were used (Table 4).

For the COM vs. POMA comparison, these sensitivity analyses scenarios included the following:

- A. Base case
- B. Mean T-score of −3.5 (severe osteoporosis)
- C. No discounting
- D. Discounting 5%/year
- E. 50% initiate FPT
- F. 75% initiate FPT
- G. 10% adherent to FPT at 5 years
- H. 30% adherent to FPT at 5 years
- I. No disutility due to FPT
- J. DXA cost of €124.00 (the most affordable cost based on the cost review)
- K. DXA cost of €381.26 (the expected cost based on the cost review)
- L. PEUS test cost assumption of €20.00
- M. PEUS test cost assumption of €35.00
- N. Institutionalization costs of €154.00/day (elderly home)[63]
- O. Fracture costs decreased by 25%
- P. Fracture costs increased by 25%
- Q. No travel costs included (direct health care costs only)
- R. Travel costs doubled
- S. DXA-related travel costs doubled
- T. Mean of sensitivity analysis scenarios B–S.

For the COM vs. POMB comparison, the reported sensitivity analysis scenarios included the following:

- U. Base case
- V. Mean T-score of −3.5 (severe osteoporosis)
- W. 30% adherent to FPT at 5 years
- X. No travel costs
- Y. No disutility due to FPT.

Based on the sensitivity analyses, the results were most sensitive to the large-scale changes in FPT (initiation proportion, disutility), DXA (cost, traveling), and T-score. Yet, POM remained the most cost-effective option and the base case analyses were conservative (i.e., did not benefit POM). For example, the analyses demonstrated that osteoporosis should be detected early and preferably before the first osteoporotic fracture, baseline T-score has significant impact on the cost-effectiveness, FPT should be initiated for osteoporosis and

Table 4 Sensitivity analyses presenting incremental cost-effectiveness ratios and their changes: COM pathway vs. POM pathways

Outcome Population	ICER (€/QALY gained) COM vs. POMA					Relative change in the ICER				
	65 years, SOFPT	75 years, POFPT	75 years, SOFPT	85 years, POFPT	85 years, SOFPT	65 years, SOFPT	75 years, POFPT	75 years, SOFPT	85 years, POFPT	85 years, SOFPT
A	307,527	60,478	87,808	90,387	101,120	0%	0%	0%	0%	0%
B	106,632	36,329	36,437	71,102	75,406	–65%	–40%	–59%	–21%	–25%
C	277,233	50,788	70,979	80,992	89,877	–10%	–16%	–19%	–10%	–11%
D	370,968	67,643	100,197	99,678	108,871	21%	12%	14%	10%	8%
E	736,976	153,302	222,338	205,894	223,221	140%	153%	153%	128%	121%
F	455,350	91,241	129,624	129,711	141,149	48%	51%	48%	44%	40%
G	441,273	89,747	128,015	120,965	133,275	43%	48%	46%	34%	32%
H	251,611	44,868	64,221	76,150	82,704	–18%	–26%	–27%	–16%	–18%
I	301,715	162,729	121,130	237,198	235,259	–2%	169%	38%	162%	133%
J	386,754	79,653	110,185	115,000	124,890	26%	32%	25%	27%	24%
K	867,136	176,648	251,845	234,590	253,622	182%	192%	187%	160%	151%
L	428,712	77,996	113,259	112,764	123,413	39%	29%	29%	25%	22%
M	340,647	69,718	100,488	102,231	111,567	11%	15%	14%	13%	10%
N	300,647	57,528	78,936	90,864	98,197	–2%	–5%	–10%	1%	–3%
O	294,639	58,489	81,381	90,739	98,035	–4%	–3%	–7%	0%	–3%
P	318,927	63,252	92,466	94,118	104,055	4%	5%	5%	4%	3%
Q	181,697	29,905	42,728	53,457	58,394	–41%	–51%	–51%	–41%	–42%
R	502,468	91,773	130,201	128,363	139,178	63%	52%	48%	42%	38%
S	437,742	96,665	141,486	136,277	149,386	42%	60%	61%	51%	48%
T	384,666	82,040	110,722	119,499	129,033	25%	36%	26%	32%	28%
COM vs. POMB	*65 years, SOFPT*	*75 years, POFPT*	*75 years, SOFPT*	*85 years, POFPT*	*85 years, SOFPT*	*65 years, SOFPT*	*75 years, POFPT*	*75 years, SOFPT*	*85 years, POFPT*	*85 years, SOFPT*
U	Dom.	Dom.	Dom.	Dom.	Dom.	na	na	na	na	na
V	Dom.	169,931	54,706	425,108	514,020	na	na	na	na	na
W	Dom.	Dom.	Dom.	Dom.	Dom.	na	na	na	na	na
X	Dom.	Dom.	Dom.	Dom.	Dom.	na	na	na	na	na
Y	149,093	125,290	63,170	178,992	167,249	na	na	na	na	na

Notes: A. Base case; B. mean T-score –3.5; C. discounting 0%/year; D. discounting 5%/year; E. 50% initiate fracture prevention treatment; F. 75% initiate fracture prevention treatment; G. 10% adherent to fracture prevention treatment at 5 years; H. 30% adherent to fracture prevention treatment at 5 years; I. no disutility due to fracture prevention treatment; J. DXA €124.00; K. DXA €381.26; L. PEUS test €20.00; M. PEUS test €35.00; N. institutionalized €154.00/day; O. fracture costs –25%; P. fracture costs +25%; Q. no travel costs; R. travel costs doubled; S. DXA travel costs doubled; T. mean of sensitivity analysis scenarios; U. base case; V. mean T-score –3.5; W. 30% adherent to fracture prevention treatment at 5 years; X. no travel costs; Y. no disutility due to fracture prevention treatment.

Abbreviations: COM, conventional osteoporosis management; Dom., POM more effective and less costly vs. COM; DXA, dual-energy X-ray absorptiometry; ICER, incremental cost-effectiveness ratio; PEUS, pulse-echo ultrasonography; POFPT, primary osteoporotic fracture prevention treatment; POMA, proposed osteoporosis management A (PEUS used for testing and diagnosis); POMB, proposed osteoporosis management B (PEUS used for testing); QALY, quality-adjusted life year; SOFPT, secondary osteoporotic fracture prevention treatment; na, not applicable.

used persistently, DXA travel has the largest impact regarding traveling costs, and any increase in the potentially underestimated DXA-associated costs can significantly decrease the cost-effectiveness of COM.

Based on the simulations for different base case testing outcomes, the expected additional cost/patient due to the FPT assignment being based on the results of a slightly inaccurate PEUS was small (€35–61 for POMA, average being €46, and €0–22 for POMB, average being €7, over the 10 years; varying by risk group) in comparison with the total costs or cost savings. Based on a face validity assessment scenario with 100% sensitivity–specificity for PEUS, the QALYs were similar for COM and POM, and the expected average cost difference of €165 (average value's range €162–168 dependent on the patient group) in favor of POM was observed (i.e., POM would be strongly dominant in the case of similar sensitivity–specificity of PEUS and DXA). On the other hand, in an unrealistic extreme sensitivity analysis scenario with 82% sensitivity–specificity threshold for PEUS, the average QALY difference increased with 0.001 between COM and POM in comparison to the COM vs. POMA base case, and the average cost difference decreased to €91 between COM and POM, resulting in €42,604/QALY gained for COM vs. POM.

POMA had 96%–100% probabilities for cost-effectiveness vs. COM at the €24,406 willingness to pay/QALY gained and depending on the patients modeled (Figure 3). The respective results for POMB were 95%–100%. With

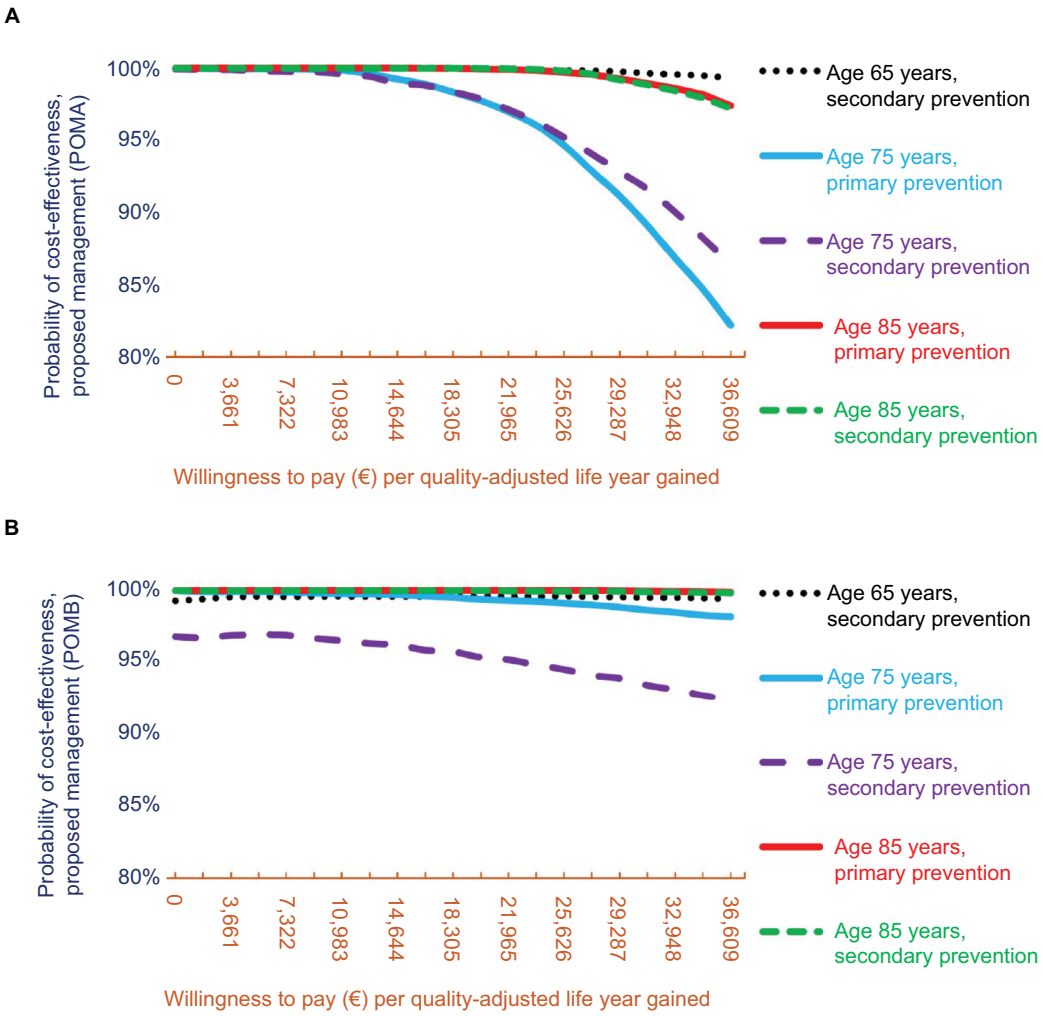

Figure 3 Cost-effectiveness acceptability frontiers with sensible willingness-to-pay values of €0–36,609 per quality-adjusted life year gained present high probabilities (82%–100%) of cost-effectiveness for POMA (upper part [**A**], PEUS is used for the osteoporosis testing and diagnosis) and POMB (lower part [**B**], patient tested with PEUS).
Abbreviations: PEUS, pulse-echo ultrasound technology; POMA, proposed osteoporosis management pathway A; POMB, proposed osteoporosis management pathway B.

the €36,609 willingness to pay/QALY gained, POMA had 82%–99% probabilities for cost-effectiveness. The respective probabilities for POMB were 92%–100%. With the €0 willingness to pay/QALY gained, POMA and POMB had 100% and 97%–100% probabilities for cost-effectiveness, respectively.

Finally, for descriptive purposes, Table 5 reports the number of simulated fractures based on the treatment allocation and over the maximum time horizon of 10 years (mortality included) for a 75-year-old female without any significant clinical risk factors and with an average T-score of −2.8. Generally, the most frequent fractures include hip and other fractures. Given the incidence and unit cost of fractures, the highest expected cost impact for the first 3 months after a fracture was estimated for hip fractures.

Discussion

Recently, the cost-effectiveness of FPTs has been reviewed,[39] and the cost-effectiveness of osteoporosis testing and FPT has been debated.[30] This study assessed for the first time the incremental cost-effectiveness of two proposed (POMs: FRAX→PEUS-when-needed→DXA-when-needed) vs. conventional (COM: FRAX→DXA-when-needed) osteoporosis management pathways in Finland using generic alendronate FPT for osteoporotic individuals. POMs could result in payer cost savings, regardless of whether PEUS is used for both osteoporosis testing–diagnosing (POMA) or testing only (POMB). POM and the societal perspective appraised in countries such as Sweden would result in additional cost savings, as most of the indirect costs would be associated with the DXA measurement.

Table 5 Simulated fractures during the maximum time horizon of 10 years for a 75-year-old non-smoking female with no parental hip fracture, no oral glucocorticoid, no rheumatoid arthritis, no alcoholism, and an average T-score of −2.8

Patient allocation			
FPT, osteoporosis (true positive)	*Mean*	*95% CI*	*Expected first 3-month cost (€)*[a]
Hip fractures	0.058	0.036–0.092	453
Vertebral fractures	0.012	0.000–0.025	86
Wrist fracture	0.008	0.000–0.021	29
Other fracture	0.022	0.000–0.071	76
Sum	0.100		644
No FPT, osteoporosis (false negative)	*Mean*	*95% CI*	*Expected first 3-month cost (€)*[a]
Hip fractures	0.075	0.059–0.118	586
Vertebral fractures	0.015	0.000–0.030	107
Wrist fracture	0.010	0.000–0.025	36
Other fracture	0.022	0.000–0.070	75
Sum	0.122		804
FPT, without osteoporosis (false positive) or no FPT, without osteoporosis (true negative)	*Mean*	*95% CI*	*Expected first 3-month cost (€)*[a]
Hip fractures	0.017	0.010–0.026	131
Vertebral fractures	0.006	0.000–0.011	41
Wrist fracture	0.004	0.000–0.010	14
Other fracture	0.008	0.000–0.027	29
Sum	0.035		215

Note: [a]Expected first 3-month costs were estimated for the demonstration purposes only and were based on the simulated mean incidence over the maximum 10 years' time horizon and the average unit costs of first 3 months with a fracture.
Abbreviation: FPT, fracture prevention treatment (alendronate, persistence accounted for).

The incremental cost-effectiveness ratios of COM vs. POMA were high and POMB dominated COM, which indicated that COM would not be cost-effective in comparison to POMs in the Finnish setting or in most of the European settings. Although COM produced marginally more QALYs (0.001) vs. POMA due to false positives and negatives related to PEUS use, it was far too expensive to achieve reasonable cost-effectiveness. At €24,406 willingness to pay/QALY gained, POM had 95%–100% cost-effectiveness probability.

The osteoporosis management costs were reduced when PEUS was included. The additional cost due to the FPT assignment being based on the PEUS was small in comparison with the total costs. The results were sensitive to the large-scale changes in the FPT, DXA-associated costs, and T-score. However, POMs remained cost-effective vs. COM in the extensive sensitivity analyses.

Based on the explorative analyses, osteoporosis should be detected early and preferably before osteoporotic fracture, T-score has significant impact on the cost-effectiveness, and FPT should be initiated for osteoporosis and used persistently. If 40,000 women were screened per year and FPT was initiated for the osteoporotic, POMA or POMB could easily result in average annual savings of ~€5 or €3 million in the limited social and health care budgets, respectively.

However, evaluation with decision analytical modeling is a simplification of the complex reality. A typical approach is analysis using trial-based efficacy outcomes alone and a demonstration that the intervention may work in optimal and controlled settings. A more difficult and realistic modeling framework was carried out here. As examples, real-world, evidence-based health-related quality of life and persistence, and conservative sensitivity and specificity thresholds for PEUS were used.

Further conservative assumptions were made. For example, DXA measurement was assumed to be 100% accurate, which may not be true due to various human errors, calibration issues or hardware faults. Alendronate FPT was assumed to result in disutility. Sensitivity and specificity of PEUS were accounted for. A partial consequence of this was that especially POMA led to marginally fewer QALYs in comparison with COM. However, the average difference was only 0.001 QALYs (0.03%), which is a negligible difference.

In a larger scope, the PEUS[25–29] just recently received a new reimbursement code (0508T: pulse-echo ultrasound bone density measurement resulting in indicator of axial bone mineral density, tibia) from the American Medical Association.[72] Considering the previously published evidence on the PEUS method,[25,26,29] the American Medical Association reimbursement,[72] and the cost-effectiveness results reported here, the use of PEUS as a part of the POM pathway for screening and diagnostics in 65- to 80-year-old postmenopausal Caucasian women is supported.

In addition, access to DXA can be more expensive than assumed here, or even impossible in remote areas. Using an affordable cost of DXA based on the current DXA tests and potentially underestimated traveling costs, PEUS can easily be cost-effective at a cost-per-single-site test of up to around €110 (i.e., 2.2 times the probably overestimated cost used in the base case) in all modeled cohorts. If the costs associated with DXA were higher (e.g., if there is a long distance to the nearest DXA device), an even higher price per PEUS test could be economically justifiable. The Finnish results of POMs with PEUS may underestimate the savings in other countries, but studies in other settings regarding the traveling cost and the optimal location of DXA are needed to confirm such a conclusion.

Finally, more flexible and agile, economically justifiable methods for screening, detecting, and predicting the course of any important or frequent disease or situation are supported governmentally by the encompassing digitalization of social and health care services as well as by the secondary use of health and social welfare data in Finland. More specifically, the assessment and implementation of digitalized customer-responsive health and social care services including, for example, Omahoito ja Digitaaliset Arvopalvelut (ODA) - digitalized services for primary health and social care,[73,74] together with the associated Health Village are under their way. Moreover, the secondary use data lakes covering social and health data have been tested through so-called Isaacus pre-production projects,[75,76] and the remote use platforms for the data lakes together with scientist tools are being built to enable knowledge management and research.[75] Tools with novel data collecting software such as PEUS[25–29] are likely to fit well to this ongoing development.

Conclusion

A significant unmet need for new, safe, and effective osteoporosis diagnosis exists. This cost–utility analysis indicated that FPT should be initiated for osteoporotic patients and used persistently, and that PEUS is a cost-saving method with acceptable results in the osteoporosis testing–diagnosing process or the testing process alone, as POMs can result in cost savings with very similar health outcomes in comparison with COM. POM probably also provides a cost-effective alternative for osteoporosis management in other countries utilizing DXA measurements, but further studies in other settings are needed to confirm this conclusion.

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Author contributions

Management (ES, OR), conceptualization (ES, OR, JPK, HK), design (all), data acquisition (ES, OR, JPK, PM), data analysis (ES) and interpretation (all), health economic modeling (ES), initial drafting (ES), and critical revision (all). All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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ES, PM, or TH did not receive any direct financial support as individuals. HK works as an invited member of the national Käypä Hoito care guidance working group for osteoporosis. HK has received consultancy fees and lecture payments from Amgen Ltd and Eli Lilly ltd, and is a partner of Bone Index. ES, PM, and TH are employees of ESiOR Oy, Kuopio, Finland. ES and TH are also partners and directors of ESiOR. OR and JPK are employees and partners of Bone Index. Bone Index is the manufacturer and marketer of PEUS (Bindex®). The authors report no other conflicts of interest in this work.

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