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Cost-effectiveness of vitamin D and calcium supplementation in the treatment of elderly women and men with osteoporosis

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Background: The supplementation with vitamin D and calcium has been recommended for elderly, specifically those with increased risk of fractures older than 65 years. This study aims to assess the cost-effectiveness of vitamin D and calcium supplementation in elderly women and men with osteoporosis and therefore to assess if this recommendation is justified in terms of cost-effectiveness. **Methods:** A validated model for economic evaluations in osteoporosis was used to estimate the cost per quality-adjusted life-year (QALY) gained of vitamin D/calcium supplementation compared with no treatment. The model was populated with cost and epidemiological data from a Belgian health-care perspective. Analyses were conducted in women and men with a diagnosis of osteoporosis (i.e. bone mineral density *T*-score ≤ -2.5). A literature search was conducted to describe the efficacy of vitamin D and calcium in terms of fracture risk reduction. **Results:** The cost per QALY gained of vitamin D/calcium supplementation was estimated at €40 578 and €23 477 in women and men aged 60 years, respectively. These values decreased to €7912 and €10 250 at the age of 70 years and vitamin D and calcium supplementation was cost-saving at the age of 80 years, meaning that treatment cost was less than the costs of treating osteoporotic fractures of the no-treatment group. **Conclusion:** This study suggests that vitamin D and calcium supplementation is cost-effective for women and men with osteoporosis aged over 60 years. From an economic perspective, vitamin D and calcium should therefore be administrated in these populations including those also taking other osteoporotic treatments.

Introduction

Osteoporosis is an increasingly major public health problem. It is a disease characterised by low bone mass with microarchitectural disruption, leading to increased fracture risk. In the Europe Union, approximately 3.5 million new fragility fractures occur annually.[1] In 2010 alone, these fragility fractures resulted in costs of €37 billion and were responsible of 43 000 deaths.[1]

The supplementation with calcium and vitamin D is essential to maintaining bone health. Several studies have shown that the combination of calcium and vitamin D prevent bone loss and significantly reduce the risk of hip and of all osteoporotic fractures.[2,3] Vitamin D and calcium are generally recommended in patients receiving anti-osteoporotic drugs, because most randomised controlled trials are based on the co-administration of calcium and vitamin D supplements.[4] Recently, a working group from the European Society for Clinical and Economic aspects of Osteoporosis (ESCEO) has recommended the supplementation with vitamin D and calcium in patients aged over 65 years with an increased risk of fractures.[5]

Although this recommendation is claimed to be justified both in terms of efficacy and cost-effectiveness, relatively few studies have targeted the cost-effectiveness of calcium and vitamin D supplementation. The need for economic analysis of calcium and vitamin D supplementation has already been emphasised in 2007 by Tang et al.,[3] but no studies have been conducted since this date.[6] Under continuing economic pressure, the assessment of cost-effectiveness could be important for decision makers in terms of allocation of resources and could potentially result in changes in the use of health resources with prevention of fractures. The objective of this study was therefore to assess the cost-effectiveness of vitamin D and calcium supplementation in the treatment of elderly women and men.

Methods

Economic model

The cost-effectiveness of calcium and vitamin D supplementation was compared with no treatment using a Markov microsimulation model which has been validated[7] and extensively used to assess the cost-effectiveness of osteoporosis management programs in women and men.[8–11] The model was programmed using the software TreeAge Pro 2011 (TreeAge Pro Inc., Williamston, MA).

The Markov model health states are 'no fracture', 'death', 'hip fracture', 'clinical vertebral fracture', 'wrist fracture', 'other fracture' and the corresponding post-fracture states. All the patients, one at a time, began in the 'no fracture' state and had, every 6-month (cycle length), a probability of having a fracture at the hip, clinical vertebrae, wrist or other site or of dying.[11] Patients in a fracture state can stay in the same fracture state if they re-fracture, change to another fracture state, die or change in the next cycle to the post-fracture state. Patients being in any post-fracture state might have a new fracture (all fracture types are possible), die or move to the 'no fracture' state. Prior fractures were recorded by tracker variables and used in calculations of

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

Parameter	Women	Men
Incidence (annual rate per 1000) of first fracture[12]		
Hip	0.88 (60–64 years), 1.55 (65–69 years), 2.97 (70–74 years), 6.87 (75–79 years), 12.97 (80–84 years), 23.75 (85–89 years), 28.75 (90–94 years), 33.55 (95+)	0.84 (60–64 years), 1.18 (65–69 years), 1.87 (70–74 years), 3.97 (75–79 years), 8.50 (80–84 years), 17.18 (85–89 years), 25.21 (90–94 years), 36.63 (95+)
Vertebral	1.09 (60–64 years), 1.72 (65–69 years), 3.41 (70–74 years), 4.75 (75–79 years), 6.09 (80–84 years), 9.18 (85–89 years), 11.12 (90–94 years), 12.97 (95+)	2.68 (60–64 years), 1.41 (65–69 years), 3.13 (70–74 years), 3.92 (75–79 years), 5.22 (80–84 years), 12.13 (85–89 years), 17.80 (90–94 years), 25.87 (95+)
Wrist	2.50 (60–64 years), 3.32 (65–69 years), 4.40 (70–74 years), 4.91 (75–79 years), 6.87 (80–84 years), 8.42 (85–89 years), 10.20 (90–94 years), 11.90 (95+)	1.66 (60–64 years), 1.64 (65–69 years), 0.56 (70–74 years), 1.11 (75–79 years), 1.45 (80–84 years), 3.28 (85–89 years), 4.81 (90–94 years), 7.00 (95+)
Other	1.94 (60–64 years), 3.74 (65–69 years), 3.63 (70–74 years), 8.29 (75–79 years), 10.82 (80–84 years), 23.91 (85–89 years), 28.95 (90–94 years), 33.78 (95+)	3.14 (60–64 years), 4.33 (65–69 years), 4.80 (70–74 years), 4.82 (75–79 years), 17.87 (80–84 years), 24.62 (85–89 years), 36.11 (90–94 years), 52.50 (95+)
Direct fracture costs (estimated in €2012)[13–16]		
Hip, first 6-month	From 9817 to 12 949 (depending on age)	From 10 411 to 12 864 (depending on age)
Hip, extra costs in the year following the fracture	8438	8438
Hip, yearly long-term costs	From 1762 to 5422 (depending on age)	From 1798 to 14 678 (depending on age)
CV, first 6-month	From 2441 to 2986	From 2545 to 2959
Wrist, first 6-month	From 2033 to 2489	From 2119 to 2468
Other, first 6-month	From 2437 to 2981	From 2540 to 2958
Health state utility values[17]		
Hip (first year/subsequent years)	0.80 (0.770–0.825)/0.90 (0.885–0.910)	
CV (first year/subsequent years)	0.72 (0.660–0.775)/0.93 (0.916–0.946)	
Wrist (first year/subsequent year)	0.94 (0.910–0.960)/1.00	
Other (first year/subsequent year)	0.91/1.00	

Note: CV, Clinical Vertebral.

transition probabilities, costs and utilities to reflect the long-term effects of fractures. A lifetime horizon was considered to fully capture the long-term impact of fractures on costs and quality of life.

A description of the different components of the model is provided below. Model data are included in Table 1. Please also refer to previously published research for further details, additional clinical information and limitations of the model.[7]

Population risk

The study population included women and men aged over 60 years with osteoporosis (bone mineral density (BMD) T-score ≤ -2.5). The incidence of first hip fracture in the general population was derived from the national database of hospital bills (average of the years 2005–2007).[12] Since the incidence of other fractures was not known, we assumed that the age-specific ratio of index fracture to hip fracture in Belgium was the same as found in Sweden.[18] This assumption, used in the development of many FRAX® models including Belgium,[19] appears to hold true for West European countries, the USA and Australia.[20]

The incidence of fracture in the general population was further adjusted to accurately reflect the fracture risk in patients with low BMD. The relative risk for BMD was calculated using a method previously described.[20] Into the model, an increased risk of subsequent fractures was also modeled for women who had a prior fracture at the same location.[7,10]

Age-specific mortality rates (estimated in 2012) were obtained from the National Institute of Statistics. According to data from a recent meta-analysis,[21] hip fractures increased female (male) death probabilities by 4.53 (5.75) in the first 6 months following the fracture, by 1.75 (2.31) in the period 6–12 months and by 1.78 (1.69) in subsequent years. The same impact was assumed after hip and clinical vertebral fractures. Because excess mortality may also be attributable to comorbidities, we conservatively assumed that only 25% of the excess mortality following a hip or vertebral fracture could be directly or indirectly attributable to the fractures themselves.[22,23]

Fracture cost

As recommended by the Belgian methodological guideline for pharmacoeconomic evaluations, we adopted a health-care payer perspective that includes direct health-care costs paid by the compulsory national health insurance and the patient's out-of-pocket contribution.[24] All costs were expressed in the year 2012 and were inflated using the national health-care product price index. Discount rates of 3% for costs and of 1.5% for health benefits were assumed for the base-case analysis as recommended in Belgium.[24] The direct hospitalization cost of hip fracture was retrieved from the Belgian national database of hospital bills for the year 2007.[25] Extra costs in the year following the hip fracture was derived from the study of Autier et al.,[26] which was based on a prospective controlled study including 159 women. Hip fractures are also associated with long-term costs. They were based on the proportion of women (men) being institutionalised following the fracture, ranging from 5% (6%) (for those aged 60 years) to 30% (65%) (for those aged over 90 years).[27] The cost of non-hip fractures was quantified relative to hip fracture cost.[13] Non-hip fractures were not associated with long-term costs.

Fracture disutility

Utility values in the general population as well as relative reductions due to fractures in the year following the fracture and in subsequent years were derived from a systematic review.[14] In the case of an occurrence of a second fracture at the same site, the disutility applied to the first fracture event was reduced by 50%.[7,15,16]

Treatment effects

Following general recommendations to supplement patients with both calcium and vitamin D,[4,5] we conducted a literature search of articles describing the efficacy of vitamin D in combination with calcium in terms of fracture risk reduction, using the following databases: MEDLINE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews. The searches were limited to human studies, English language publications and citations from 2000 to June 2012. The electronic search was supplemented by bibliographies of relevant review articles. The search terms were the following: vitamin D ('cholecalciferol,' 'ergocalciferol,' 'calcitriol,' 'alfacalcidol,' 'dihydrotachysterol', 'colecalciferol', 'ergocalciferol') and 'calcium' and 'fractures'. The searches were limited to meta-analysis. Since 2000, 11 meta-analyses have evaluated the effect of vitamin D (or analogues) with calcium on fracture rates in older adults (list of articles available at the first author upon request). Vitamin D with calcium supplementation, compared with placebo, reduces the risk of fractures. The reduction in risk ranged from 8 to 20% for total fracture, from 16 to 30% for hip fractures and from 6 to 23% for non-vertebral fractures.

In the base-case scenario, anti-fracture efficacy of vitamin D with calcium supplementation was derived from the meta-analysis of Boonen et al.[17] Based on this study, vitamin D and calcium supplementation reduced the risk of hip fractures by 18% (relative risk = 0.82, 95% confidence interval 0.71–0.94; data from six randomized controlled trials (RCTs) including 45 509 patients). The hip fracture efficacy was similar to that estimated by the meta-analysis of Bischoff-Ferrari et al.[17] for high doses of vitamin D with or without calcium, i.e. a reduction of 18% (95% CI: 0.69–0.97) using a meta-analysis based on five RCTs with 31 872 patients.[28] For the effect of calcium and vitamin D on vertebral fractures, a reduction of 13% (95% CI: 0.75–1.01) was selected based on the meta-analysis of Tang et al. including 45 184 patients.[3] Calcium and vitamin D were also assumed to reduce the risk of non-vertebral fractures by 20% (relative risk = 0.80, 95% confidence interval 0.72–0.89; data from nine RCTs including 33 265 patients).[28]

In the model, patients were assumed to receive treatment for 3 years. The effect of calcium and vitamin D on fracture risk was assumed to decline linearly for a period equal to the duration of therapy (called offset time), in line with prior cost-effectiveness analyses of osteoporosis medications.[29]

The cost of vitamin D (800 IU) was estimated at €4.75 for 4 months (source: official listings of the Belgian Centre for Pharmacotherapeutic Information, May 2013) and the cost of calcium ('magistral formula', 1000 mg) was estimated at €13.3 for 60 days (source: Mutualité Chrétienne). We also assigned the cost of one physician visit (€22.67 per visit) per year of treatment and the cost of one bone density measurement at years 1 and 3 [estimated at €58.05, including the cost of bone densitometry (€35.38) and of one additional physician visit (€22.67)].

Analyses and presentation of results

Results are presented in terms of incremental cost-effectiveness ratio (ICER), which is defined as the difference between vitamin D/calcium supplementation and no treatment in terms of total costs (expressed in €2012) divided by the difference between them in terms of effectiveness, expressed in accumulated QALYs. It represents the cost of calcium and vitamin D supplementation (compared with no treatment) per one QALY gained. Each model ran 10 times with 200 000 patients to enable variability analyses. Mean ICER and 95% confidence interval were calculated for each simulation.

To draw a conclusion about the cost-effectiveness, the ICER has to be compared with a cost-effectiveness threshold. This threshold represents the maximum amount that the decision makers are willing to pay per QALY gained. In Belgium as in most countries, there is no consensus on cost-effectiveness. Commonly accepted thresholds for cost-effectiveness are in the range of €40 000–50 000.[30]

Uncertainty related in the model parameters was investigated using one-way and probabilistic sensitivity analyses. One-way sensitivity analyses (OWSAs) were used to assess the impact of single parameter variations on the results. First, as a marked variation on the incidence of fracture has been observed in European countries,[31] an OWSA was performed on fracture risk using ranges (−30%; +45% for women, −45%; +45% for men) similar to the European country with the lower (i.e. Spain) and the highest (i.e. Austria) fracture risk (at the exception of Scandinavian countries with very high fracture risk).[31] Since drug therapy cost differs in Belgium and in other countries, another OWSA was conducted with the highest cost of calcium and vitamin D in Belgium, i.e. €38.45 for 90 days. Additional OWSAs were performed on discount rates, fracture cost and fracture disutility in a reference population (women aged 70 years). In addition, we also assessed the impact of including a mortality reduction of 9% (95% CI: 0.84–0.98) with calcium and vitamin D.[32] Probabilistic sensitivity analyses were then performed to analyse the effects of uncertainty in all model parameters simultaneously. Parameter values were randomly selected from their respective distributions for each simulation. Log-normal distributions were assumed for relative risk parameters such as fracture risk reduction with therapy and mortality excess. Gamma distribution was used for the incidence of hip fracture and beta distributions were assumed for the effects of fracture on QALYs. Normal distributions, with a standard deviation assumed to be 15% of the mean, were used for non-hip fractures incidence, the probability of being admitted to nursing home and fracture cost variables given a standard error was not available for these parameters. Cost-effectiveness acceptability curves were then constructed for 200 simulations to show the probability that calcium and vitamin D supplementation is cost-effective compared with no treatment, for a range of decision-maker's willingness to pay.

Results

The cost per QALY gained of vitamin D and calcium supplementation was estimated at €40 578 and €23 477 in women and men aged 60 years, respectively. These values decreased when increasing age and vitamin D and calcium supplementation was cost-saving at the age of 80 years, meaning that treatment cost was less than the costs of treating osteoporotic fractures of the no-treatment group (Table 2).

OWSA suggests that the ICERs of calcium and vitamin D are quite sensitive to baseline fracture risk and medication costs (Table 3). When reducing fracture risk to the level of the European country with the lower fracture risk,[31] the cost per QALY gained of calcium and vitamin D was estimated at €50 582 and €53 529 in women and men aged 60 years. Similar ICERs were obtained when using the higher cost for vitamin D and calcium supplements. Interestingly, vitamin D and calcium supplementation remains always cost-saving in women aged over 80 years. Additional OWSA are included in figure 1 as a tornado diagram for women aged 70 years. The ICERs of calcium and vitamin D compared with no treatment is slightly sensitive to fracture disutility, while fracture cost, discount rates and offset time (i.e. the duration for which the effect on fracture persists after the treatment is stopped) could impact the results. Assuming mortality reduction with vitamin D and calcium supplementation also substantially improves the cost-effectiveness. Similar findings were observed across age and gender.

The cost-effectiveness acceptability curves (figure 2), which summarise information on uncertainty in cost-effectiveness, show the probability that vitamin D and calcium supplementation is

Table 2 Lifetime costs, QALYs, and incremental cost-effectiveness ratio (cost in € per QALY gained) of vitamin D and calcium supplementation compared with no treatment for women and men aged 60–80 years with a BMD *T*-score ≤ -2.5

	Women			Men		
	No treatment	**Ca/Vitamin D**	**Incremental**	**No treatment**	**Ca/Vitamin D**	**Incremental**
Age 60 years						
Costs, €	9107	9424	316	7136	7410	274
QALYs	15.195	15.202	0.008	13.439	13.451	0.012
ICER, € (95% CI)		40 578 (19 600; 61 556)			23 477 (19 277; 27 678)	
Age 65 years						
Costs, €	9967	10 177	211	7414	7645	230
QALYs	12.642	12.655	0.013	11.060	11.072	0.012
ICER, € (95% CI)		16 266 (11 703; 20 829)			19 695 (16 990; 22 400)	
Age 70 years						
Costs, €	10 427	10 553	127	7861	7999	138
QALYs	10.056	10.072	0.016	8.666	8.680	0.013
ICER, € (95% CI)		7912 (6216; 9608)			10 250 (8910; 11 589)	
Age 80 years						
Costs, €	9512	9242	−270	7257	7158	−99
QALYs	5.550	5.571	0.021	4.623	4.637	0.014
ICER, € (95% CI)		−12 815 (−14 350; −11 280)			−6723 (−8945; −4501)	

Note: BMD, bone mineral density; CI, confidence interval; QALY, quality-adjusted life years.

Table 3 One-way sensitivity analyses on fracture risk and treatment cost on the cost in € per QALY gained of vitamin D and calcium supplementation compared with no treatment for women and men aged 60–80 years with a BMD *T*-score ≤ -2.5 (95% CI are given in parentheses)

	60 years	**70 years**	**80 years**
Women			
Base-case analysis	40 578 (19 600; 61 556)	7912 (6216; 9608)	Cost-saving
Fracture risk −30%	50 582 (−35 280; 136 444)	24 897 (17 827; 31 968)	Cost-saving
Fracture risk +45%	20 017 (15 850; 24 184)	Cost-saving	Cost-saving
High treatment cost	52 394 (11 927; 92 860)	23 444 (20 431; 26 457)	Cost-saving
Men			
Base-case analysis	23 477 (19 277; 27 678)	10 250 (8910; 11 589)	Cost-saving
Fracture risk −45%	53 429 (−186 891; 293 748)	39 034 (23 778; 54 290)	15 352 (12 792; 17 913)
Fracture risk +45%	9355 (7250; 11 460)	Cost-saving	Cost-saving
High treatment cost	33 755 (−199; 67 708)	23 092 (18 600; 27 584)	3872 (2812; 4933)

Note: BMD, bone mineral density; CI, confidence interval; QALY, quality-adjusted life years.

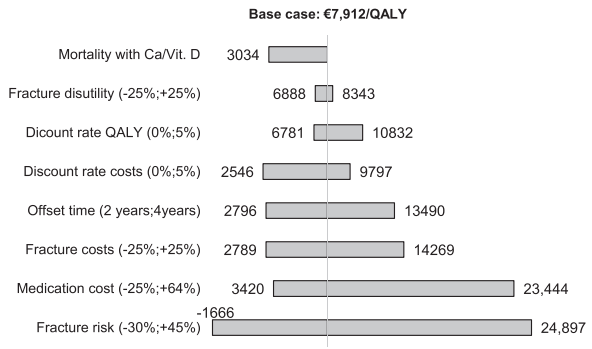

Figure 1 Tornado diagram for one-way sensitivity analyses on the cost-effectiveness of vitamin D with calcium supplementation. Analyses performed in women aged 70 years with BMD *T*-score ≤ -2.5. Base-level discount rates: QALY = 0.015; costs = 0.03. Offset time is the duration for which the effect on fracture persists after the treatment is stopped (base level = 3 years)

cost-effective as a function of the decision maker's willingness to pay per one QALY. In women, vitamin D with calcium supplementation was cost-effective, at an assumed willingness to pay of €45 000 per QALY, at 49, 87 and 99% of the simulations at the age of 60, 70 and 80 years, respectively. In men, these were 80, 94 and 99%, respectively. Lower uncertainty was thus observed at the age of 60 years for men than women.

Discussion

This study suggests that the supplementation of vitamin D and calcium is cost-effective for women and men aged over 60 years with osteoporosis. Our finding justifies the recommendation of the ESCEO working group to supplement all patients aged over 65 years with increased risk of fractures with calcium and vitamin D. These results could be useful for decision makers, especially given the high prevalence of calcium and vitamin D insufficiency in the elderly[4] and the increasing role of economic evaluation in health-care decision making.

This study is at our knowledge the first economic analysis since more than 10 years that estimates the cost-effectiveness of calcium and vitamin D supplementation to prevent osteoporotic fractures. Cost-effectiveness analyses in the field of osteoporosis have mainly concerned active osteoporotic agents.[6] Since most RCTs estimating the efficacy of active osteoporotic drugs are based on the co-administration of calcium and vitamin D supplements, vitamin D and calcium supplements should also be administrated for patients taking other osteoporotic treatments and the assessment of their cost-effectiveness is therefore very important.

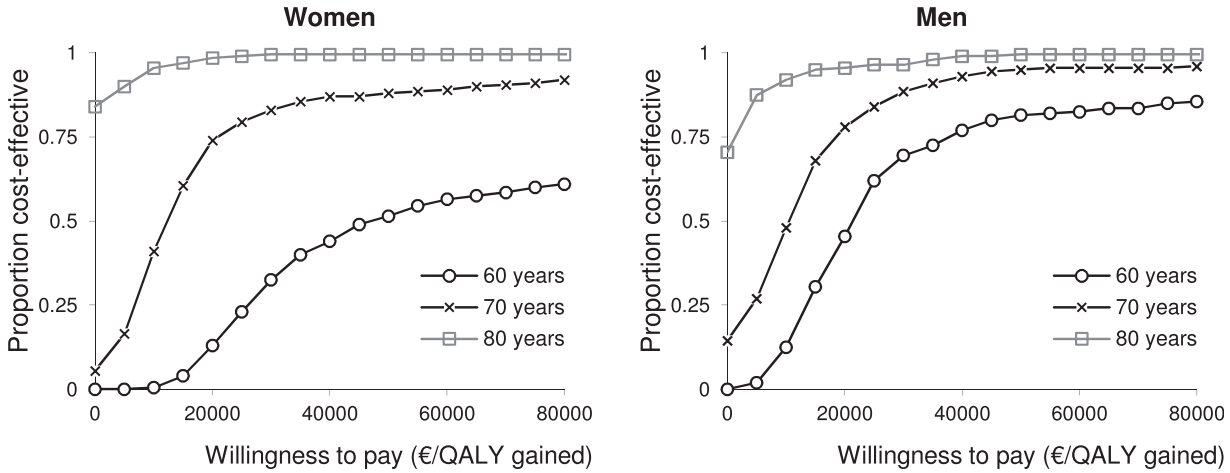

Figure 2 Cost-effectiveness acceptability curves of vitamin D with calcium supplementation compared with no treatment in women and men with BMD *T*-score ≤ -2.5

Sensitivity analyses reveal that fracture risk and medication costs could have a large impact on the cost-effectiveness of vitamin D and calcium supplementation. Marked variations in the incidence of hip fracture has been observed worldwide[31] and drug costs could substantially differ within and across country. Strength of this study includes the conduct of a rigorous systematic review on meta-analyses was performed to assess the effects of calcium and vitamin D on fracture risk. Our estimates are also probably conservative for several reasons. First, different studies showed that calcium and vitamin D supplementation have other health benefit effects. So, studies suggested that calcium and vitamin D may reduce the risk for breast cancer in premenopausal women and colon cancer in older women[33] and a meta-analysis indicated that vitamin D may have a small beneficial effect on cardiovascular risk and mortality.[34] Second, we used a conservative assumption about the efficacy of calcium and vitamin D on hip fracture. In the article of Boonen et al., high doses of calcium and vitamin D were associated with a slightly greater reduction of hip fracture risk (21 vs. 18%).[2] Third, as recommended for pharmacoeconomic analysis in Belgium, we used a health-care payer perspective. Using a societal perspective and incorporating indirect costs for workers would lead to improve the cost-effectiveness in younger groups.

Our study could have some potential limitations that could inform further economic evaluations. First, we did not incorporate adherence with calcium and vitamin D supplements which could potentially affect the cost-effectiveness of osteoporotic drugs.[9] Limited information about adherence to calcium and vitamin D supplements are currently available including the impact of non-adherence on treatment efficacy. Second, our analysis was restricted to patients with osteoporosis. Calcium and vitamin D supplements could also be used in the general population. There is however actually no agreement for universal supplementation of calcium and vitamin D. Recently, the U.S. Preventive Services Task Force concluded that the current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men.[35] Further research and cost-effectiveness analyses would be required in the general population. Third, we only assessed the combination of calcium and vitamin D as recommended by international guidelines.[4,5] Recently, a meta-analysis also suggests that high doses of vitamin D alone could significantly reduce the risk of hip fractures and any non-vertebral fractures in persons 65 years of age or older.[36]

In conclusion, this study suggests that vitamin D and calcium supplementation is cost-effective for women and men with increased risk of fractures aged over 60 years. From an economic perspective, vitamin D and calcium should therefore be administrated in these populations including those also taking other osteoporotic treatments.

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Key points

- The supplementation of vitamin D and calcium supplementation is cost-effective for women and men with osteoporosis aged over 60 years.
- From an economic perspective, vitamin D and calcium should be administrated in women and men with osteoporosis aged over 60 years including those also taking other osteoporotic treatments.
- The recommendation of an ESCEO working group for vitamin D and calcium supplementation in patients with osteoporosis older than 65 is justified in terms of cost-effectiveness.

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