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Cost-effectiveness of alendronate in the treatment of osteoporois in Denmark: An economic evaluation based on the fracture intervention trial

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Cost-Effectiveness of Alendronate in the Treatment of Osteoporosis in Denmark – An Economic Evaluation Based on the Fracture Intervention Trial

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Abstract

Background: The Fracture Intervention Trial (FIT) showed that the bisphosphonate alendronate reduces the risk of fractures in women with low bone mass in the United States.

Objective: To estimate the cost-effectiveness (cost per life-year gained and cost per quality-adjusted life-year, QALY, gained) of treating osteoporotic women in Denmark with alendronate, compared with no treatment.

Design: A Markov model earlier used in the economic evaluation for Sweden was adapted using epidemiological and cost data for Denmark. In the base-case alendronate was assumed to have a fracture-risk reducing effect for ten years; a treatment duration period of 5 years followed by a 5-year period where the effect declined linearly to zero.

Results: Treating a 71-year old (the mean age in the vertebral arm of the FIT) osteoporotic woman with one prior vertebral fracture with alendronate was found to be associated with a cost of DKK 52,311 per QALY gained. The cost-effectiveness ratio when treating a 69-year old woman with low bone mass and without previous vertebral fractures was higher (DKK 205,816) but still within the limits of what can be considered good value for money.

Conclusions: The results of this study indicate that treatment with alendronate in Denmark is cost-effective, provided the treatment is targeted towards high-risk patients corresponding to the patient groups in the FIT study.

KEYWORDS: osteoporosis, cost-effectiveness, quality of life, Markov models, acceptability curve

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Summary

Osteoporosis (bone fragility) leads to increased risk of fractures primarily of the hip, spine and wrist in elderly (post-menopausal) women. Fosamax (alendronate) has been shown to decrease the risk of fractures in a large US clinical trial (the FIT study). By using a computer simulation model, we applied the clinical results from the FIT to a hypothetical cohort of Danish women, and calculated the impact on health care costs and quality of life (measured as quality adjusted life-years, QALYs).

We found that treatment with alendronate for women with prior vertebral fractures leads to increased life expectancy (about 0.08 extra life-years for a treatment period of 5 years), improved quality of life (0.09 QALYs), and increased total health care costs by less than DKK 5,000. This translates into a favourable cost-effectiveness ratio of 52,311 DKK per QALY which is well below the assumed threshold for cost-effectiveness (about 500,000 DKK). Treating women without prior vertebral fractures with alendronate was found to be 205,816 DKK per QALY gained.

This means that treatment with alendronate gives good value for money compared with alternative uses for our scarce health care resources.

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Introduction

In osteoporosis the bone mass is decreased, thereby increasing the risk of fractures, primarily of the hip, wrist and the spine [1]. Osteoporosis mainly affects elderly women. Besides the negative impact on the quality of life of the individual it is also a costly disease for society. The costs for osteoporosis-related fractures are expected to increase in the future, partly due to the increasing (age-specific) incidence of fractures and also because of changes in demographics and improved life expectancy. The number of hip fractures in the world is estimated to increase from 1.7 million in 1990 to more than 6 million in 2050 [2, 3]. The importance of developing treatments that reduce the fracture incidence is evident, both from an individual and a societal perspective.

Fosamax® (alendronate, Merck & Co., Inc.) has been shown in clinical trials to reduce the risk of fractures by nearly one half. The largest study was called the "Fracture Intervention Trial" (FIT), and was conducted at 11 clinical centers in the United States and included 6 459 women with a femoral neck BMD value of 0.68 g/cm^2 or less. The FIT consisted of two study arms; the Vertebral Fracture Arm (VFA) including 2 027 women with radiographically identified vertebral fractures at baseline and the Clinical Fracture Arm (CFA) with 4 432 women without vertebral fractures at baseline.

The objective of this study is to estimate the cost-effectiveness (expressed as the cost per quality adjusted life-year gained) of treatment with alendronate for Danish women with osteoporosis in a societal perspective.

Cost-effectiveness is estimated in a model where the risks and costs of fracture are defined to be relevant for Denmark. The model simulates a cohort of patients similar to the cohort in the clinical study with respect to fracture risk and age. The analysis focuses on the patients in the vertebral fracture arm of the FIT, i.e. women with low BMD (femoral neck t-score of 1.6 or less) and at least one previous vertebral fracture. Also, the cost-effectiveness of treating patients who have low BMD (femoral neck t-score of 2.5 or less) but no earlier vertebral fracture is evaluated, based on a subgroup of the Clinical Fracture Arm of the FIT.

1 Methods

1.1 Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) is defined as

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_1 - C_0}{E_1 - E_0} \qquad (1)$$

where ΔC is the difference in total cost between interventions and no intervention, and ΔE is the difference in effectiveness between intervention with alendronate and no intervention.

Costs can be divided into two different categories: direct and indirect costs. Direct costs consist of medical costs, which are costs directly attributed to health care interventions e.g. hospitalisations, outpatient visits and drugs etc, and non-medical costs that can be associated with provision of medical services, e.g. transportation, home help and informal care etc. Indirect costs are costs related to lost productivity due to illness or treatment. Only direct costs are considered in this study since the age of the relevant patient group will be so high that any productivity losses incurred are negligible.

In this study two effectiveness measures were included: life years gained and quality adjusted life years (QALY) gained. The QALY outcome measure is the most relevant in a health-policy perspective, since by using a common denominator it allows for comparisons of the value of interventions across disease states.

At what costs per QALY can an intervention be considered favourable? No generally established threshold has been established but in a survey of health economists about the threshold value per QALY gained the mean value was US$60,000. [4] This is equivalent to approximately DKK 500,000. In our analysis we consider any cost-effectiveness ratio below this value to be indicative of good value for money.

1.2 A brief introduction to Markov models

Markov models are a certain type of discrete state-transition simulation models. The simulated cohort of patients is divided into a finite number of states based on, for example, the current health status of the patient. The states are mutually exclusive and collectively exhaustive. The most important assumption of the Markov model is that future events only depend on the current state the patient is in, and not on prior events [5]. This is called the **Markovian property**, and means that all patients within each state are treated the same irrespectively of their (medical) history.

Time is handled as discrete periods of the same length (cycles). Let s_t^i denote the health state of patient *i* at time *t*, where $s_t^i = \{1..S\}$ and *S* is the number of states in the model. The **transition probability** from state a to state b at time *t* can be written T

(a,b,t) = P ($s_t = b | s_{t-1} = a$). The Markovian property requires that the transition probability be independent of s_{t-i} for all i>1.

Markov models are a commonly used tool in medical decision analysis. The model is especially appropriate to use when the disease in focus is characterised by recurrence of certain events and these are based on continuous risk over time [6].

1.2.1 Half cycle correction

In the Markov model the state transitions occur at the end of the cycle. In reality fractures occur continuously in time. If the membership is counted at the end of the cycle the survival will be overestimated. Therefore the method of half-cycle correction is used, by adding one extra cycle and assuming that the first and last cycle in the model is half as long as the cycles in between the overestimation will be corrected.

1.2.2 Cohort simulations

Using a cohort simulation approach is the most frequently used method in Markov model analyses. The cohort simulation considers a hypothetical cohort of persons which all begins the process with some determined distribution among the states. In the following cycle the cohort will be divided among the states according to transition probabilities, which gives a new distribution of the cohort among the states. This will continue in the subsequent cycles until the process has reached its cycle limit.

The *cycle sum* which is the utility or cost[1] accrued in each cycle can be calculated by the formula:

$$\text{Cycle sum} = \sum_{s=1}^{S} f_s * U_s \qquad (2)$$

Where S is the number of states, f_s is the fraction of the cohort in state s and U_s is the utility of state s. *Appendix 1* provides a numeric example of a cycle sum calculation.

1.2.3 Monte Carlo simulations

Another method used in Markov models is Monte Carlo simulations, which makes it possible to perform stochastic analyses. Monte Carlo simulations take the uncertainty in the underlying parameters of the model into account by allowing some or preferably all of them to vary over a given range with a given distribution. By letting a cohort go through the model a number of times a distribution of cost-effectiveness ratios is obtained. In order to produce accurate results in Monte Carlo simulations it is

[1] Formula in the case of costs: $\text{Cycle sum} = \sum_{s=1}^{S} f_s * C_s$

important to have good estimates of the mean and variances of the underlying parameters [6].

1.3 Acceptability curves

Acceptability curves can be used to capture the uncertainty surrounding the estimate of the ICER. An acceptability curve shows the proportion of estimates of the ICER that falls below different values of willingness to pay for one unit of health effect (*Figure* 1). By assuming distributions for mean costs and mean effects the acceptability curve can be derived using data from clinical trials, or alternatively the distribution of the ICER can be obtained by bootstrapping from the observed samples. Simulating effects and costs within a modelled framework, for example a Monte Carlo Markov model, can also be used to estimate an acceptability curve. By assigning distributions to the parameters of the model and letting the model run a large number of times with resampling gives a distribution of the ICER.

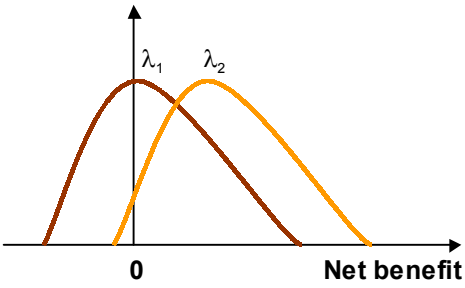
Based on the net benefit approach Löthgren and Zethraues [7] defined the cost-effectiveness acceptability curve and established a formal relation between statistical inference and the acceptability curve.

The net benefit is defined, as the incremental effect multiplied with the price society is willing to pay per unit of effectiveness (λ), minus the incremental cost:

$$NB(\lambda) = \lambda \cdot \Delta E - \Delta C \qquad (3)$$

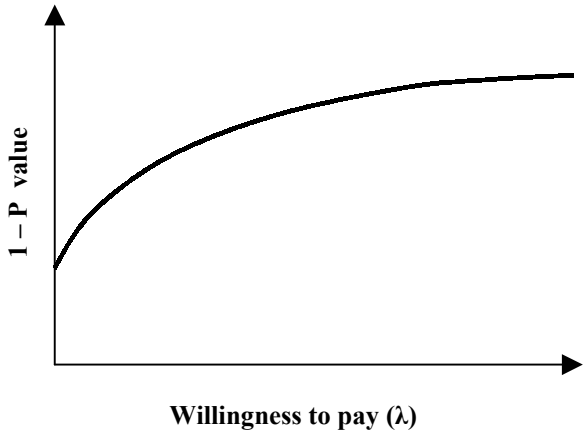
As long as the $NB(\lambda)>0$ (or equivalently ICER< λ) the intervention under scrutiny should be implemented. If incremental cost and effects follow a bivariate normal distribution, the net benefit will be normally distributed. *Figure 2* shows the distribution of the net benefit for different values of λ.

Figure 1 Distributions of net benefits at different values for λ



At each value of λ, there is possible to perform a statistical test with the null hypothesis: H_0: $NB \leq 0$, that is a non-positive net benefit (no implementation of intervention), against the alternative hypothesis: H_1: $NB>0$, i.e. a positive net benefit (intervention should be implemented). Provided that the mean incremental effect is positive, the higher the value for λ, the higher the chance that the null hypothesis will be rejected. By plotting the proportion of the net benefit distribution greater than zero for different values of λ (see *Figure 2*) the acceptability curve is obtained.

Figure 2 Cost-effectiveness acceptability curve



The acceptability curve shows the relation between the willingness to pay and the 1 – P value from the hypothesis test above. For a given significance level the curve gives information at what values of λ the intervention can be considered cost-effective. For example if the curve is above 0.95 for all willingness to pay values exceeding DKK 1,000 then the null hypothesis (*NB≤0)* can be rejected at the 5% significance level.

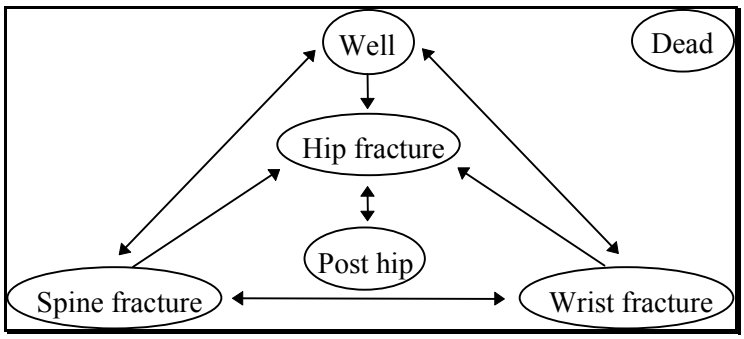
Using a Bayesian framework instead of a frequentistic approach as above makes it possible to interpret the acceptability curve in terms of probabilities that an intervention is cost-effective at different values of λ. Assuming an non-informative prior the calculation of the acceptability curve will produce the same numerical values as in the frequentist setting.

The acceptability curve summarises in a convenient way the uncertainty surrounding the estimate of the ICER. For the decision makers the acceptability curve can be a useful piece of information since the willingness to pay for one more unit of health effect is often unknown. Together with the point estimate of the incremental cost-effectiveness ratio, the acceptability curve may be part of the standard way of presenting results from economic evaluations in the future.

1.4 The model

The Markov cycle tree model in this study has been designed using DATA, a program, which has been developed for the building of Decision tree- and Markov models. The cycle length is one year and the structure of the model can be seen in the state transition diagram in *Figure 3*.

Figure 3 Structure of the model in the analysis



There is always a probability to remain in the same state or to die, but these transitions are excluded from the figure for simplification. All the patients begin in the *well* health state. Each year a patient has a probability of having a fracture remaining healthy or to die. If a patient dies, he will move to the *dead* health state and remain there for the rest of the simulation. If he has a fracture he will move to the *hip fracture*, *spine fracture* or *wrist fracture* state. After one year in one of these states the patient can move back to the *well* health state, have a new fracture or die or end up in the *post hip* state if he previously had a hip fracture.

A patient cannot have a spine or a wrist fracture after a hip fracture, although it is possible to have multiple hip fractures. This assumption was made in order to simplify the model. If wrist and spine fractures after a hip fracture would have been allowed, two more health states would have been needed. Since the probabilities of this kind of fractures are low, the introduction of the extra health states would not significantly alter the results.

In this study we primarily use cohort simulations. However, in sensitivity analysis assumptions about the distributions for some of the variables are made in order to produce an acceptability curve, which can only be derived from a Monte Carlo simulation.

2 Materials

2.1 Costs

A discount rate of 3% was used for both effects and costs in the base case analysis. All costs are in year 2000 values.

2.1.1 Cost of a Hip fracture

To estimate the cost of hospitalisation of a female hip fracture, data from inpatient records was extracted from the database of *The National Board of Health* for 1000 female patients 50 years or older who suffered a hip fracture during the year 1997. The 1000 patients were chosen randomly in the group of people with the ICD-10 codes S72.0, S72.1 and S72.2 [8] conditioned that the hip fracture had been a falling accident and not a high-energy trauma, i.e. in the range of EUS01-EUS19 in the SKS classification system [9]. The data set made it possible to calculate the costs of all the patients' hospital stays one year before and one year after the fracture. The DRG costing system was used to assess the hospitalisation costs[10]. The mean incremental cost of inpatient stays (CYA-CYB in table 3) is DKK 126,600. There is rather high mortality the first year after hip fracture (>25%). The cost estimates were produced including all patients, also those who died during the year, not to overestimate the total cost of fracture. The part of the hip fracture costs, which are not attributed to hospitalisations are derived from a Danish study [11, 12] by Ankjaer-Jensen et al. They estimated that the incremental cost per patient for rehabilitation in primary care, aids/alterations of the home and increased need for home care and nursing the year after hip fracture was DKK 31,929. Adding this cost to the cost of hospitalisations gives DKK 158,529, which was used as the cost of a hip fracture in the model.

The mean cost the year before fracture (CYB) and the mean cost the year after fracture (CYA) in the sample is shown in *Table 1*. Both costs were rejected as normally distributed when using the Shapiro-Wilk W′-test for normality (p-values<0.0001)[13]. Therefore, when testing the equality of means the year before and year after the non-parametric Wilcoxon matched-pairs signed rank test was used [14]. The Wilcoxon test rejected the hypothesis about equality of means (p-value<0.0001).

Table 1 Cost of hospitalisation of a hip fracture

n	Mean age	CYB	CYA	CYA-CYB	P-value*
1000	81.1	35,179	161,779	126,600	<0,0001

*Wilcoxon matched-pairs signed rank test

2.1.2 Cost the second and following years after a hip fracture

A hip fracture does not only incur costs the first year after a hip fracture but also the second and following years. Jönsson et al calculated the post-hip cost of fracture based on the assumption that 10% of all hip fracture patients will be long-term admitted to nursing homes. The yearly cost of accommodation at a nursing home per patient is DKK 290,700 [15]. This gives an average annual cost of DKK 29,070 per hip fracture patient in the "post hip" state.

2.1.3 Cost of spine and wrist

The costs of spine and wrist fracture are assumed to be DKK 8,274 and DKK 7,188, respectively. These are inflated estimates derived from Ankjaer-Jensen et al[11]. In our analysis clinical vertebral fracture incidences are used, therefore the cost of spine has been doubled since the original estimate included patients that never came to clinical attention, which was assumed to be 50% of the patients. All fracture costs used in the model are summarised in *Table 2*.

Table 2 Annual costs in the model (DKK)

	First year	Subsequent years
Hip	158,529	29,070
Spine	8,274	0
Wrist	7,188	0

2.1.4 Cost of intervention

The cost of intervention consists of drug cost and costs for monitoring bisphosfonate therapy. The annual public drug cost of alendronate in Denmark is DKK 4,273 [16] . The monitoring costs includes the cost of a specialist visit (DKK 1,202) [17] every year and a Bone mineral density measurement every (DKK 500) second year, resulting in an annual average monitoring cost of DKK 1,452 per patient. In the model, during the intervention period, it was assumed that all patients received medication. Thus, the annual cost of intervention was added to the incremental cost of all health states (except health state *dead*) in the model. No cost of intervention incurred after the intervention period. Both the treatment and control groups in the FIT received calcium and vitamin D supplements, which made it possible to exclude the costs of these agents.

2.1.5 Cost in added life years

Recently it has been argued that the difference between consumption and production for the patients in the study should be included in cost-effectiveness analyses with a societal perspective [18]. Individuals that work often produces more than they consume while non-working (often elderly people) individuals consume more than they produce. If these costs are not included in the cost-effectiveness analysis

treatments that prolong life will be favoured compared to more quality of life enhancing treatments in older age groups. The age-differentiated estimates of the yearly production and consumption (public and private) in *Table 3* are based on numbers for year 2000 from the website of *Statistics Denmark* (*www.dst.dk*). Johanneson et al. [19] estimated the yearly difference in consumption and production for people 65 years and older in Sweden to be approximately DKK 135,600 (inflated to year 2000 prices), which compares reasonable well with our own Danish estimate of DKK 153,784 for the same age group. However, since our calculations are rough estimates they are only included in the sensitivity analysis.

Table 3 Age differentiated consumption and production (DKK)

	Consumption	Production	Consumption-Production
65-69	165,643	20,898	-144,744
70-74	153,567	4,407	-149,159
75-	162,000	1,251	-160,749

Source: Statistics Denmark and own calculations

2.2 Quality of life

Compared to a person with full health the quality of life for a person with a hip fracture was assumed to be 0.8 the first year and 0.9 the second and following years [20]. These weights relates closely to the estimates assessed by Hillner et al. [21]. They calculated the quality of life weight to be 0.95 the year after an uncomplicated hip fracture, 0.76 for a disabling hip fracture and 0.36 for a fracture leading to a nursing home placement. Assuming that the relative share of patients were 0.5, 0.4 and 0.1 respectively, the average quality of life is 0.82. For the following years the quality weights of long-term disability and stay at nursing home were appraised to 0.8 and 0.4, which gives an average of 0.86.

The quality of life the year following spine and wrist fracture was assumed to be 0.90 and 0.95 of the quality of life of a healthy person, respectively[22]. The loss of quality of life for wrist and spine fracture corresponds well with those recommended by the National Osteoporosis Foundation (NOF) guidelines [23]. Brazier et al. [24] suggests the use of generic preference based quality of life measures of 0.797 for hip fracture, 0.909 for spine fracture [25] and 0.981 for wrist fracture [26].

In the model the relative quality of life weights were compared with average population values for the quality of life in different age groups [27]. The age-specific quality of life weights for each health state are shown in *Table 4.*

Table 4 Quality of life weights in different age groups and health states

State	50-59	60-69	70-79	80-
Well	0,91	0,87	0,70	0,60
Hip fracture	0,73	0,70	0,56	0,48
Spine fracture	0,82	0,78	0,63	0,54
Wrist fracture	0,86	0,83	0,67	0,57
Post hip fracture	0,82	0,78	0,63	0,54

Source: [20, 27]

2.3 Risk in the model

2.3.1 Baseline risk of fracture

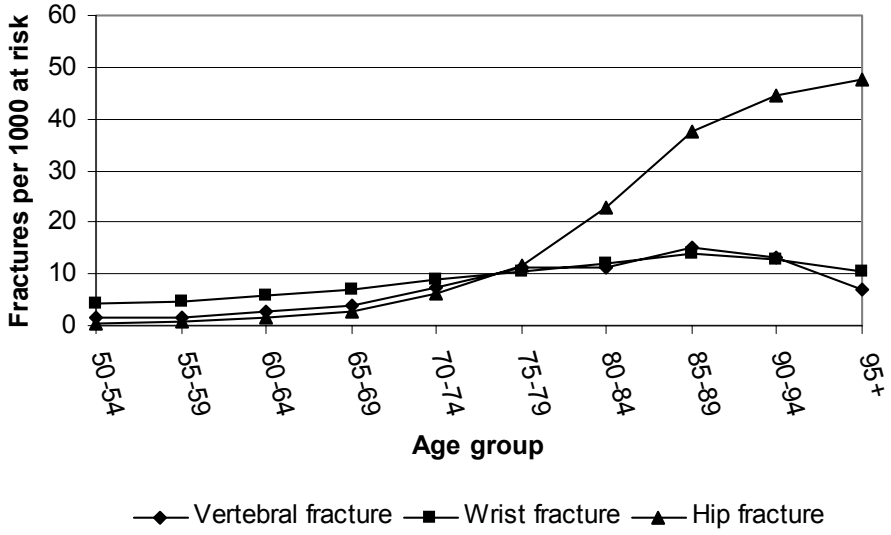
The age-specific risks of hip, spine and wrist fracture for Danish women were assumed to be the same as in an observational study in Malmö, Sweden [28]. Due to the geographic closeness, the fracture risks in Sweden should not differ significantly from Danish fracture risks. The risks of fractures are shown in *Table 5.* To capture the exponential increase in the risk of a hip fracture (see *Figure 4*) with age a logistic regression was fitted to the observational data. For each age group, the middle of the 5-year interval was used in the regression. The coefficient for the intercept in the logistic risk function was estimated to 14.19959 and the coefficient for age 0.1258271. For spine and wrist the fracture risk in each age group was the same for the whole interval. The incidence for the age group 85-89 is used for all ages above 89 years for spine and wrist fracture while the regression is used to estimate the risk of hip fracture above 89 years of age.

Table 5 Incidence of female osteoporotic fractures, per 1000

Age group	Spine	Wrist	Hip
50-54	1,61	4,17	0,61
55-59	1,58	4,56	0,55
60-64	3,03	5,68	1,94
65-69	4,39	6,91	3,11
70-74	7,78	9,04	5,52
75-79	11,11	10,32	13,08
80-84	11,63	12,08	21,57
85-89	16,41	13,87	36,99

Source: [28]

Figure 4 Baseline risk of fracture



2.3.2 Risk reduction of alendronate

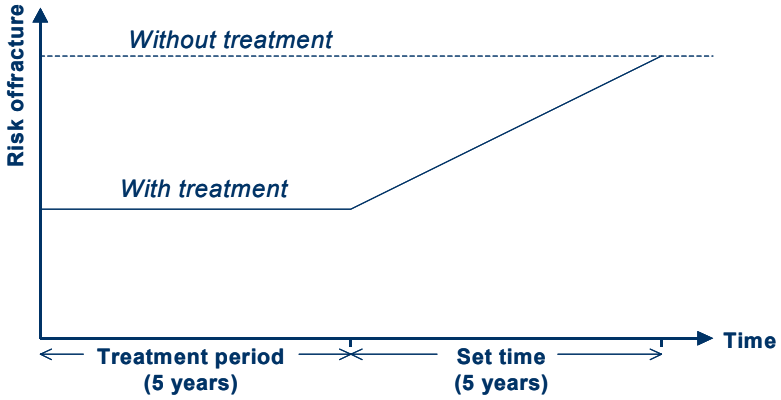
The FIT-trial was a US based study including women. No similar study has been conducted in Denmark, therefore it is assumed that alendronate has the same effect on Danish women with the same characteristics as the patients in the FIT. In *Table 6* the fracture-specific relative risk reductions of alendronate in the 3-year Vertebral Fracture Arm and the 4,2-year subgroup of the Clinical Fracture Arm of the FIT is presented [29, 30]. In the base-case the treatment period is assumed to be 5 years, with a following 5-year period where the effect of treatment declines linearly to zero. This period of loss is called "set time" period [22]. *Figure* 5 illustrates how the treatment and set-time period is structured in the model. In sensitivity analysis we tested a 10-year treatment period and a longer set-time of 10 years. The relative risk reductions, which in the FIT are based on 3 and 4,2-year treatment with alendronate, are assumed to be the same reductions that would be observed after 5 and 10 years of treatment. This is a rather conservative assumption since no benefit is added for the extra years of treatment.

Table 6 Fracture-specific relative risk reduction alendronate in the FIT

Fracture type	Vertebral arm	Clinical arm
Hip	0.51	0.56
Wrist	0.48	0
Clinical vertebral	0.54	0

Source: [29]

Figure 5 Treatment and set-time



2.3.3 Relative risk of fracture for persons meeting FIT inclusion criteria

To make an accurate analysis based on the clinical trial, the simulated cohort in the model should have the same risk of fracture as the subjects in the FIT. By calculating the ratio for the risk of fracture in the FIT-group and the general US female population the relative risk of fracture is obtained. The fracture-specific relative risks for the VFA and the subgroup of the CFA studies are presented in *Table 7.*

Table 7 Relative risk of fracture

Fracture type	Risk* in Vertebral Fracture Arm FIT (placebo group)	Risk* in Clinical Fracture Arm FIT (placebo group)	Risk in general female US population[1]	Relative risk Vertebral Fracture Arm (FIT vs. general U.S. population)	Relative risk Clinical Fracture Arm (FIT vs. general U.S. population)
Hip	0.0077	0.0053	0.0029	2.63	1.81
Vertebral	0.0176	0.0041	0.0074	2.40	0.56
Wrist	0.0144	0.0113	0.0072	1.99	1.80

* risk is one year risk
1. Source: [29, 30]

2.4 Mortality

Patients who did not suffer any hip fractures in the model were assumed to have the same mortality rates as the general population [25]. The general population mortality rates are shown in *Table 8.* After suffering a hip fracture the mortality rate is higher than the normal. The mortality rates the year after a hip fracture, presented in *Table 9*, used in this analysis are deduced from the data set from *The National Board of Health,* which contained information about the patients' possible event of death the year after fracture. The mortality rates for the post-hip, spine and wrist health states are assumed to be the same as in the general population.

Table 8 Normal mortality for women in Denmark (per 1000)

50	3.79	60	9.74	70	23.76	80	60.10	90	183.95
51	4.16	61	10.62	71	25.64	81	66.28	91	204.56
52	4.42	62	11.76	72	28.25	82	74.63	92	230.17
53	4.79	63	13.06	73	30.45	83	83.40	93	254.18
54	5.47	64	14.28	74	33.08	84	93.68	94	288.70
55	5.97	65	15.53	75	36.51	85	104.71	95	304.88
56	6.59	66	16.79	76	40.33	86	115.79	96	346.96
57	7.41	67	18.59	77	44.14	87	131.76	97	371.62
58	7.87	68	19.50	78	48.05	88	148.42	98	408.30
59	8.65	69	21.74	79	53.77	89	162.55	99	489.61

Source: [31]

Table 9 Mortality the year after hip fracture

Age Group	Own estimates
50-74	0,14
75-84	0,17
85-	0,35

Source: Own estimates

2.5 Age

The mean age in the Vertebral Fracture Arm of the FIT was 71 years, which is used as the starting age for the cohort in the base-case. The standard deviation of the age in the FIT was 5,6 years, which implies that approximately 70% of the patients in the study were between 65 and 77 years. These ages are used as starting ages in sensitivity analysis. In the Clinical Fracture Arm the mean age was 69 years, with a standard deviation of approximately 6 years. At all starting ages the cohort is followed through the model until they are 100 years old or dead.

3 Results

3.1 Base-case simulation

3.1.1 Estimated risk of fracture

The expected number of fractures per patient when treated with alendronate and given no treatment for the Vertebral Fracture Arm scenario is shown in *Table 10*. A longer study perspective results in proportionally fewer prevented fractures, which is expected since treatment duration and set-time were both 5 years in the base-case.

Table 10 Expected number of fractures

	10-year perspective			**Lifetime perspective**		
Strategy	*hip*	*verteb.*	*wrist*	*hip*	*verteb.*	*wrist*
Untreated	0.16	0.15	0.13	0.42	0.22	0.18
Alendronate	0.10	0.08	0.08	0.36	0.16	0.14

3.1.2 Cost analysis

The discounted expected lifetime cost of all fractures, shown in *Table 11*, for a 71 year old woman with previous vertebral fractures and low bone mass (VFA) was calculated to be DKK 105,054. Treatment with alendronate in the 5-year intervention base-case would provide DKK 19,880 in savings and the cost of the intervention would be DKK 24,785, which results in an incremental cost of DKK 5,759. The total discounted cost per patient administered alendronate, i.e. the expected lifetime costs plus the incremental cost, would be DKK 109,958.

Table 11 Cost analysis, discount rate 3% (DKK)

	Vertebral Fracture Arm	**Clinical Fracture Arm**
Expected lifetime fracture costs without intervention	105,054	74,353
Saved cost of fracture	19,880	13,133
Cost of intervention	24,785	25,073
Incremental cost	4,905	11,940
Total cost	109,958	86,293

3.1.3 Cost-effectiveness analysis

Results of the cost-effectiveness analysis are presented in *Table 12.* The cost per QALY gained for 5-year intervention of alendronate was DKK 52,311 for the VFA and DKK 205,816 for the subgroup of the CFA, which is below the assumed threshold value of DKK 500,000 per QALY gained for a treatment to indicate good value for money. The cost-effectiveness of alendronate for a woman without any prior vertebral fractures is worse compared to a woman with prior fractures. This is mainly because the lower risk of fracture for this patient type.

Table 12 Cost-effectiveness analysis

	Vertebral Fracture Arm	Clinical Fracture Arm
Incremental cost	DKK 4,905	DKK11,940
Life-years gained	0.0818	0.05145
Cost per life-year gained	DKK 60,000	DKK 232,078
QALYs gained	0.09376	0.05801
Cost per QALY gained	DKK 52,311	DKK 205,816

3.1.4 Acceptability curve

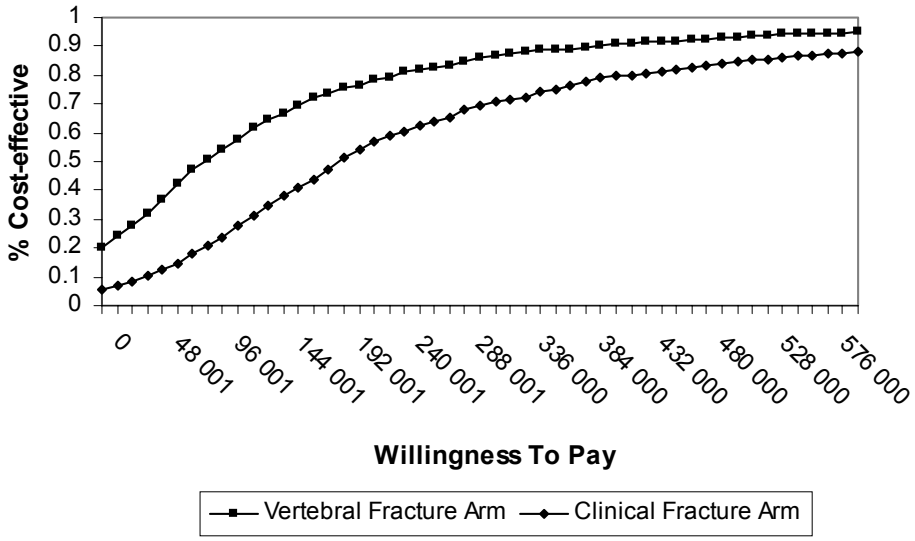
To capture some of the uncertainty in the cost per QALY gained some Monte-Carlo simulations were undertaken for the base case. To perform a Monte-Carlo simulation distributions have to be attributed to the parameters used in the model. The hip fracture cost was assumed to have a log normal distribution, mean and standard error was calculated by taking the logarithm of the patients´ incremental costs of inpatient stays in the database from The National Board of Health. Wrist, vertebral and "posthip" fracture costs were assumed to be uniformly distributed, the endpoints of their inter-quartile ranges were used as min and max values. Since the risk reduction of alendronate for the different fractures was estimated with non-parametric methods [29] a triangular distribution was judged to best capture the asymmetric data. The confidence intervals of the fracture-specific risk reductions were used as min and max values.

In *Figure 6* acceptability curves derived from Monte-Carlo simulations with 1000 iterations are presented for the Vertebral and the Clinical Fracture Arm. For women with prior vertebral fractures the cost-effectiveness ratio was below the threshold value 933 times out of the1000 iterations, or equivalently at a significance level of 6.7 % the null hypothesis of a non-positive net benefit is rejected at a willingness to pay of DKK 500,000. In 201 times out of 1000 (where the curve crosses the y-axis) alendronate dominated the no treatment alternative, i.e. lower costs and higher quality gains. For the clinical fracture arm patients the hypothesis of a positive net benefit could be accepted at a significance level of 16%, i.e. the cost-effectiveness ratio was below the threshold value 840 times out of the 1000 iterations.

The results of the acceptability curve have to be interpreted with some caution. Distributions were not attributed to all parameters in the model (only effects and fracture costs) and any covariation between the parameters was not available.

Although the curves do not capture all of the uncertainty in the cost-effectiveness estimates it captures some, which could be valuable information for decision-makers.

Figure 6 Acceptability curves



3.2 Sensitivity analysis

3.2.1 Length of intervention

When the intervention period was extended to 10 years, the cost-effectiveness ratio was higher compared to the base-case (*Table 13*). The main reason is that mortality increases and quality of life decreases with age. Thus the cost savings and the outcome do not increase proportionally to the increase in cost of treatment.

Table 13 Sensitivity analysis: 10-year intervention

	Vertebral Fracture Arm	Clinical Fracture Arm
Incremental cost	DKK 10,804	DKK 21,568
Life-years gained	0.1485	0.09621
Cost per life-year gained	DKK 72,778	DKK 224,181
QALYs gained	0.15788	0.10207
Cost per QALY gained	DKK 68,428	DKK 211,305

3.2.2 Set-time

As can be seen in *Table 14* the cost per QALY gained improves when the effect of treatment was assumed to decline linearly over 10 years instead of 5 years after the intervention period. This is expected since the effect of alendronate diminishes over a longer time period while the cost of intervention is the same.

Table 14 Sensitivity analysis: 10 years set- time

	Vertebral Fracture Arm	Clinical Fracture Arm
Incremental cost	DKK 768	DKK 7,646
Life-years gained	0.1150	0.07379
Cost per life-year gained	DKK 6,678	DKK 103,619
QALYs gained	0.12554	0.07992
Cost per QALY gained	DKK 6,116	DKK 95,661

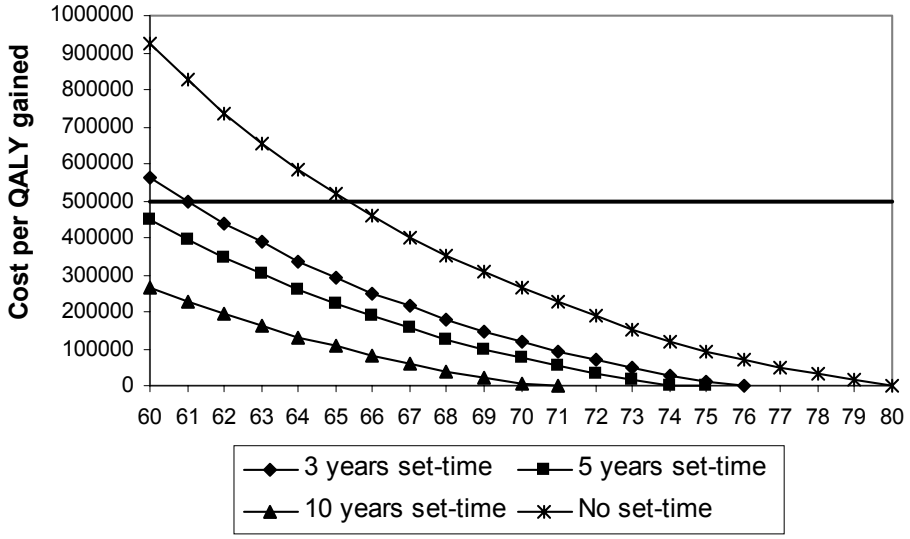
3.2.3 Starting age of cohort

When the starting age of the cohort is one standard deviation above the mean age treatment with alendronate is both more efficient and less costly than no treatment for both women with and without prior fractures (*Table 15*). At the lower starting age the cost per QALY gained is markedly higher. This is not surprising since the baseline risk for fracture is lower at this age (consider the increase in risk of hip fracture by age in *figure 5*). In *Figure 7,* which shows the cost per QALY gained at different starting ages of the cohort and assumed set-times of 0, 3, 5 and 10 years for women with prior vertebral fractures, it easy to see that longer set-times and higher starting ages gives lower cost-effectiveness ratios. When making the conservative assumption of no set-time, i.e. no effect of alendronate after the treatment period, the cost per QALY gained is below the threshold for starting ages of 65 years and above.

Table 15 Sensitivity analysis: Different starting ages

	Incremental cost	QALYs gained	Cost per QALY gained
VFA: Starting age 65	DKK 13,061	0.05899	DKK 221,418
VFA: Starting age 77	DKK -4,573	0.15107	Dominating
CFA: Starting age 63	DKK 14,475	0.04412	DKK 334,179
CFA: Starting age 75	DKK -911	0.12524	Dominating

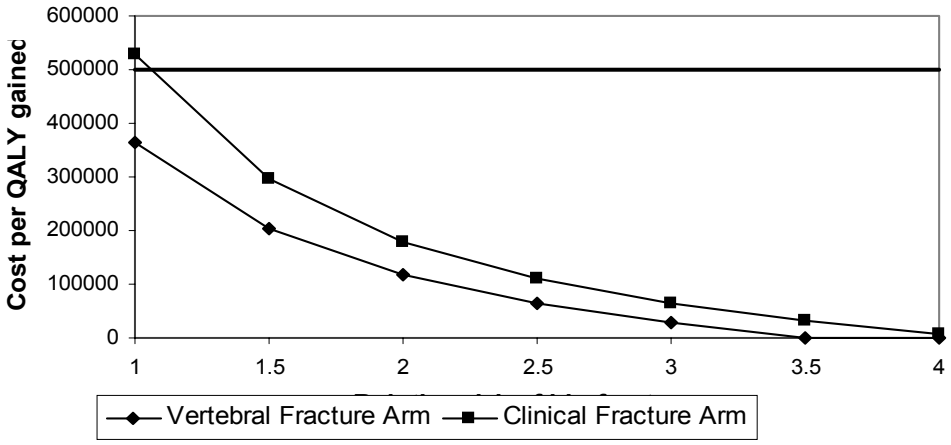
Figure 7 Sensitivity analysis: Different starting ages and set-times



3.2.4 Relative risk of hip fracture

Figure 8 shows the cost per QALY gained at different levels of relative risk of hip fracture holding the relative risk of wrist and vertebral fracture constant. Assuming a relative risk of one, which is equal to the baseline risk, the cost-effectiveness is above the assumed threshold for patients without prior vertebral fractures.

Figure 8 Sensitivity analysis: Relative risk of hip fracture



3.2.5 Cost in added life years

The cost-effectiveness ratios are higher when cost in added life years are included in the analysis (*Table 16*). Alendronate has a prolonging effect on life compared to no treatment and this gain in extra lifetime is associated with costs for the society since the age group in focus consumes more than they produce. The inclusion of cost in added years of life increases the cost-effectiveness ratio, but it will also increase the "bench-mark" value for good "value for money". The inclusion of these costs will thus not change the conclusions, but will have consequences for the rankings of programs which are mainly life saving compared to those that mainly improve quality of life.

Table 16 Cost-effectiveness including cost in added life years

	Vertebral Fracture Arm	Clinical Fracture Arm
Incremental cost	DKK 18,014	DKK 20,147
Life-years gained	0.0818	0.05145
Cost per life-year gained	DKK 220,366	DKK 391,604
QALYs gained	0.09376	0.05801
Cost per QALY gained	DKK 192,127	DKK 347,290

4 Discussion

As in all modelling exercises, several assumptions were made in this study leading to uncertainties in the results. Despite the fact that sensitivity analyses were conducted to address them, there are still limitations that have to be considered.

The risks used in the model are total risks, i.e. not the risk of having a first fracture but the total number of fractures during the year divided by the number of patients. This means that this risk has to be applied to the entire cohort (except for the dead, of course) in order to produce the correct number of fractures. This is reflected in the way the model is constructed. In each cycle, every patient who is alive is exposed to the risk of fracture. The only deviation from this principle is that patients who have had a hip fracture will no longer be exposed to the risk of spine- or wrist fracture. This assumption is made in order to simplify the model. To allow for these fractures, two new states would have to be introduced, but the results would not be significantly different since the probability of this event is very low. The current model, thus, slightly underestimates the number of spine- and wrist fractures and is thereby possibly conservative with respect to the effectiveness of treatment with alendronate.

The cost of treating a fracture increases with the age of the patient [32]. Introducing age dependent costs of fractures would have improved the model. However, the change in cost-effectiveness ratios would likely to be marginal.

In the analysis a compliance rate of 100% was assumed. However, in the vertebral and clinical fracture arm of the FIT, 87% and 84% of the placebo group and 89% and 83% of the alendronate group were still taking medication at the time of closeout. The assumption of full compliance in the model likely leads to overestimated intervention costs in relation to the assumed effectiveness of treatment, which included non-compliers in the FIT. In real clinical practice the compliance is almost never full, which leads to lower effectiveness, however this is somewhat balanced by a lower intervention cost.

There was no significant difference in adverse experiences between treatment groups in the FIT, and therefore no adjustments on costs or quality of life for side effects were included in the model.

In the base case a five-year decline, i.e. set-time, of the effect of alendronate after discontinue of treatment was assumed. There is evidence that the effect of alendronate may also remain after the cessation of therapy. In a study by Stock et al. [33] the difference in bone density between the alendronate and placebo groups at the end of trial was maintained for up to two years. Thus a 10-year set-time, which was tested in a sensitivity analysis, may be a more suitable assumption since no accelerated bone loss is observed after discontinuation of treatment.

The cost-effectiveness ratios were lower than the assumed threshold value of DKK 500,000 per QALY gained for patients with and without prior vertebral fractures. Except for a few of the scenarios in the sensitivity analysis the cost per QALY gained remained below the threshold value. Even at a more conservative threshold value of

DKK 335,000 ($40,000), which has been suggested in the literature [34, 35] alendronate is cost-effective for the majority of the scenarios.

Taking the above-mentioned limitations and uncertainties in consideration the conclusion is that the results in this study indicate that alendronate is cost-effective for the treatment of high-risk women in Denmark. This means that, compared with alternative uses of scarce health care resources, treatment with alendronate gives a comparatively high health benefit (improvement in quantity and/or quality of life) for the money spent on treatment.

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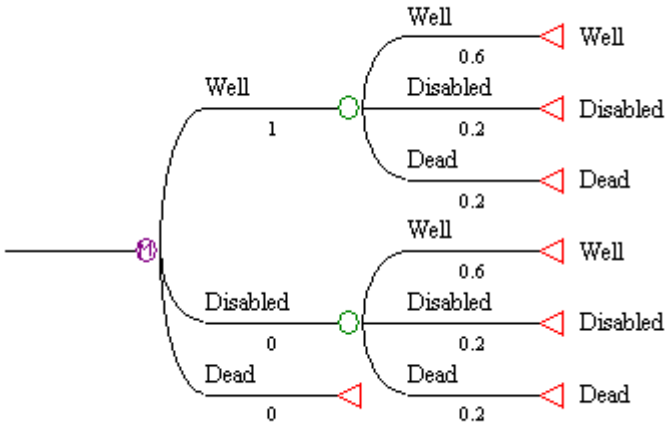
Appendix 1. Example cycle-sum calculation

The structure of the model used in the example is displayed in the *Markov cycle tree* in *Figure A:1*.

Figure A: 1 Markov cycle tree



Attached to the *Markov node* are branches, which define the *health states* in the model. From the health states stem the *terminal nodes*, which define the allowed transitions from each state. At each terminal node the estimated transition probability is defined. A person is always in a state and during each cycle he has some certain probabilities to make one transition between the defined states. A person in the *Well* state can make transitions to all the three states but a person who ends up in the *Dead* state can not make any further transitions. The transition probabilities can be time dependent, e.g. they can change for different ages. To terminate the Markov process an *absorbing state* is needed, that is a state, which the person cannot leave. In the above example the *Dead* state is an absorbing state. There is an option between letting the cohort run through a certain number of cycles (e.g. up to a specific age) or let the process terminate when a predetermined share of the cohort has ended up in the absorbing state.

Calculation of the cycle-sum based on the Markov cycle tree and the health state utilities presented in *Table A:1* is shown in *Table A:2*.

Table A: 1 Health state utilities

Health state	*Utility*
Well	1
Disabled	0.7
Dead	0

Table A: 2 Example of cycle sum calculations

Cycle	*Well*	*Disabled*	*Dead*	*Cycle sum*	*Cumulative Utility*
Start	1000	0	0	*(1000*1)/2*=500	500
1	600	200	200	*(600*1+200*0.7+200*0)*=740	1240
2	480	160	360	*(480*1+160*0.7+360*0)*=592	1832
3	384	128	488	*(384*1+128*0.7+488*0)*=474	2306
*	*	*	*	*	*
19	11	4	985	*(11*1+4*0.7+985**0)=14	4146
20	9	3	988	*(9*1+3*0.7+988*0)/2*=6	4152

The hypothetical cohort is 1000 persons[2] which all begins in the *Well* state. In the following cycle simulations the cohort is distributed among the states according to the transition probabilities. For example, the number of patients in the *Well, Disabled* and *Dead* states in cycle 2 are obtained by multiplying the number of alive patients in the in the preceding cycle with its transition probabilities, i.e. *800*0.6=480* for the *Well* state, *800*0.2=160* for the *Disabled* and *Dead* states. The accumulative number of dead of the original 1000 persons adds up to 360 in cycle 2. The process is set to terminate after 20 cycles. The number of patients in each state times the respective state utility adds up to the cycle sum. The cycle sum in the first and the last cycle is divided by two due to half cycle correction. The running total of the cycle sum is called the cumulative utility.

[2] The number of people in the cohort is actually irrelevant for the results in the model, since it is the incremental utility and cost that is important in the cost-effectiveness analysis.