Cost-effectiveness of alendronate in the treatment of low bone mineral density in the time of price competition

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Master thesis

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Foreword

In the process of writing this master thesis, our quality of life has varied from 0.05 to 1. Initially we were very enthusiastic and full of energy. Sadly we later started falling in and out of "Markov madness", which led to confusion and circular reasoning. The good thing was that it usually attacked only one of us at a time, meaning that we could calm each other down or cheer each other up, dependent on the requirements of the situation.

Although working together, each of us have been responsible for different parts of the thesis. Gunhild has been responsible for writing about fractures (1.3.1 and 1.3.2), economic evaluation and priority setting (1.5), quality of life (2.3.2), mortality (2.2.6-2.2.9), incidence (2.2.1 and 2.2.2), sequela (2.2.3 and 2.2.4) findings of other CE studies (4.2) and policy implications (4.3).

Janicke has been responsible for writing the introduction about osteoporosis (1.1 and 1.2), treatment of osteoporosis (1.4.1 and 1.4.2), costs (2.3.1), effects of alendronate (2.2.5) and the result chapter (3). The chapter about the model (2.1.1 and 2.1.2) and assumptions and limitations (4.1) are joint work.

Both of us received scholarship from HERO for the work on this master thesis.

We would like to thank our supervisor Ivar Sønbø Kristiansen for his outreaching and enthusiastic approach, Christian Kronborg Andersen for letting us develop DOOM into OOOM (Oslo Osteoporotic Outcome Model), Jan Falch for being our osteoporosis expert, Cathrine Lofthus for entrusting us with her data and Torbjørn F. Wisløff for helping us model our way out of the mortality problem.

Oslo, May 2007

Gunhild Hagen and Janicke Nevjar

Abbreviations and acronyms

BMD	Bone marrow density
CBA	Cost benefit analysis
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CFA	Clinical fracture arm in the FIT study
CI	Confidence interval
CUA	Cost utility analysis
CVA	Cost value analysis
DOOM	Danish Osteoporosis Outcome Model
DRG	Diagnosis related groups
EMBASE	Excerpta Medica Database
FIT	Fracture Intervention Trial
GP	General practitioner
HS	Health state
ICER	Incremental cost effectiveness ratio
IOF	International Osteoporosis Foundation
MAU	Multiattribute utility instrument
NMA	The Norwegian Medical Association
NOK	Norwegian crowns
RR	Relative risk
RRR	Relative risk reduction
Shdir	Directorate for health and social affairs
QALY	Quality adjusted life year
UI	Utility instrument
VFA	Vertebral fracture arm in the FIT study
WHO	World Health Organisation

Abstract

Background: Norwegian guidelines recommend treatment with bisphosphonates for women considered at high risk of osteoporosis. Alendronate is the most used bisphosphonate. Recently the price of alendronate has fallen by 75% due to the expiring of the patent. This may influence the cost effectiveness of the drug.

Objective: To estimate the incremental costs and effects of treating postmenopausal, osteopenic women with alendronate in addition to calcium and vitamin D instead of calcium and vitamin D alone.

Design: Markov model with seven health states: well, well after fracture, mild hip fracture sequela, moderate hip fracture sequela, severe hip fracture sequela, vertebral sequela and dead. The model encompasses three events: hip, vertebral and forearm fracture.

Data sources: Literature searches in the databases Medline, EMBASE and Cochrane to identify data on fracture incidence, efficacy, of alendronate and quality of life. Costs are estimated using Norwegian fee schedules for 2006. Mortality rates for 2006 from Statistics Norway.

Target population: Postmenopausal women, aged 65-75 with femoral neck T-score between -1.5 and -2.5 living in Oslo.

Time horizon: Until death or age of 100.

Perspective: Broad health care

Interventions: Four years of treatment with alendronate. Offset time three years.

Outcome measures: The results are expressed as incremental costs, incremental quality adjusted life years, and costs per QALY gained.

Results: Treatment with alendronate was cost saving and more effective for all groups.

Results of sensitivity analysis: The results of the one-way sensitivity analyses indicate that this conclusion is robust to any realistic change of the model input.

Limitations: Results apply mainly to postmenopausal, Caucasian women in Oslo.

Conclusions: The results indicate that treatment with alendronate, at the current price level, is cost saving and more effective compared to no treatment for a wide group of women.

Content

1. Introduction

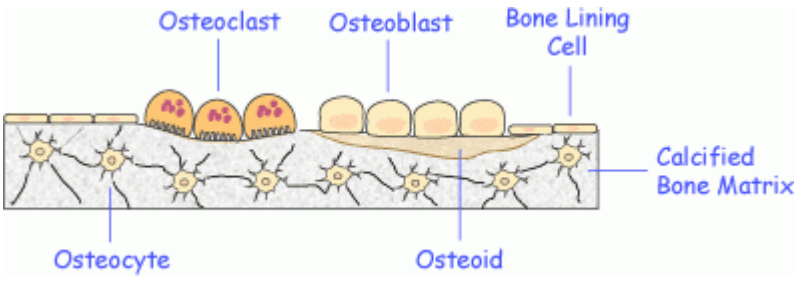
1.1 Osteoporosis

Osteoporosis is an asymptomatic but still clinically important condition because of its association with fractures, particularly fractures in hip, forearm and spine. It is characterised by low bone marrow density (BMD), which is a measure of bone strength.

Bone strength encompasses both bone quantity and quality. It depends on peak bone mass at early adulthood and subsequent rate of bone loss. Peak bone mass is determined by heredity, sex, dietary factors, endocrine factors, mechanical forces and exposure to risk factors. Bone loss accelerates after the menopause, but may also result from age-related conditions such as reduced calcium absorption. Certain drugs and medical conditions can produce so-called secondary osteoporosis [35].

The balance between bone resorption and bone deposition, and thus whether bone is made, maintained or lost, is determined by the activities of two cell types, the osteoblasts who are responsible of bone synthesis and subsequent mineralisation, and the osteoclasts that function in resorption of mineralized tissue. These mechanisms are not yet fully understood [36].

Figure 1; Osteoblasts and Osteoclasts [98]



Both men and women, and all age groups are at risk of osteoporosis, but it is most common in postmenopausal women. Approximately 30% of all postmenopausal women in Europe have osteoporosis [35]. There are few studies on incidence of osteoporosis in Norway, but in 1998 it was estimated that 14-36% of women above 50 years, living in Oslo, had

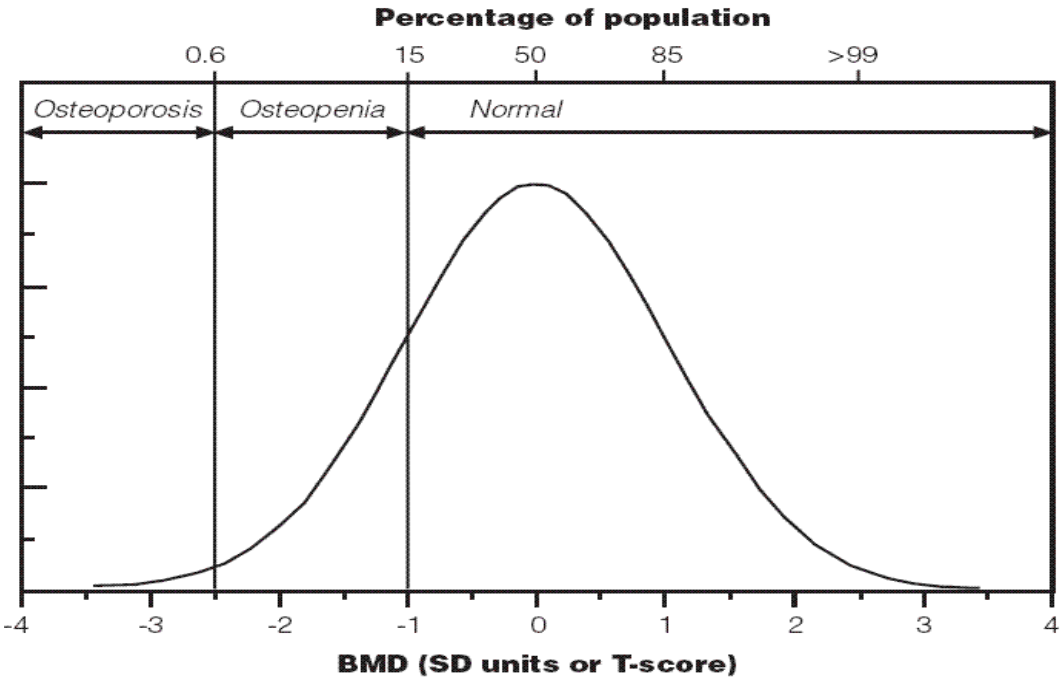
osteoporosis. Extrapolated to the Norwegian population, this corresponds to 96 000-255 000 women with osteoporosis [24].

Both the incidence and the financial and health related costs of osteoporosis will increase in the future as life expectancy, and thus the number of elderly individuals, is increasing [35].

1.2 Definition of T-score and Z-score

BMD is often expressed by T-score, which is the number of standard deviations (SD) above or below the mean BMD values for a young healthy adult.

Figure 2; Osteoporosis and Osteopenia, [98]:



Four general diagnostic categories for women, based on BMD values, have been proposed by a WHO Study Group [98]:

- Normal BMD: T-score above or equal to -1
- Osteopenia: T-score below -1 and above -2.5
- Osteoporosis: T-score above or equal to -2.5

- Established osteoporosis: T-score below or equal to -2.5 in addition to one or more fragility fractures.

Another measure is Z-score, which is the number of standard deviations above or below the mean BMD values for a population of the same age and gender [35]. Figure 3 shows how BMD varies with age

Figure 3; BMD and Age [98]:

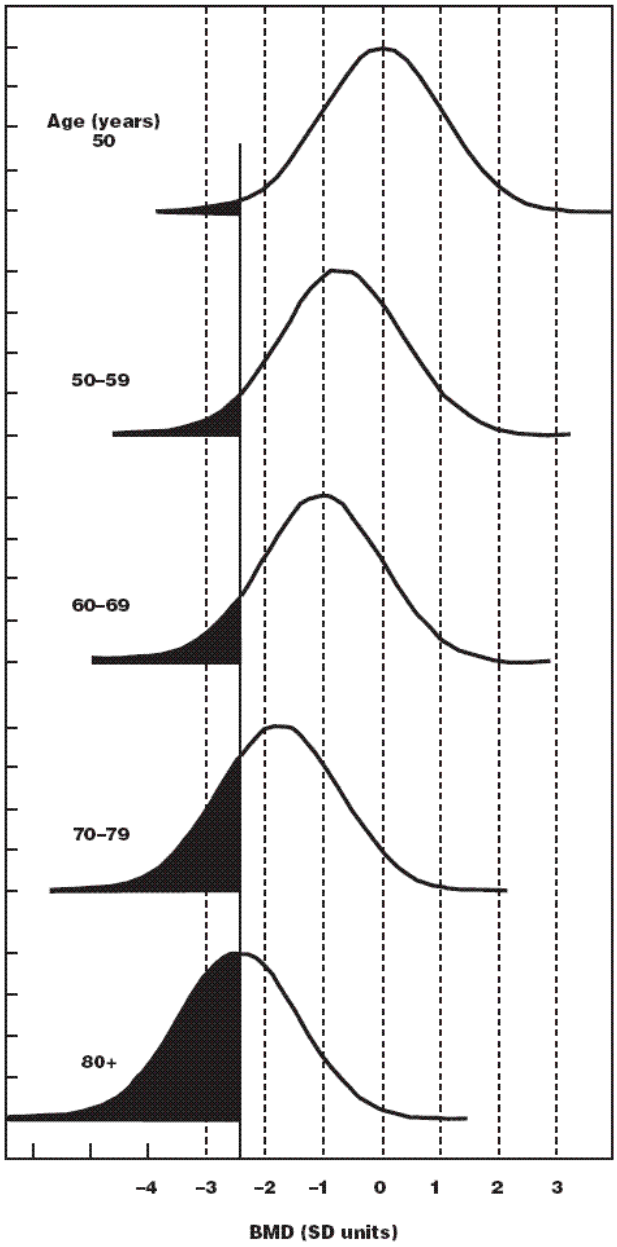


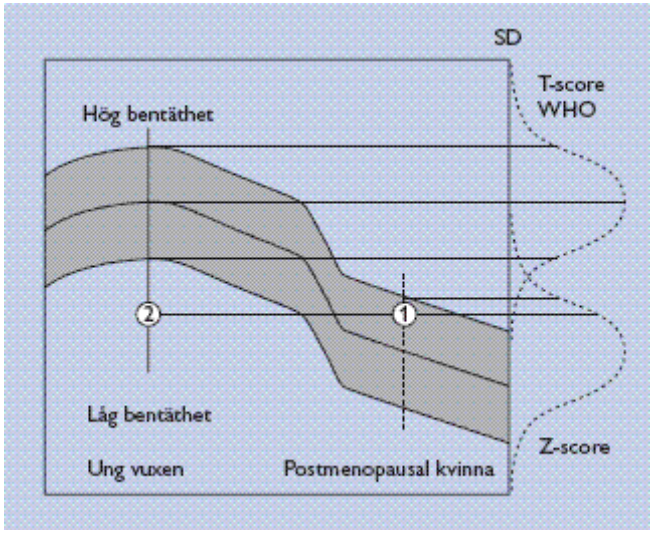
Table 1 shows the relationship between T-score and Z-score. The table was calculated for us by Jan Falch MD based on a reference material from Oslo [23].

Table 1; Relationship between T-score and Z-score for women of 65, 70 and 75 years old, living in Oslo [23]:

T-score 65 years old	Z-score 65 years old	T-score 70 years old	Z-score 70 years old	T-score 75 years old	Z-score 75 years old
0	1.2	0	1.4	0	1.6
-0.5	0.7	-0.5	0.9	-0.5	1.1
-1	0.2	-1	0.4	-1	0.6
-1.5	-0.3	-1.5	-0.2	-1.5	0.1
-2	-0.8	-2	-0.6	-2	-0.4
-2.5	-1.3	-2.5	-1.1	-2.5	-0.9
-3	-1.8	-3	-1.6	-3	-1.4
-3.5	-2.3	-3.5	-2.2	-3.5	-1.9

As shown by figure 4, a woman can have a BMD corresponding to osteoporosis but a normal value for her age [81].

Figure 4; T- and Z- score [81]:



The BMD values can be measured in several ways, each method has pros and cons and no method is suitable for measuring BMD in all parts of the body. The diagnostic categories suggested by WHO are based on BMD values measured by dual energy X-ray absorptiometry (DXA). Although quite expensive, this method gives high precision and low doses of radiation compared to the other methods available; quantitative ultra sound and quantitative computer tomography. Because of limited precision and low correlation between the different methods, BMD values from different methods should not be compared [81].

1.3 Fractures

Osteoporosis is in itself asymptomatic, but manifests itself trough the related fractures. Most common are fractures of the hip, spine and forearm. Fractures can be seen as a function of a trauma and the fragility of the bones. Both these factors increase the probability of a fracture. It is possible to suffer a fracture with minimal trauma for patients who have very fragile bones. And it is of course possible for a healthy, young person to break a leg without being osteoporotic

The main problem with osteoporosis is that, as the bones grow more fragile, the impact needed for bones to break diminishes rapidly.

1.3.1 Societal impact of fractures

Scandinavia has the highest incidence of osteoporotic fractures in Europe [38].These fractures represent a considerable burden to the patients and to society as a whole, as the fractures are associated with a significant increase in mortality, morbidity, loss of function [31] and health and social care costs [73]. It has been estimated that there are approximately 9000 hip fractures in Norway each year and that the direct societal costs of these fractures amount to 1.5 billion NOK [50]. In the US osteoporosis related fractures were estimated to 13.8 billion, of witch approximately 62% were spent on in-patient care, 28% on nursing homes and 10% on out-patient care [73].

The EU has estimated that the treatment costs of osteoporotic fractures will increase with more than 20% by 2020 [91].

It should be clear from the discussion above that osteoporosis related fractures pose a large burden on the health care system in the form of both capacity and money, both of which have an opportunity cost. In other words; these resources could have been spent on other patient groups, if the fractures had been avoided.

1.3.2 Patient outcomes

"Quality of life data obtained in patients with osteoporotic fractures show that loss of quality of life is more severe in patients after hip or multiple vertebral fractures than in patients' with a single vertebral fracture or distal radius fracture" [51].

Hip fractures

Hip fractures are the most serious of the osteoporosis related fractures, as they are the ones which are most strongly associated with loss of function, decreased quality of life, excess mortality and health and social care costs. Hip fractures are considered to be as big a treat to the health of old people as a heart attack or a cancer [12]. All people suffering a hip fracture will be admitted to a hospital for an operation and will also require physiotherapy. Many of the patients will have a permanently impaired functional level. Loss of function is an important element, as it to different degrees can limit the individual's ability to lead an independent life.

Hip fractures also have a significant negative effect on the individuals' quality of life.

"Quality of life depends on co- morbidity, mobility, activities of daily life, independence and fracture complaints" [51].

Qualities of life estimates after a hip fracture vary a great deal between different studies. Estimates ranging from 0.05 up to 0.885 have been reported in the literature. Possible reasons for this will be discussed further in chapter about quality of life.

Vertebral fractures

Vertebral fractures are divided into morphometric and clinical fractures. Morphometric fractures are defined as fractures identified by a change in the shape of a bone, rather than pain or other symptoms [82]. Clinical fractures are, as the name implies, fractures that come to clinical attention because the patient contacts their GP or other health care providers. There is however no consensus in the definition of vertebral fractures [17].

Research done by Kanis and co-workers [45] indicate that only 23% of vertebral fractures in women in Malmo, Sweden came to clinical attention. The reason for this, is that unlike the hip fractures which often occur trough a fall from standing height [17], the vertebral fractures

can occur during daily activities, without any identifiable trauma [73]. The patients may thus be unaware that they have had a fracture, as the only symptom of an incident vertebral fracture may be back pain.

Vertebral fractures often reoccur and multiple prevalent vertebral fractures are associated with impaired physical function, height loss, sleep disturbance, depression, fear of falling and loss of self esteem [73]. An incident vertebral fracture cause pain and the pain may last for three years or longer. Recurring fractures may cause vertebral deformity (kyphosis), which may again lead to loss of lung function, height loss and significant loss of function. Vertebral deformity may also lead to social isolation and depression, as a consequence of the decline in physical function and change in appearance [74]. Unlike the hip fractures however, the vertebral fractures have not been shown to increase the likelihood of moving to a nursing home.

We will in our model only look at clinical fractures, as costs, incidence and quality of life associated with morphometric fractures are very uncertain.

Wrist fractures

Wrist fractures cause considerable utility loss in the first few months, due to pain and loss of function. Most patients do, however fully recover within one year [12, 51].

Mortality

Low BMD is associated with increased mortality. Increased mortality has also been documented after hip and vertebral fractures. Whether or not this post-fracture mortality is causally related to the fracture remains an unresolved question. For details see the chapter about BMD and mortality.

1.4 Prevention and treatment of osteoporosis

The focus in this thesis is alendronate. This is however only one of many ways to prevent and treat osteoporosis. In this chapter we make a short summary of some of the options.

There are two main strategies in the prevention of osteoporosis and osteoporosis related fractures, and interventions can use either one or both. The first strategy targets the bone density, either by increasing the making of new bone or by decreasing the bone resorption. The second strategy is to prevent trauma, so called false prevention.

The prevention can be either primary or secondary. Primary prevention means that it is targeted at people with no symptoms or other detectable signs of disease, while secondary prevention means that it is targeted only at people at increased risk.

Some of the strategies for prevention are based on medical interventions while others are non-medical, like promoting certain kinds of life style and diet.

1.4.1 Medical prevention and treatment

Several pharmacologic options are available. Strong evidence shows that supplement of calcium and vitamin D in combination reduce fracture risk in elderly women [81]. Calcium and vitamin D supplement can be used alone or in combination with other drugs. Hamdy emphasises that based on the available evidence, it is important to ensure calcium and vitamin D sufficiency in all patients. Calcium and vitamin D will not reduce the risk of vertebral fractures in women with symptomatic osteoporosis, but they will complement the anti-fracture efficacy of other drugs [31].

The other drugs are oestrogen, selective oestrogen receptor modulator (SERM), parathyroid hormone (PTH) and bisphosphonates. Oestrogen prevents loss of bone mass and reduces the risk of fractures [81]. It was previously used to prevent osteoporosis, but is no longer recommended as the primary choice of treatment by the Directorate for health and social affairs because of serious side effects like increased risk of breast cancer [92]. SERM reduces the incidence of vertebral fractures, but gives no significant reduction in other types of fractures. SERM also increases BMD, but the effect is smaller than the effect of oestrogen

and bisphosphonates [81]. Daily injections of PTH stimulate bone formation, and reduce the risk of new morphometric vertebral fractures by 65% in postmenopausal women with established osteoporosis. Non-vertebral fractures are decreased by 53%. PTH also increases BMD in hip and vertebra in elderly women with postmenopausal osteoporosis [81].

A much used option is bisphosphonates. According to Hamdy [30], the bisphosphonates alendronate and risedronate produce the most robust fracture risk reductions of all treatment modalities: approximately 40 to 50% reduction in vertebral fracture risk; 30 to 40% in non-vertebral fracture risk; and 40 to 60% in hip fracture risk". The Directorate for health and social affairs recommend bisphosphonates combined with vitamin D and calcium as the primary choice of treatment for osteoporosis for several groups of postmenopausal, Caucasian women [92].

Sales data

The use of bisphosphonates and other medicinal products that could be used for prevention/treatment of osteoporosis has increased since 2001. The sale of bisphosphonates has increased steadily during the last years. In 2005 it increased by 15% and totalled NOK 194 million, pharmacy retail price. While bisphosphonates have increased, the sales of estrogens used in the menopause have decreased by 14% in 2005. Since 2001 there has been a total reduction of 45% for oestrogen. These changes in the sales could be results of the 2003 recommendations from the medicinal authorities not to use oestrogens as first line therapy for prevention and treatment of osteoporosis. [93]

Alendronate is the most used bisphosphonate in Norway, and the amount sold increases every year. 7.87 doses of alendronate per 1000 inhabitants per day were sold in 2005, and 8.23 in 2006. The second most sold bisphosphonate in 2006 was risedronate with 0.80 doses per 1000 per day [93].

1.4.2 Non-medical prevention

In addition to medical treatment, several non-medical actions can be taken. Both sufficient energy intake and sufficient supply of vitamins and minerals have impact on BMD level and fracture risk since both low weight and low body mass index as well as malnutrition are risk factors for osteoporosis. The Norwegian guidelines for treatment of osteoporosis [92]

recommend a diet which ensures a certain daily amount of calcium and vitamin D. Calcium increases BMD, and vitamin D is important for the absorption of calcium in the intestines [81].

Physical activity is important to build and maintain bone mass in individuals at all ages, and one possible reason for the growing incidence of osteoporosis is changed lifestyle with less activity than before. Evaluating the effects of physical activity on fracture risk and BMD can be hard because of confounding; other factors may influence the results. A physical active person might differ from a less active person in many other ways, for instance regarding smoking status and nutrition. Both the Swedish study and the Norwegian guidelines do however conclude that physical activity increases BMD and decreases fracture risk in postmenopausal women. The effect is somewhat more uncertain for women older than 65 [81].

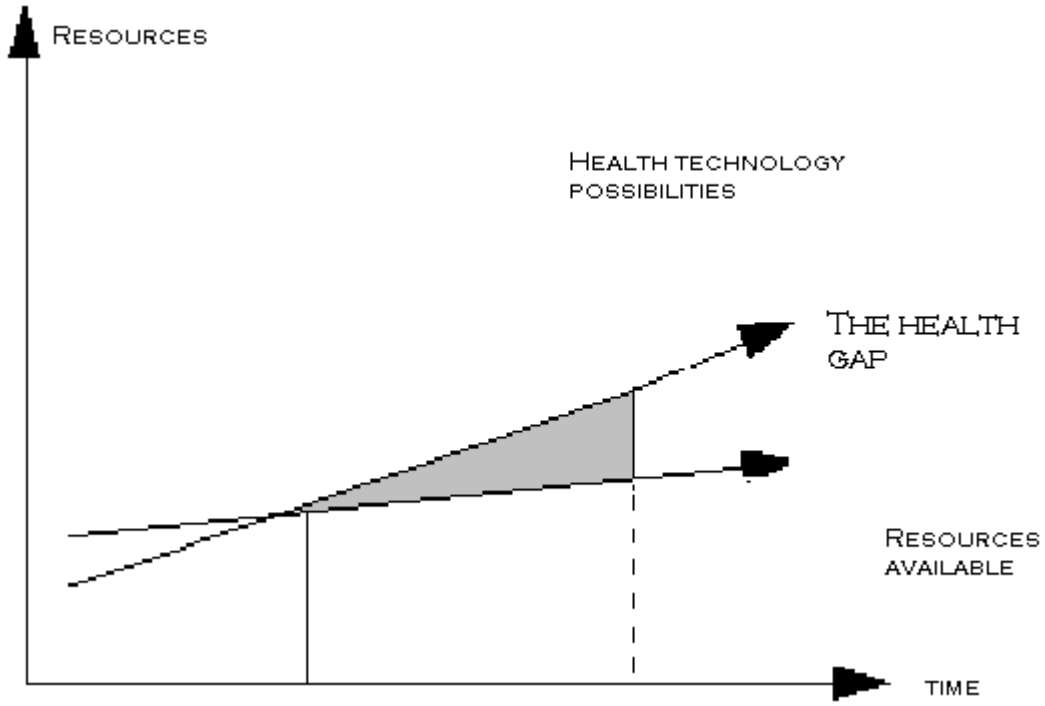
Protection against falling

Approximately 30 per cent of people above 65 years of age fall each year. The number is higher in institutions. Several factors, like reduced balance, reduced sight and hearing, insufficient nutrition and medication, can lead to falls. The risk of fracture after a fall increases when the person falling has osteoporosis [81]. Although less than 1 fall in 10 results in a fracture, a fifth of fall incidents require medical attention. Several actions can be taken to reduce the incidence of falls in elderly people. Examples that are likely to be beneficial are certain kinds of exercise and home hazard assessment and modification for people with a history of falling [28]. Hip protectors aim to reduce the impact of a fall on the hip, and thus the risk of a hip fracture. Use of hip protectors reduces the risk of hip fractures for some groups of elderly people with high risk of falling, living in institutions [78].

1.5 Economic evaluation and priority setting

"Most countries feel constant pressure because expenditure is increasing and resources are scarce" [62].

Figure 5: The Health Gap [72]



A rapid technological development in medicine has made the gap between what is technologically possible and what society can afford widen [72].

When resources are too scarce to accommodate all needs and wants, it is rational to prioritise something one values highly in relation to what it costs [64].The question then becomes, what does the Norwegian society value when it comes to health care? And what are central policy goals in this field?

Three policy documents have specifically addressed the issue of priority setting in the Norwegian health care system; NOU 1987:23 ("Guidelines for priority setting in the

Norwegian health care service"), NOU 1997:7 ("Pills, priority setting and policy") and NOU 1997:18 ("Priority setting revised"). NOU 1987:23 [70] and NOU 1997:18 [71] were both general, in the sense that they applied to the entire Norwegian health care system, while NOU 1997:7 [72] was specifically targeted at pharmaceuticals and their reimbursement. According to NOU 1997:7 criteria for priority setting for pharmaceutical interventions were (in prioritized order):

The severity of the disease; A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase it imposes of death, disability and discomfort, if treatment is postponed.

The effectiveness of the treatment; Effectiveness of treatment should be well documented.

The cost-effectiveness of the treatment; The costs of the treatment should be in a "reasonable" relationship to the effects of the treatment.

The intention of the treatment; Interventions which aim to treat a disease is prioritised before preventive measures. Preventive measures are prioritised before quality of life improvements.

This is in line with NOU 1997: 18, which also emphasises the weight on severity, effect of the treatment and a "reasonable" relationship between the costs and the effects [71].The same view is also expressed in the patient rights act of 1999, which states that a patient is entitled to necessary treatment if the expected effects are in a "reasonable" relationship to the costs [55].

The cost effectiveness of a treatment is investigated through an economic evaluation. Economic evaluations aim to aid policy makers in decision making, when it comes to priority setting. Economic evaluation is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" [19].

One type of economic evaluation is cost-utility analysis. In a cost-utility analysis, the effect of a treatment is measured in QALYs. The QALY attempts to capture both the morbidity and the mortality aspect of a specific disease or condition. An advantage with using a cost-utility

analysis and QALYs is that it makes comparison between different treatments and interventions for various diseases and conditions possible.

One feature of the QALY is that it expresses the preferences of individuals over time spent in different health states. When priorities are set, the preferences reflected should be those of society as a whole. The question then becomes whether the sum of individual preferences, as expressed in QALYs, is the same as societal preferences. There are several reasons why there may be inconsistencies between implicit QALY judgements and societal values:

- Every level change is the same in the QALY approach; severity (starting point) is not taken into account. This means that in terms of QALYs, a health gain for a seriously ill person and a nearly healthy person can give the same amount of QALYs.

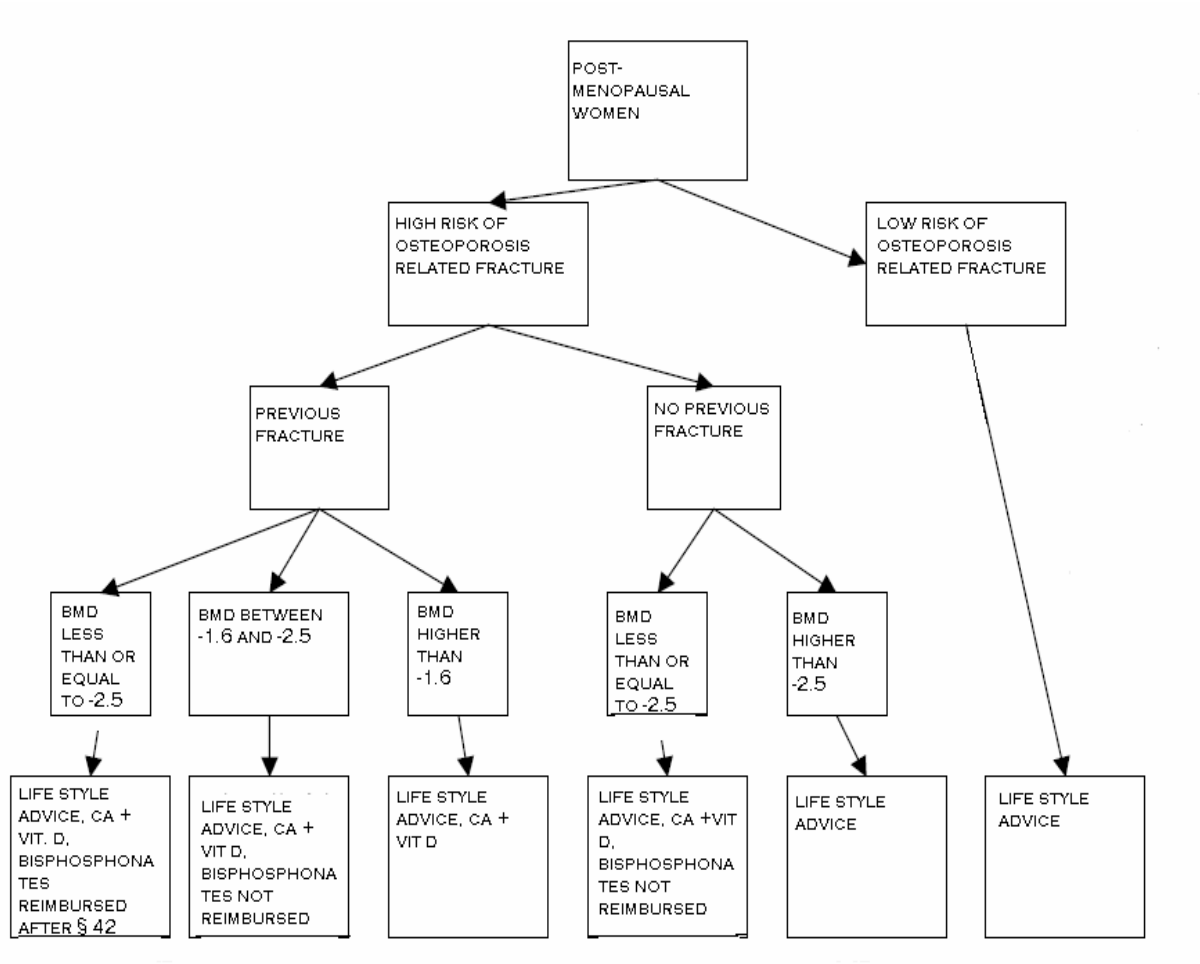
- Potential for improvement is given value in QALY calculations, but not necessarily in the eyes of the society.

- An intervention which prolongs life with ten years will give more QALY gain when given to a healthy person, than when given to a person with a handicap, as duration on QALY calculations is multiplied with the value of the health state.

Considering that QALYs don't necessarily reflect societal values, implies that results from a cost utility analysis should not be interpreted alone, but seen in relationship with other priority setting criteria. In other words, the fact that an intervention is cost effective does not necessarily mean that it should be implemented.

Treatment guidelines reflect society's value judgements [27]. This implies that the treatment guidelines should reflect the criteria for priority setting as stated in policy documents.

Figure 6: Flow chart from Norwegian guidelines for treatment and prevention of osteoporosis and osteoporosis related fractures [90].



The current treatment guideline for treatment and prevention of osteoporosis and osteoporosis related fractures [90] recommends that treatment with bisfosfonate is given to postmenopausal women who are considered high risks, that is women who have a t-score of less than -2.5 or women with a t-score between -1.6 and -2.5 who have suffered a previous fragility fracture. Only women with a t-score of less than or equal to -2.5 with a previous fragility fracture will be reimbursed for their drug expenses.

Considering that osteoporosis related fractures, the hip fractures in particular, are associated with excess mortality, pain and suffering and that they in addition can have a significant negative impact on functional level, they can be viewed as fulfilling the first criterion for priority setting listed above, that is the severity criterion. The effect of alendronate is well

documented, at least in women with established osteoporosis. The question then becomes; for which groups of women is prevention of osteoporotic fractures trough treatment with alendronate cost-effective?

1.6 Research question

What are the incremental costs and effects associated with treating postmenopausal women aged 65, 70 and 75 years and T-scores equal to -2.5, -2 and -1.5 with alendronate 70 mg per week in addition to calcium and vitamin-D supplements, compared to calcium and vitamin D supplements alone?

2. Method

2.1 Model

2.1.1 General about Markov

We have used a Markov model to simulate our cohort. Osteoporosis is a chronic disease which develops over time. Sonnenberg and Beck [83] state that Markov models are useful when a decision problem involves risk that is ongoing over time.

2.1.2 Structure of our model

Our model can follow a cohort of 10 000 women from 50 until 100 years of age or until death. It consists of seven Markov health states: well, well after fracture, mild hip sequela, moderate hip sequela, severe hip sequela, vertebral sequela and death. In addition the model contains four temporary health states of first year sequelae.

All women start in “well” and can experience a hip-, vertebral- or forearm fracture during the first cycle. These are events which the individuals can pass through, but not spend any time in. Passing through an event accumulates disutility and costs.

After sustaining a hip fracture, a woman will have mild-, moderate- or severe sequelae. From the mild and moderate sequelae health states she can move to “well after fracture”. It is not possible to recover to “well after fracture” from severe hip sequelae.

After vertebral fractures one can have sequelae or move to “well after fracture”.

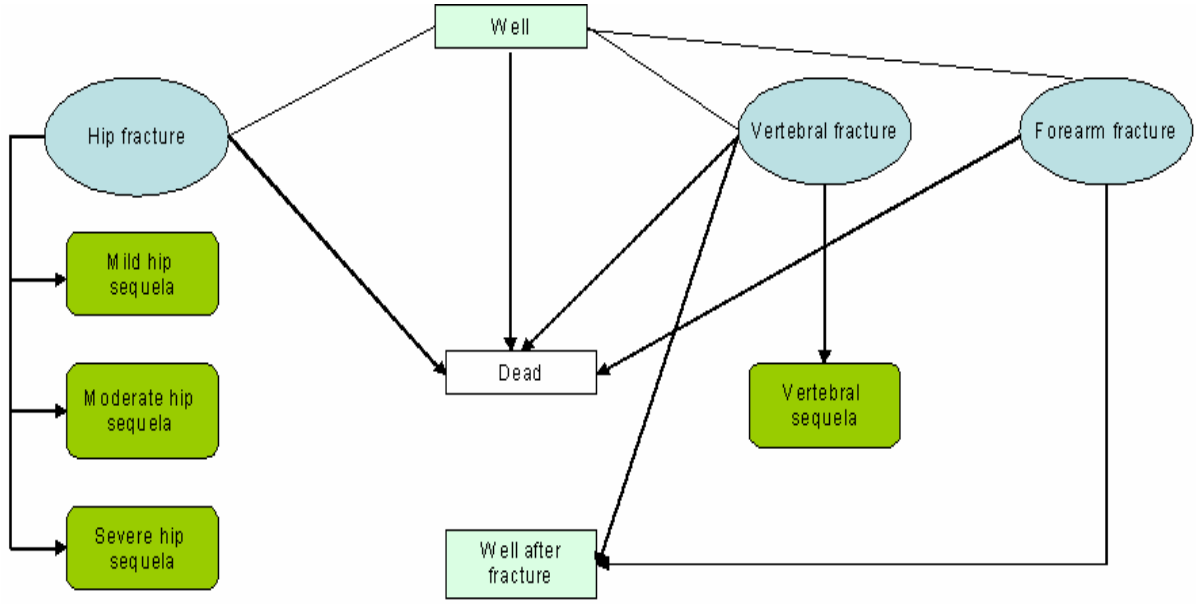
From all sequelae health states, it is possible to sustain new fractures of any kind, meaning that for example a woman in “moderate sequela hip” can still break her fore arm.

All women having a forearm fracture return to “well after fracture” at the end of the cycle. Women who do not sustain a fracture, can die or remain in the same state.

Age dependent transition probabilities determine how the individuals move from one state to another. The transitions occur in one year cycles.

"Death" is an absorbing state, meaning that it is not possible for an individual to leave this state once it is entered.

Figure 7; Model Structure: Transitions possible in the first year.



2.2 Input probabilities

2.2.1 Incidence of fractures

The incidence of osteoporosis related fractures vary both within and between countries. Research indicate that the Scandinavian countries have a generally higher incidence than the rest of Europe [38].

Table 2; Incidence of fracture per 1000 person years [38]

Region	Hip	Distal forearn
Scandinavia	4.4 (1.7, 7.0)	10.0 (6.2. 15.5)
Southern Europe	1.4 (0.0, 2.7)	6.1 (3.3, 9.0)
Eastern Europe	0.6 (0.0, 1.4)	10.3 (7.4, 13.1)
Western Europe	0.8 (0.3, 1.3)	5.6 (4.3, 7.0)

The reason for the high hip fracture incidence in Scandinavia is not known, and can seem paradoxical considering the high dietary intake of calcium in this region. Possible explanations include; low exposure to sunlight during the winter months, slippery sidewalks and thus more falls, environmental and genetic factors.

Rural areas generally have lower incidence of fractures than urban areas within the same country. The reason behind this variation is unknown [17].

Bulajic-Kopjar and co-workers [10] studied differences in incidence of hip fracture between different counties in Norway. They found that the incidence rate varied from 8.1 per 1000 in Finmark to 14.0 per 1000 in Oslo. They found a clear regional pattern, where the counties in the south and south-east had the highest incidence rate [10]. Falch and co-workers also looked at geographical differences in fractures and found that incidence in Sogn og Fjordane was only 65% of the incidence in Oslo [22]. Given these great variations in fracture rates, it is important to choose incidence rates which are representative for the population simulated in a model used for economic evaluation.

In order to find the incidence of hip fractures in Norway, one possibility could have been to use data from The Norwegian Patient Register. Research undertaken by Lofthus and co-

workers [53], do however indicate that register data have a low degree of validity. Lofthus and co-workers studied medical records of hip fracture patients in three hospitals in Oslo and compared the identified number of cases with the number in The Norwegian Patient Registers (NPR) database for each hospital. They found that the register-data underestimated the number of hip fracture patients treated at one of the hospitals with 46%, for the other two hospitals the NPR database overestimated the number of patients with 17% and 19%.

For the future modeller, the Norwegian Hip Fracture Register [63] may become a good source of incidence data, but we find it unrealistic to assume that the reporting routines to this register are working perfectly in so early on. The register started up 01.01.05 and we can only find data from 2005 published. The data from 2006 is likely to be of better quality, but these data are not available in time for thesis submission.

We do however have good data for Oslo, and we have decided to use the study by Lofthus and co-workers [54] as incidence input in our model. Given the variation between rural and urban areas, an extrapolation from the Oslo data to the entire country would most likely overestimate the hip fracture incidence in Norway. This would make treatment with alendronate seem more cost effective than it truly is. On these grounds we have decided to limit our model to Oslo for the time being.

The input chosen for incidence of forearm fractures is new, not yet published incidence data from Oslo [52].

For vertebral fractures no valid data can be found from Oslo. Based on the advice from Cathrine Lofthus MD and Jan Falch MD at Aker Hospital, we chose to use incidence data from Malmo, Sweden [46]. According to our experts, the incidence in Malmo is a good estimator of the incidence in Oslo. We have used the incidence of the first time clinical fractures for women in the relevant age range.

2.2.2 Fracture risk connected to BMD

For each standard deviation decrease in BMD measured at the hip, the risk of hip, vertebral and forearm fracture increase with respectively 2.6, 1.8 and 1.4 [57]. Our model does not permit for different BMD-risks connected to different types of fractures. We therefore used 2 as an overall estimate of fracture risk connected to each standard deviation in BMD. We used

this number in combination with table 1 in order to calculate the increased fracture risk for the nine different groups of women.

2.2.3 Distribution between and duration of sequelae

We have in this model defined “severe sequela” as impairments in functional level, which are so severe that patients in this health state will require long term care in a nursing home.

According to the study by Osnes and co-workers [76], 17% of patients who lived at home before the hip fracture, will move to a nursing home after the fracture. This is close to the result found by Melton [58], who reported 19%. Finsen and co-workers [26] found that 21% of the patients were bedridden after a hip fracture. We assume that all bedridden patients will require long term care in an institution. We chose to use Osnes’ more conservative estimate of 17%.

We defined “moderate sequelae” as needing assistance in the home from either family or a home help service. Osnes and co-workers [76] found that 55% of the patients who did not receive any help pre-fracture, needed help post-fracture. This number is much larger than the one found by Melton [58], which was 10%, but close to the one used by Christensen and co-workers [13], which was 60%. We chose to use the result found by Osnes and co-workers of 55%.

As we assume that all patients suffering a hip fracture will have some sort of sequelae, this means that 28% will go to “mild hip sequela”. Mild sequela in this setting will mean some pain and discomfort, but not enough to limit the patients’ independence.

As seen from figure /, all patients who have sequela will be in a “sequela 1” health state in the first cycle. While we assume that the patients who move into a nursing home will stay there for their remaining lifetime, patients in mild or moderate sequela are able to recover and move to the “well after fracture” health state.

While in a sequela health state, a patient can suffer a new hip-, vertebral or wrist-fracture, they can remain in sequela and move onto sequela two, they can become “well after fracture” or they can die. We have not modelled the patients who have a previous fracture as having any increased risk of fracture.

The probability of remaining in “moderate hip sequela” is assumed to be 50%. The probability of remaining in “mild hip sequela” is assumed to be 10%.

We have used the same assumption as Christensen and co-workers [13] and assumed that 25% of patients with incident vertebral fractures will have vertebral sequela and that the probability of remaining in vertebral sequela is also 25% .

2.2.4 Probabilities of “well” health states

The probabilities of remaining in “well” or “well after fracture” depend on the probabilities of new fractures. Likewise, if a person starts in a sequela health state, the probability of becoming “well after fracture” depends on the probability of remaining in the sequela health state and of the probabilities of new fractures.

2.2.5 Effect of alendronate

Effect can be expressed in several ways. Efficacy is measured under ideal circumstances, i.e. when the patients fully comply with the associated recommendations while effectiveness is a measure of effects when the patients are in real life circumstances. Effectiveness includes efficacy, but in addition it takes into account the acceptance by those to whom the treatment is offered. Data on effectiveness are preferred to data on efficacy in economic evaluation studies, but they are hard to obtain and may not be available [19]. Randomized controlled trials measure efficacy as the patients are followed up carefully.

To find literature on effect of alendronate, we searched Cochrane and found two relevant meta-analyses [15, 77] and several clinical trials. We found no studies from Norway, Sweden or Denmark, so we chose to use studies from other countries than the Scandinavian. While it is not recommended to transfer data on costs between different countries, data on effectiveness can more easily be transferred as long as there are no important differences in biologic factors and treatment patterns [99]. We excluded studies which include other patient groups than postmenopausal, Caucasian women, and articles which compare different treatments. We use relative risk reduction as measure of effect. We found no studies of effectiveness, all the studies we found are studies of efficacy.

Several of the relevant hits were based on the Fracture Intervention Trial (FIT). The FIT study was conducted at 11 clinical centres around the United States. It was a randomised, blinded and placebo-controlled trial, designed to test whether alendronate reduces the risk of fractures in women aged 55-80 years with low hip bone marrow density [2]. 6457 women were included and assigned to one of two sub studies; the Vertebral Deformity Study which included women with at least one previous vertebral fracture, and the Clinical Fracture Study which included women without previous vertebral fractures. The women were given 5 mg alendronate per day for two years, followed by 10 mg per day for the rest of the trial. Only the clinical fracture arm is relevant to us, as our study concerns women with no previous fractures.

In one of the articles based on the clinical fracture arm of the FIT study [16], alendronate increased BMD at all sites studied and reduced the risk of clinical fractures by 36% (RR 0.64, CI 0.50-0.82) in women with T-score equal to or less than -2.5. No statistically significant reduction was observed for hip fractures or forearm fractures or in those with T-score above -2.5. The risk of clinical vertebral fractures is not reported.

The meta-analysis by Cranney and collaborators [15] includes 11 trials that randomised women to alendronate or placebo and measured bone density for at least one year. They found among other things a pooled relative risk of 0.52 (CI 0.43-0.65) for vertebral fractures in patients given 5 mg or more per day of alendronate. Forearm was reduced by 52% (RR 0.48, CI 0.29-0). No statistically reduction was found for hip fractures.

The meta-analysis by Papapoulos and co-workers [77] proves a consistent effect of alendronate on hip fracture reduction among populations of different ages and differing levels of BMD. Relative risk reduction was 0.45 (CI 0.28-0.71) in patients with T-score of -2.5 or less.

Christensen and collaborators [13] assumed that alendronate reduce the risk of fracture by 50%. This corresponds well to what we found from our literature search. On the basis of these studies, we also ended up assuming that alendronate reduces the risk of all fractures by 50%. The risk reduction is varied in the sensitivity analysis. We chose to use the confidence interval for overall risk reduction (0.32-0.66) from the meta- analysis of Cranney and co-workers as our lower and upper value.

Table 3; Effect of alendronate

Authors	Sample size (alendronate / control)	Duration	Dosage	RR (95 % CI)			
				Hip	Vertebral	Forearm	Overall
Cummings et al. (1998)	2214 / 2218	4 years	5 mg/d for two years, then 10 mg/d	**RR 0.79** (0.43-1.44)	**RR 0.56** (0.39-0.80)	**RR 1.19** (0.87-1.64)	**RR 0.64** (0.50-0.82)
Cranney et al. (2002)		2-4 years	>= 5 mg/d	**RR 0.45** (0.18-1.13)	**RR 0.52** (0.43-0.65)	**RR 0.48** (0.29-0.78)	**RR 0.46** (0.32-0.66)
Papapoulos et al. (2005)	4842 / 4181	1 - 4.5 years	5-20 mg/d	**RR 0.45** (0.28-0.71)	-	-	-

There are several important factors to consider when the effect of alendronate is to be measured. These include dosage, age, treatment duration, effect after discontinuation, adverse effects and adherence.

Dosage

The effect varies with dosage, and in their meta analysis Cranney and collaborators [15] found that effect sizes were smaller in all fracture categories for dosage of 5 mg than for 10-40 mg of alendronate. The FIT study used a dosage of 5 mg per day for two years followed by 10 mg per day for the remainder of the trial [16]. The Physician desk reference [79] recommends a dosage of 10 mg per day or 70 mg once a week. According to Falch the latter is the most usual dosage. We chose to use a dosage of 70 mg once a week and assume that this dosage has the same effect as what was found in FIT where a daily dosage was used.

Age

When it comes to age, another article based on the FIT study studied the effect of alendronate on the age specific incidence of symptomatic osteoporotic fractures, and found that the relative risk reduction was consistent among women aged 55-80 [34]. Based on their conclusion, we assume constant risk reduction of alendronate for all age groups included in our study.

Treatment duration

The effect of alendronate also varies with treatment duration. Several recent studies concern this topic, but there is still uncertainty around what is the optimal treatment duration. Briot found that gains in BMD still persisted after 10 years of treatment with alendronate, but conclude by recommending treatment for four to five years, as no proof of fracture prevention with further treatment exists [8]. Black and co-workers [3] came to a similar conclusion; that discontinuing alendronate after five years had a small decline in BMD, but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. According to Jan Falch MD at Aker hospital eight years is considered to be optimal treatment duration, but patients tend to stop taking the drug after a while. This low adherence makes it unrealistic to assume treatment duration of eight years, and Falch recommended using four years. This goes well with the FIT study which had an average treatment duration of 4.2 years [16].

Effect after discontinuation

The effect of alendronate will persist after discontinuation. In the long term extension of the FIT study, the effect on BMD and bone turnover was found to persist for up to three years after stopping treatment [20]. A later study from the same group concludes that discontinuation of alendronate after five years for up to five more years does not significantly increase fracture risk [3]. Based on this we assume that the effect of alendronate persists for three years after discontinuation. In the sensitivity analysis we vary this from no effect in the years after discontinuation and up to full effect for five years after discontinuation.

Adverse effects

Like any other drug, alendronate has adverse effects. According to the Physician desk reference [79] more than 1/100 of patients treated with 10 mg alendronate per day have gastro intestinal problems like abdominal pain, nausea and heartburn; more than 1/1000 have problems like oesophagitis and oesophageal ulceration, and less than 1/1000 have problems like oesophageal blockage or perforation. Weekly administration of alendronate instead of daily can reduce gastro-oesophageal discomfort [4]. Other adverse effects can be bone- and joint pain, muscle pain and headache [79]. Osteonecrosis of the jaw associated with long term use of alendronate has been reported, but in most of the cases it happened after high-

dose intravenous therapy to treat cancer [8]. We were not able to identify any studies which showed statistically significant results of gastrointestinal side effects. The reason why none of the results are statistically significant could be that the samples of the studies are too small. Adverse effects happen rarely, and for rare events it takes large samples to get significant results. We have not included adverse effects in our model.

Adherence

For various reasons, patients do not always take a drug as prescribed. The full benefits of medication can not be reached if adherence is low. According to Rossini and collaborators [80] poor adherence has been reported with rates close to 50% for chronic conditions considered "clinically silent" to the patient. They found that the most frequent reasons for discontinuation of treatment were side effects, fear of side effects and lack of motivation for treatment. Poorly compliant patients had lower BMD and greater risk of fracture than patients adhering to the prescribed therapy. Patients who were prescribed to take alendronate weekly were found to have a higher adherence than those prescribed to take it daily; 6.9% versus 20.9% respectively had stopped treatment after 12 months.

2.2.6 Background mortality

We found age and gender specific mortality rates for 2006 at the webpage of Statistics Norway [84]. Table can be found in the appendix.

2.2.7 BMD and mortality

We searched Medline and Embase using the combination of "bone density" and "mortality". In Embase this resulted in 328 hits, four of which were relevant [9, 40, 42, 97].

Browner and co-workers [9] followed 9704 women from Oregon, US over 2.8 years and found that the relative risk of mortality was 1.19 per standard deviation decrease in BMD. BMD in this study was measured in the underarm (proximal radius bone).

The Rotterdam study [97] also looked into the association between BMD and mortality. BMD was measured in the hip. They found no significant relationship between BMD and mortality in women.

Kado and co-workers [42] followed 6046 prospectively for 3.2 years. After correcting for age, baseline BMD, diabetes, hypertension, incident fractures, smoking, physical activity, health status, weight loss and calcium intake, they found that each standard deviation decrease in BMD was associated with a 1.3 fold (95% CI 1.1-1.4) increase in total mortality.

The relationship between mortality and BMD has also been studied in a Swedish population [40]. In this study 1924 individuals, 1074 of which were women, from Gothenburg was followed for seven years. Johansson and co-workers found that one standard deviation decrease in BMD was associated with a relative risk of dying of 1.39 in both men and women. BMD in study was measured in the heel (calcareous).

We chose to use the result from Johansson and co-workers. The reason for this choice was that the follow-up time in this study was twice that of the other studies. We also considered that that mortality associated with BMD might be related to the prevalence of osteoporosis, as it has been found that mortality after hip fractures vary between areas with high and low incidence [49]. In this respect it seemed appropriate to choose a study from an area with a similar incidence as in Oslo.

The risk increase for the different groups was calculated using table 1 and the findings of this study.

2.2.8 Incident fractures and mortality

Osteoporosis related hip and vertebral fractures are highly correlated with excess mortality [48]. For hip fractures, most of the mortality increase occurs in the first year following the fracture. Mortality thereafter declines, but remains higher than the general population [47]. Mortality following vertebral fractures follows a somewhat different pattern. The excess mortality in the first year is not as high as for hip fractures, but it remains higher than the hip fracture excess mortality in the long run (one year and onwards).

Hip

The relationship between hip fractures and excess mortality has been studied in a Norwegian population. Meyer and co-workers [59] followed 248 hip fracture patients and their controls for three and a half years with respect to mortality. They found that otherwise healthy and fit

hip fracture patients did not have increased mortality following their fracture compared to their controls. Excess mortality following a fracture was limited to patients with reduced mental status, reduced somatic health and low physical ability.

Farahmand and co-workers studied the impact of co-morbidity on the mortality after hip fractures. The used followed a set of 2245 incident hip fracture patients and 4035 controls over five years. They found that after adjusting for age and previous hospitalization (indicator of co-morbidity), the relative risk of mortality for hip fracture cases versus controls, was 2.3 (95% CI 2.0-2.5). The highest risk were found in the first six months after the fracture, where the relative risk was 5.7 [25].

We chose to use a relative risk of death of 1.25 for the hip fracture patients. This is the value used in DOOM and lies between the value found by Meyer and the value found by Farahmand. In our model, we will reverse part of the excess mortality after hip fractures, and choosing the value found by Farahmand could thus make the treatment look more effective. We will vary this parameter in the sensitivity analysis, in order to see if this choice has any impact on the result.

Vertebral

Kado and co-workers [43] found that women with at least one new vertebral fracture had an age-adjusted excess mortality of 32% compared to those without incident vertebral fractures. However, after adjusting for potential confounders, there was no longer any significant difference between the groups. This result is similar to the findings of The European Prospective Osteoporosis Study (EPOS), which looked at mortality associated with vertebral deformity [37]. They found only a modest excess mortality in women with vertebral deformity, after age adjusting, but this difference was no longer significant when they adjusted for smoking, alcohol consumption, general health, previous hip fracture, body mass index and steroid use.

The European Vertebral Osteoporosis Study (EVOS) also studied the relationship between prevalent vertebral deformity and mortality. They found an association between the two, even after controlling for confounders. For women 65 years old, they found that the ones with a vertebral deformity, had a relative risk of 2.2 compared to the mortality the women

without [32]. This study had a longer time frame, but smaller sample size than the EPOS study.

Due to modelling difficulties, we have not included any excess mortality after vertebral fractures in our model. We will discuss the implications of this limitation in the discussion.

2.2.9 Deaths causally related to fractures

The core question here is whether or not the relationship between the fractures and the excess mortality is a causal one. In other words; are the fractures causing women to die prematurely or are the fractures simply an indicator of a poor general health status? And what percentage of the excess deaths can be prevented by preventing the fractures? There is a clear potential for confounding here, as many of the risk factors for osteoporosis, such as smoking, inactivity and alcohol consumption are also risk factors for other diseases or conditions, like for example cancer and cardio vascular diseases.

The distinction between causally related and associated mortality is an important one when it comes to economic evaluation of preventive measures, as only the causally related deaths have the potential of being postponed by preventing the fractures. Reversibility of causally related deaths is a common assumption in economic evaluations of fracture prevention [48]. There is however no empirical evidence to support this assumption.

“The extent to which early prevention for osteoporosis might avoid some of these deaths is unknown” [41].

“There are, however, no empirical data to indicate that there is indeed a survival advantage associated with the prevention of fracture” [48].

As pointed out by Kanis and co-workers, one would need a very large sample in order to find significant results in an empirical trial of the reversibility of deaths associated with prevented fractures [48].

In our model we will assume that part of the causally related excess mortality after hip fractures can be reversed by preventing the fractures. The reason for this partial reversal is that we believe that women avoiding a fracture are likely to die in from other causes.

Hip

Farahmand [25] states that much of the increased mortality after hip fractures seems to be due to the interaction between the fracture event and pre-existing co-morbidity, but that the fact that the relationship is found even in women with no apparent co-morbidity suggests that at least some part of the excess mortality is causally related to the fracture.

Kanis and co-workers studied excess mortality after hip fractures by using register data from Sweden. They assumed that the excess mortality after a hip fracture was a function of causally related deaths and pre-existing co-morbidity. They estimated that 24% (17-32% depending on age) of the deaths following a hip fracture were causally related to the fracture itself. The fraction was dependent upon and increased with age [48]. We will use the estimate of 24% as input in our model.

Vertebral

Johnell and co-workers [41] followed a somewhat different approach. They assumed that a high mortality immediately after the fracture was a function of both co-morbidity and causally related deaths, while the long term (one year and onwards) mortality was mainly due to co-morbidity. They calculated that there was a significant and high mortality associated with clinical vertebral fractures and that the risk increase was as large as for hip fractures. Their estimate was that 23% of the deaths in the first year after a vertebral fracture were related to the fracture itself.

Kanis and co-workers [47] studied excess mortality after hospitalisation for vertebral fractures. The study was based on register data from Sweden. They found that 28% of all deaths associated to the fracture were causally related. According to these authors, the estimates of mortality associated with vertebral fractures vary both with the time frame and the definition of vertebral fractures used in the different studies.

We will not include any deaths causally related to vertebral fractures in out model, due to modelling difficulties.

2.3 Input payoffs

2.3.1 Costs

To identify articles on costs related to osteoporosis and fractures we searched EMBASE and Medline using the Mesh-terms “health care costs”, “osteoporosis”, “hip fracture”, “vertebral fracture”, combined with “Norway”, “Sweden” and “Denmark”. This resulted in no relevant hits on Norwegian costs, but two Swedish ones. They both use a societal perspective and include both direct and indirect cost. One of them assessed the costs related to hip, vertebral and wrist fractures in 635 male and female patients for one year after the fracture [5]. The other followed 1080 menopausal women admitted for primary hip fracture surgery in Stockholm in 1992 and collected costs for one year before and one year after the fracture [100]. In addition to these studies we used Christensen and co-workers [12].

According to Drummond [19], the theoretical proper price for a resource is the opportunity cost, defined as the value of the forgone benefits because the resource is not available for its best alternative use. In lack of opportunity costs we have to use other kinds of costs, like average cost per patient and market prices. We used among other things the Norwegian fee schedule for GPs [66], Norwegian DRG prices [89] and data from Statistics Norway [85]. Using market prices unadjusted may lead to bias as they do not necessarily reflect marginal costs because of market imperfections in health. To account for this, certain adjustments are made, like subtracting value-added tax, as this is not a cost to society, but a transfer. Another thing we did, based on personal communication [39], was to assume that co-payment and reimbursement cover 40% of the total costs for out-patient clinics.

The estimation of costs has three steps, identifying cost components, quantifying them and valuing them in monetary terms [19]. Using Christensen and co-workers [12] for the first two steps, we decided to do the third step in the cost estimating process, the costing, based on Norwegian tariffs. All costs are expressed in 2006 Norwegian crowns (NOK). Our costs reflect, as far as possible, the societal perspective chosen for our analysis, meaning that all costs to whomsoever they accrue (the patient, hospital, society etc.) are included [19].

Both the article by Borgström and the article by Zethraeus include costs only for the first year after fracture. For our model we also need costs of subsequent years for the patients having sequelaes. Christensen and co-workers estimated the costs of all fractures, including sequelaes [12]. We used their article to identify and quantify the costs related to the different events and health states. Their numbers are partly based on empirical data and partly on expert opinions. We made some changes, based among other things of a Norwegian study of consequences of hip fractures [76] and on expert opinions. Christensen and co-workers used Zethraeus [100] for costs of hip fractures first year, and we decided to use the same, adjusted for inflation and currency [65].

Drummond emphasises that the more important the cost item is for the analysis, the greater effort should be made to estimate it accurately. Important costs in our analysis are the treatment costs as they concern all individuals. To be sure that these costs are as correct as possible, we asked for expert opinion on both identification and quantification of resource use related to treatment with alendronate. For cost of alendronate we used the price from Physician Desk Reference [79] of the least costly alternative. Costs of treatment with vitamin D and calcium are left out as they apply to all individuals and will not affect the choice between the two programmes.

Transferring costs between countries can be problematic due to differences in resource use and price levels between countries [99]. In lack of Norwegian data, we still chose to use cost data from the Sweden and Denmark although there are differences also between the Scandinavian health care systems.

Costs are discounted to reflect a positive rate of time preference. Guidelines for economic evaluations from NMA suggest using a discounting rate between 2.5-5%. We discount at 4% in our analyses.

Productivity costs and indirect costs like costs of informal care are not included.

In the sensitivity analysis lower and upper boundaries were assigned to all costs by using 70% and 130% percent of the estimates of total costs found in table 4. The discount rate was varied by using 0% and 7% as boundaries.

Total costs are presented in the table below. Details on how the costs were calculated can be found in appendix 1.

Table 4; Total costs of events, health states and treatment with alendronate

	Total costs (NOK)
Events	
Hip fracture	See table in appendix
Vertebral fracture	8 855
Forearm fracture	10 781
Health states	
Mild hip sequelae	0
Moderate hip sequelae	19 864
Severe hip sequelae	585 903
Vertebral sequelae	19 864
Treatment costs	
First year	2 461
Subsequent years	2 142

2.3.2 Quality of life

Theory

"In the QALY approach, the quality adjustment is based on a set of values or weights called utilities, one for each possible health state, which reflects the relative desirability of the health state" [19].

As seen in the quote from Drummond, two things are needed in order to find a QALY weight; a health state and the value attached to the specific health state

Health state profiles

"Health state profiles are instruments that attempt to capture all important aspects of HRQL" [29].

Health state profiles are elicited through a questionnaire. Each questionnaire will contain a number of dimensions, e.g. pain, ability to perform daily activities and so on. To each dimension, there are different levels, e.g. no problem or severe problems. Different

questionnaires will contain different dimensions and levels and will result in various possible numbers of health states. The number of possible health states in each questionnaire will be a function of the number of dimensions and levels. Number of possible health states equals the number of levels to the power of number of dimensions [19].

A quality of life instrument may be specific or generic. In the literature, only generic questionnaires are described as health profiles.

Generic instruments are designed to capture not only symptoms, but to what degree different symptoms affect the patient in his or her daily life. The advantage to using a generic questionnaire is that it makes comparison across diseases and conditions possible [61].

Specific instruments may be designed to capture the problems or symptoms connected to a specific disease, population, function or condition [29]. The advantage of a specific instrument is that it will contain dimensions which are central to the area in question. It follows from this that specific questionnaires may be more responsive to change in the patients' health. Specific instruments are also closely related to clinical practise [29].

Several instruments have designed specifically for osteoporosis. Most of these focus specifically on the impact of vertebral fractures.

Figure 8; Osteoporosis Specific Questionnaires [96]:

Table I. Osteoporosis-specific health-status instruments

Instrument	Target population	Number of questions	Health domains assessed
OQLQ[a] [12]	Women: osteoporosis; vertebral fracture	OQLQ: 30; Mini-OQLQ: 10	Symptoms, physical function, activities of daily living, emotional function, leisure/social activity
OPAQ[13]	Women: osteoporosis; vertebral fracture	OPAQ 1.0: 84; OPAQ 2.0: 60; OPAQ-SV:[b] 34	Physical function, emotional status, symptoms (just pain in SV), social interaction (not in SV), overall health-related quality of life (not in SV)
QUALEFFO[14]	Women: osteoporosis; vertebral fracture	41	Pain, physical function, social function, general health perception; mental function
OPTQoL[15]	Women	32	Physical difficulty, adaptations; fears
OFDQ[16]	Men/women: osteoporosis; vertebral fracture;	59	Pain, depression, functional ability, social activity, confidence in treatment
QUALIOST[17]	Women: osteoporosis; verterbral fracture	23[c]	Physical repercussions, emotional repercussions, global

a Interviewer administered.

b Short version.

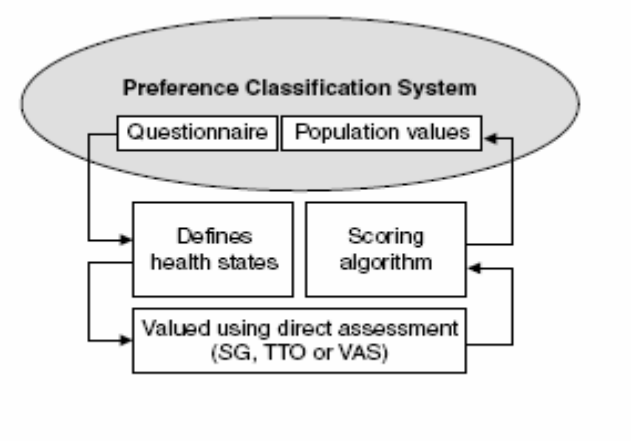
c Intended for use with SF-36.[18]

OFDQ = Osteoporosis Functional Disability Questionnaire; **OPAQ** = Osteoporosis Assessment Questionnaire; **OPAQ-SV** = Osteoporosis Assessment Questionnaire Short Version; **OPTQoL** = Osteoporosis-Targeted Quality-of-Life Questionnaire; **OQLQ** = Osteoporosis Quality-of-Life Questionnaire; **QUALEFFO** = Quality-of-Life Questionnaire of the European Foundation for Osteoporosis; **QUALIOST** = Quality-of-Life Questionnaire in Osteoporosis; **SF-36** = 36-item Medical Outcomes Study Short Form.

Multi Attribute Utility Instruments (MAU):

Multi attribute utility instruments (also referred to as preference instruments) are instruments which contain both a generic health profile questionnaire and a table of population-values connected to each health state profile.

Figure 9; Structure of MAUs [96]:



Different MAUs are combinations of different questionnaires and different value sets. The value sets will differ both in the elicitation method used (TTO, VAS or SG), the population sample from which the preferences are elicited and scoring algorithms used [19]. It is important to realize that the results from different MAUs may not be directly comparable due to these diversities. Some widely used MAUs are EQ-5D (also referred to as the EuroQoL), SF-36, HUI and 15D.

Table 5; Characteristics of different utility instruments: [19, 33, 87, 96]

MAU	Valuation method	Population sampled	Number of possible health profiles	Scoring algorithm	Ratio empirical (50)versus interpolated
15D	VAS	Finland	3.052.000.000	Additive	1:610.000.000
EQ-5D	TTO	UK	245	Regression	1:5
HUI:3	VAS/SG	Canada	960.000	Multi-linear	1:19.400
SF6D	SG	UK	18.000	Additive	1:180

Choice of input:

We needed three types of input for quality of life in our model; population norms, utility loss connected to the fracture events and utility connected to long term effects after fracture (sequela).

Population norm utilities will be assigned to all persons in the "well" and "well after fracture" health states. All time spent in these health states will generate QALYs equal to the ones found in the general population. When a person suffers a fracture, we will assign a utility loss to this event, in order to reflect the short term pain and discomfort connected to the fracture. Utility loss connected to these events will be counted one time only, as it is not possible to spend time in the events. The utility loss connected to events will be multiplied to the population norm values. This means that for example a hip fracture, will be more burdensome the older the person is.

Many people will suffer long term effects of the fracture, in the form of reduced functional level. This is modelled in the sequelae health states. We thus need to assign utility values to the sequelae health states, which reflect the reduced quality of life for persons in these health states. As in the fracture events, the utility loss is multiplied with the population norms.

Population norms

We will assume that patients have population norm ("normal") quality of life before a fracture occurs. This may not be a valid assumption, as our population may be more likely to suffer from co-morbidity and may thus have lower quality of life than their matched age and sex group.

Quality of life reflects the value or desirability connected to a specific health state. It is therefore conceivable that quality of life may vary across time and place, as it can be seen to reflect cultural attitudes. We therefore aimed to use population values elicited from a Scandinavian population if possible.

We searched Medline and Embase using the mesh terms "quality of life", "population research" and "rating scale", which gave us 0 hits in Medline and 124 hits in EMBASE.

Based on the fact that we wanted general population values and not values connected to a specific disease or condition and that we wanted a Scandinavian population, we were left

with two studies; one by Lundberg and co-workers [56] and one by Burstrøm and co-workers [11].

Lundberg and co-workers elicited values from a sample from Uppsala County trough a questionnaire containing a rating scale and a time trade-off. Out of the 8000 questionnaires they sent out, they received 5404 in a usable form. In the study undertaken by Burstrøm and co-workers, a representative sample was drawn from Stockholm County. They sent out 4950 questionnaires and received 3112. The values were elicited trough the EQ-5D classifier and a rating scale.

Table 6; Population norms from Sweden** [11, 56] **:

Age	20-29	30-39	40-49	50-59	60-69	70-79	>=80
Burstrøm et al. 2001 EQ-5D	0.88 (0.010)	0.86 (0.010)	0.85 (0.011)	0.82 (0.012)	0.78 (0.015)	0.78 (0.017)	0.74 (0.026)
Lundberg et al. 1999 TTO	0.93 (0.16)	0.93 (0.16)	0.93 (0.16)	0.91 (0.18)	0.87 (0.19)	0.70 (0.26)	0.60 (0.33)

Rating scale values are excluded.

We chose to use the population norms Lundberg and co-workers, as this was based on a larger sample than the study by Burstrøm and co-workers. We also believe that a TTO measurement is more in line with population preferences than one from EQ5D.

Empirical estimates of utility values for osteoporosis-related health states

Utilities from systematic reviews

We searched Medline and EMBASE using the terms “Quality of Life” combined with “osteoporosis” or “hip fracture” or “spinal fractures”. This gave us 1351 hits in EMBASE. A search in the Cochrane database gave us one additional hit; Kanis et al. 2002 [44].

We found three systematic reviews over osteoporosis-related utility values; one by Brazier and co-workers [6], one by Kanis and co-workers [44]and one by Stevenson and co-workers[86]. All of these studies contained studies with a vide range of utility values after osteoporosis-related fractures.

In the article by Brazier and co-workers [6] the utilities after a hip fracture ranged from 0.05 up to 0.885. The very low value was found in a study by Salkeld and co-workers, where older people at risk of fracture valued a health state described as a "bad" hip-fracture, which included living in a nursing home. The high value was found in a NOF review, and was based on the judgement of an expert panel.

Kanis and co-workers [44] also found a large variation in the utilities connected to a hip-fracture. Here the utilities varied from 0.28 to 0.72. These utilities were both from the same study. The lowest value was given by a sample with a mean age of 68 years, who valued a hypothetical, disabling hip fracture state trough a TTO exercise. The high value was given when patients who had previously experienced a hip fracture valued their own health state on a visual analogue scale.

The articles all discuss a number of possible reasons for the vide range in utilities. The reasons are closely connected to what we have described above and we therefore only give a brief description of the individual points.

- Descriptive system of health states/Health profiles:

What method is used to describe the health state? Alternatives are a disease specific or generic profiles or vignettes. Who is presented with the disease description? Are the patients asked to describe their own, current health state or is a group of people asked to value a hypothetical description of the state?

- Valuation technique:

Which method is used to put a value on the different health profiles? The most used methods are SG, TTO and VAS. These methods often give different values for the same health states; values found trough SG is generally larger than those found by TTO, which is again larger than VAS values.

- Choice of anchor states:

The question here is what equals one and what equals zero in the valuation of health states. Is zero death or worst imaginable health state (negative utilities are conceivable for health states considered to be worst than death)? Is one full health or best imaginable health?

- Source of values:

Who are the values elicited from? Are the patients valuing their own health state, is an expert opinion being used or is a sample of the general population represented by a description of the health state in question? Research has shown that patients often put a higher value on their own health state than the general population do.

- Approach for estimating the health loss from an event:

Which value is put on the patients' pre-fracture health state? Two approaches are widely used; to assume pre-fracture utility of one or to assume that pre-fracture utility is equal to that of some control group.

Utilities from Swedish studies

We also preformed a search where we combined "osteoporosis" and "Quality of life" with Norway, Sweden or Denmark. This last search gave us three hits in Medline, two of which were relevant Kanis et al. 2002 [45] and Borgstrom et al. 2006 [5].

Table 7; Utilities after hip fracture

Study	Time after fracture	Value (SD or 95% CI)	Valuation technique	Population	Source of values	Type of fracture
Gabriel et al. 1999	Fracture in the last five years	0.68 (0.18)	HUI-2, SG	Patients n=37	Parents of school children n=203	Hip fracture
Gabriel et al. 1999	Fracture in the last five years	0.65 (0.45)	TTO	Patients n=33		Hip fracture, "disabling"
Brazier et al. 2000	12 months after fracture	0.48 (0.38)	EQ-5D, TTO	Patients n=39	General population n=3381	Hip fracture
Tosteson et al. 2001	12-24 months after fracture	0.48 (0.32-0.64)	TTO	Patients n=35		Hip fracture
Tosteson et al. 2001	More than 24 months after fracture	0.79 (0.66-0.92)	TTO	Patients n=32		Hip fracture
Borgstrøm et al. 2006	12 months after fracture	0.67 (0.64-0.7)	EQ-5D, TTO	Patients n=227	General population n=3381	Hip fracture
Salkeld et al. 2000		0.31	TTO	Older people at risk of fracture n=194		Described "good" hip fracture
Salkeld et al. 2000		0.05	TTO	Older people at risk of fracture n=194		Described "bad" hip fracture

As seen from the table, a wide range of utility values after hip fracture have been found. We wanted to choose utilities which were as high as possible, in order to get a conservative estimate of the cost effectiveness ratio. We were initially concerned that choosing an estimate based on EQ-5D would give too low a value [14], but based on the above table this does not seem to be the case here.

We chose to use the estimate found by Borgstrøm and co-workers [5] for the utility connected to the fracture event, as this was the highest value reported value after 12 months and also the one with the largest sample size.

For the long term effect of the hip fracture (sequelae) we chose the value found by Tosteson and co-workers [95], measured after more than 24 months. The sample size in this study was small, but still it was the most conservative estimate.

Table 8; Utilities after vertebral fractures

Study	Time after fracture	Value	Valuation technique	Population	Source of values	Type of fracture
Oleksik et al. 2000	Fracture confirmed in the last five years	0.774 (0.231)	EQ-5D, TTO	Patients n=130	General population n=3381	Vertebral fracture
Gabriel et al. 1999	Fracture confirmed in the last five years	0.80 (0.16)	HUI-2, SG	Patients n=94	Parents of school children n=203	Vertebral fracture
Gabriel et al. 1999	Fracture confirmed in the last five years	0.81 (0.32)	TTO	Patients n=94		Vertebral fracture
Gabriel et al. 1999	Fracture confirmed in the last five years	0.68 (0.40)	TTO	Patients n=24		Multiple vertebral fractures
Tosteson et al. 2001	12-24 months after fracture	0.80 (0.68-0.91)	TTO	Patients n=31		Vertebral fracture
Tosteson et al. 2001	More than 24 months after fracture	0.85 (0.78- 0.93)	TTO	Patients n=60		Vertebral fracture
Borgstrom et al. 2006	12 months after fracture	0.73 (0.025)	EQ-5D, TTO	Patients n=81	General population n=3381	Vertebral fracture

We followed the same reasoning when choosing utilities for vertebral fracture events and sequela; we wanted the highest, most conservative estimate we could find. We chose the value reported by Tosteson after 12-24 months for the fracture event and the value after more than 24 months for the fracture sequela.

Table 9; Utilities after forearm fractures

Study	Time after fracture	Value (SD or 95% CI)	Valuation technique	Population	Source of values	Type of fracture
Dolan et al. 1999		0.982 (0.978-0.986)	EQ-5D, TTO	Patients n=50	General population n=3381	Wrist fracture
Borgstrøm et al. 2006	12 months after fracture	0.86 (0.84-0.88)	EQ-5D, TTO	Patients n=276	General population n=3381	Wrist fracture

For forearm fracture, we chose the estimate from Dolan and co-workers, as this value was higher than the one reported by Borgstrom and co-workers.

Table 10; Choice of multipliers for events

Fracture event	Multiplier	Source
Hip	0.838	Borgstrom et al. (2006)
Vertebral	0.879	Tosteson et al. (2001)
Forearm	0.982	Dolan et al. (1999)

Multipliers are calculated based on information found in the articles. For details, see appendix.

We need to assign different utilities to the different hip fracture sequelae. In order to this, we will assume that patients in moderate sequelae have the reported mean utility. We will further assume that patients in mild sequelae have utility one standard error above the mean and that patients in severe sequelae have utility one standard error below the mean. This assumption implies that 67% of the patients will be in moderate sequelae. This is somewhat above what we have previously assumed (55% in moderate sequela). Still it is the best we can do without any empirical data.

Table 11; Choice of multipliers for sequelae health states

Sequelae health states	Multiplier	Source
Mild hip	0.941	Tosteson et al. 2001
Moderate hip	0.868	Tosteson et al. 2001
Severe hip	0.795	Tosteson et al. 2001
Vertebral	0.934	Tosteson et al. 2001

Multipliers are calculated based on information found in [95]. For details see appendix.

2.4 Model parameters

The table below includes all parameters and the values used in the base case analyses.

Table 11; Model parameters

Variable	Value	Source
Incidence		
Hip fracture	Age specific	Lofthus et al. (2001)
Vertebral fracture	Age specific	Kanis et al. (2000)
Forearm fracture	Age specific	Lofthus (personal communication)
Fracture risk increase with t-score -1	2	Marshall et al. (1996)
Distribution sequela		
Mild hip sequelae	55%	
Moderate hip sequelae	17%	Osnes et al. (2004)
Severe hip sequelae	28%	Osnes et al. (2004)
Vertebral sequelae	25%	DOOM
Probability of staying in sequela		
Mild hip sequelae	0,1	DOOM
Moderate hip sequelae	0,5	DOOM
Severe hip sequelae	1	DOOM
Mortality		
General mortality	Age specific	Statistics Norway
Causal death	0,24	Kanis et al (2003)
Mortality increase with t-score -1	1,39	Johansson et al. (1998)
Mortality increase hip fracture	1,25	DOOM
Costs of events		
Hip fracture	Age specific	See appendix
Vertebral fracture	8 855	See appendix
Forearm fracture	10 781	See appendix
Costs of health states		
Mild hip sequelae	0	See appendix
Moderate hip sequelae	19 864	See appendix
Severe Hip sequelae	585 903	See appendix
Vertebral sequelae	19 846	See appendix
Treatment costs		
First year	2 461	See appendix
Subsequent years	2 142	See appendix

Quality of life		
Multipliers events		
Hip fracture	0,838	Borgström et al. (2006)
Vertebral fracture	0,879	Tosteson et al. (2001)
Forearm fracture	0,982	Dolan et al. (1999)
Multipliers health states		
Well	1	
Well after fracture	1	
Mild hip fracture sequelae	0,941	Tosteson et al (2001) and assumption
Moderate hip fracture sequelae	0,868	Tosteson et al (2001) and assumption
Severe hip fracture sequelae	0,795	Tosteson et al (2001) and assumption
Vertebral fracture sequelae	0,934	Tosteson et al (2001) and assumption
Discounting	4%	
Treatment with alendronate		
Relative risk for fractures while recieving alendronate	0,5	See discussion in the effect chapter
Treatment duration	4	See discussion in the effect chapter
Effect after discontinuation	3	See discussion in the effect chapter
Adherence	90%	See discussion in the effect chapter

3. Results

Our base case consisted of nine groups of women, constructed from the chosen ages and T-score levels. The Markov model was used to estimate the cost effectiveness of alendronate in the different groups.

The average life time osteoporosis related costs for a 65 year old woman with T-score of -1.5 was estimated to be approximately NOK 229 000 in the control group and 210 000 in the alendronate group. Similarly, average life time QALYs amounts to 9.952 for the women in the control group and 9.970 for those in the alendronate group. This entails that treatment with alendronate is cost saving and more effective; giving alendronate to one patient implies a saving to the health care system of approximately NOK 19 000 and a QALY gain of approximately 0.018 QALY. Alendronate is in other words a dominant strategy. All nine groups in the base case had similar results: treatment with alendronate was less costly and more effective to the health care system.

The average QALY gain per patient treated with alendronate is rather small in all groups. However, when aggregated to societal level, the QALY gain would be of significant impact because of the large size of the group.

Table 12; Results Base Case

	Femoral neck T-score								
	-1.5			-2.0			-2.5		
	Control	Alendronate	Incremental change	Control	Alendronate	Incremental change	Control	Alendronate	Incremental change
Age 65 y									
Costs	229 320	209 836	19 484	285 661	255 724	29 938	354 006	310 057	43 949
QALYs	9.952	9.970	-0.018	9.595	9.610	-0.015	9.215	9.235	-0.020
ICER			Dominant			Dominant			Dominant
Age 70 y									
Costs	242 443	208 052	34 392	288 425	242 215	46 210	356 460	291 097	65 364
QALYs	7.807	7.821	-0.014	7.5144	7.5313	-0.017	7.137	7.159	-0.022
ICER			Dominant			Dominant			Dominant
Age 75 y									
Costs	235 067	183 544	51 523	279 086	211 832	67 254	343 725	251 214	92 511
QALYs	6.358	6.371	-0.014	6.070	6.086	-0.016	5.703	5.723	-0.020
ICER			Dominant			Dominant			Dominant

Sensitivity analysis

Because of uncertainty around the parameters, a one-way sensitivity analysis was performed to see whether the conclusions would be altered by any change in the parameters. Lower and upper bounds were assigned to every parameter, and then one-way sensitivity analyses were performed on all variables.

The sensitivity analyses showed that the conclusion is robust to changes in the parameters. Increasing the discount rate of costs to 7% gave a cost per QALY of 125 813. Treatment with alendronate was still cost saving when the other parameters were changed one by one.

Table 13; Results from the one-way sensitivity analysis

Variable	Range			Cost per QALY gained	
	Low	Base case	High	Parameter lower	Parameter high
Distribution sequelae					
Moderate hip sequela	45%	55%	65%	Dominant	Dominant
Severe hip sequela	7%	17%	27%	Dominant	Dominant
Vertebral sequela	5%	25%	45%	Dominant	Dominant
Probabilities of remaining in sequelae					
Mild hip sequela	0	0.1	0.5	Dominant	Dominant
Moderate sequela	0.3	0.5	0.73	Dominant	Dominant
Mortality					
Causal death	0	0.24	0.3	Dominant	Dominant
Mortality increase with T-score -1	0	1.39	1.59	Dominant	Dominant
Costs events (NOK)					
Vertebral fracture	6 199	8 855	11 511	Dominant	Dominant
Forearm fracture	7 547	10 781	14 015	Dominant	Dominant
Costs health states (NOK)					
Moderate hip sequela	13 904	19 864	25 823	Dominant	Dominant
Severe hip sequela	410 132	585 903	761 674	Dominant	Dominant
Vertebral sequela	13 904	19 864	25 823	Dominant	Dominant
Treatment costs (NOK)					
First year	1 231	2 461	3 692	Dominant	Dominant
Subsequent years	1 071	2 142	3 216	Dominant	Dominant
Quality of life: multipliers events					
Hip fracture	0.527	0.838	-	Dominant	Dominant
Quality of life: multipliers events					
Hip fracture	0.527	0.838	-	Dominant	Dominant
Vertebral fracture	0,671	0.87	-	Dominant	Dominant
Forearm fracture	0.720	0.982	-	Dominant	Dominant
Quality of life: multipliers health states					
Mild hip fracture sequela	0.941	0.941	1	Dominant	Dominant
Moderate hip fracture sequela	0.49	0.868	-	Dominant	Dominant
Severe hip fracture sequela	0.07	0.795	-	Dominant	Dominant
Vertebral fracture sequela	0.83	0.934	-	Dominant	Dominant
Discounting					
Discount rate costs	0%	4%	7%	Dominant	125 813
Discount rate QALYs	0%	4%	7%	Dominant	Dominant
Treatment with alendronate					
RR of fracture while treated	0.32	0.5	0.66	Dominant	Dominant
Treatment duration (years)	1	4	8	Dominant	Dominant
Effect after discontinuation (years)	1	3	5	Dominant	Dominant

Extreme cases

The one-way sensitivity analysis showed that, with the exception of increasing the discount rate of costs, changing one variable at the time was not enough to alter the conclusions from the base case analysis. We wanted to see how changing several variables in disfavour of cost-effectiveness at the same time would influence the results, and constructed two scenarios or extreme cases. First we set the risk reduction of alendronate to 0.75 and changed back to the distribution of sequelae used in DOOM. For women aged 65, with T-score of approximately 1.5, these changes resulted in an ICER of NOK 147 753. Second; for the same group of women, using the price of alendronate from before the patent ran out in addition to the old distribution of sequelae, gave an ICER of NOK 752 647. The ICERs, or the costs per QALY gained in these cases are positive, which means that treatment with alendronate is not cost saving anymore.

This shows that changing more than one parameter at a time may influence the conclusion. Ideally we would have performed a probabilistic sensitivity analysis, but time did not allow us to do this.

4. Discussion

The main findings of this study suggest that, from a broad health care perspective, giving alendronate in addition to calcium and vitamin D supplements, to Norwegian, postmenopausal women of age of 65, 70 and 75 and T-score equal to -1.5, -2.0 and -2.5, may be more effective and less costly than treatment with calcium and vitamin D supplements alone. There are several limitations of the study, however, due to assumptions and uncertainties around the parameters, and the results must be interpreted with these limitations in mind. In this chapter we discuss the assumptions and limitations, and how they have possibly influenced the conclusions.

4.1 Assumptions and limitations

Indirect costs

Indirect costs like productivity costs and costs of informal care are not included. Our study concerns elderly women above 65 years of age, and as most women of this age are retired, productivity losses due to fractures for this group will probably not be substantial. Informal care is more relevant as many of the fracture patients still live at home but are in need of help to manage daily activities. We have assumed that the women in “moderate hip sequela” will receive home help. We do, however, believe that they in addition will need informal care from friends, relatives etc. We have not been able to identify any studies on costs or amount of informal care due to fractures in Norway. In addition, as there is little consensus on how to measure and value these costs, and whether to include them at all [19], we chose to leave them out.

The exclusion of indirect costs like informal care and productivity loss leads to an underestimation of the total societal costs of fractures and sequelae. It means in fact that alendronate is actually even a little more cost-effective than our analyses have shown.

Half cycle correction

In the model, all fractures are assumed to happen at the end of a cycle. This is not realistic, as patients in real life move between different health states continuously, not at certain points in time. This can lead to an overestimation or underestimation of costs and quality of life, and half cycle correction is a way of correcting for this. Half cycle correction is not included in our model, and since all transitions happen at the end of the cycles, this implies that total costs and health benefits are underestimated but it is unlikely to affect the results of the incremental analyses because half cycle correction was omitted in both branches of the decision tree [7].

Quality of life

We assume that our population have population norm utility pre-fracture. This may not be a valid assumption as low BMD is highly correlated with other risk factors. Our population may thus suffer from more co-morbidity and have lower quality of life without fractures, than what we have modelled.

We chose the highest utility values we could find for all health states in the model. These values are based on small a sample sizes, however. Our choice of high utility values associated with fractures and their sequelae will tend to make alendronate look less cost effective, than if we had chosen lower values. In other words; the QALY gains of the model are relatively modest. They do however compare well with the results reported by Christensen and co-workers [13]. In this study the incremental QALY gain for a woman 71-year old woman with a z-score of -1.1 (T-score of -2.9 in their reference material) was 0.0219 discounted QALYs. In our analysis the result in undiscounted QALYs gained for a 70-year old woman with Z-score of -1.1 (T-score equal to -2.5 in our reference material) was 0.0220.

We tried to run our model with the values used by Borgstrom and co-workers [5]. In order to do this we calculated multipliers based on the pre-fracture utilities stated in their study.

Table 14 Values found in Borgstrom et al. (2006)

EQ-5D utility	Hip fracture, n=277	Multiplier	Vertebral fracture, n=81	Multiplier	Wrist fracture N=275	Multiplier
Perceived quality of life before fracture	0.80		0.73		0.89	
After fracture	0.18	0.23	0.18	0.25	0.56	0.63
At 4 months	0.62	0.78	0.47	0.64	0.82	0.92
At 12 months	0.67	0.84	0.49	0.67	0.86	0.97

We then assumed that that the multipliers for the fracture events were those found after four months and that based the multipliers for the sequelae health states on the values found after twelve months. Utilities associated with the different hip sequelae were calculated based on the same assumptions as used in the base case.

Table 15 QALY gains based on utility weights from Borgstrom et al

	Femoral neck T-score								
	-1.5			-2.0			-2.5		
	Control	Alendronate	Incremental change	Control	Alendronate	Incremental change	Control	Alendronate	Incremental change
Age 65 y									
QALYs			-0.020			-0.028			-0.038
ICER			Dominant			Dominant			Dominant
Age 70 y									
QALYs			-0.024			-0.030			-0.041
ICER			Dominant			Dominant			Dominant
Age 75 y									
QALYs			-0.022			-0.031			-0.036
ICER			Dominant			Dominant			Dominant

The QALY gains are here approximately twice those found in our base case. In our analysis, the choice of quality of life input does not change the conclusion; the treatment option is still dominant. This exercise does however illustrate an important point, namely that an economic model like ours, with many sequelae health states, is potentially very sensitive to the choice of quality of life input.

Adverse effects of alendronate

Adverse effects of alendronate are not included in our analyses. However, if the patients experience adverse effects, this may imply disutility for the patients because of pain or discomfort, and additional costs to the society. Adverse effects could in theory be modelled, but data on consequences of such effects are scant. Assuming that one out hundred patients treated with alendronate develops dyspepsia for one month every year on treatment, and that this will give a utility loss of 0.014 QALY (equal to the utility loss of a forearm fracture for a 70 year old) every year, the total utility loss for four years of treatment in our cohort of 10000 will be 0.014*(1/12*4)/100=0.00005 QALY. We find it unlikely that such a small loss would have any impact on the conclusions.

Compliance

One would imagine that side effects can cause decreased adherence to drug therapy, and thus the patient will have lower effect of the treatment than under optimal circumstances. In general, a decrease in adherence will decrease the total spending on alendronate, but may also increase spending related to fractures because fewer fractures are avoided. It is not clear what effect lower adherence will have on the cost-effectiveness ratio of alendronate. It would be interesting to analyze the effect of different levels of adherence, but to be able to do this we would need more data.

Fracture risk

The absolute fracture rates stay the same over the whole course of our model.

We have not modelled increased risk of new fractures in patients with previous fractures. Presumably, we will have the correct number of fractures, but that they will be distributed across too many individuals. The consequences of this bias are unlikely to change the conclusions.

Mortality

We have assumed that mortality rates will stay the same as in 2006 for the whole course of the model. This is very unlikely to be the case, but it is impossible to estimate how mortality might change, and the impact on our result is therefore uncertain.

Excess mortality after vertebral fractures is not included. Inclusion of, and partial reversibility of this excess mortality like we have done for hip fractures would have made our result more cost effective.

Sequela after under forearm fracture

A small proportion of patients have complications after forearm fracture, but we have not included permanent sequalae in our model. Inclusion of such a sequela would increase the possible QALY gain from treatment with alendronate. The impact on our result would depend upon whether or not and to what degree a sequela would increase costs. The exclusion of this long term effect of underarm fractures is unlikely to have any significant impact on our result, as the proportion of patients affected is likely to be insignificant.

Exclusion of other fractures

Only hip, vertebral and forearm fractures are modelled, and other fractures are omitted from the model, which means that the model may underestimate the benefits of osteoporosis interventions.

4.2 Findings of other CE-studies

The findings of other studies give different results based on both model structure and choice of input. Comparisons with results from other studies are important in order to validate the structure of the model. It is however important to keep in mind that choice of input do have a large impact on the ICER. On the input side, ICERs will differ on account of factors associated with the population, i.e. differences in epidemiology like incidence and prevalence of the disease and prevalence of risk factors and co-morbidities [60]. An intervention will generally be more cost-effective in a country where the prevalence and incidence are high. In our context this will mean that prevention of osteoporosis related fractures is more likely to be cost effective in Scandinavia witch has a high incidence, than in the rest of Europe (see table). ICERs will also differ due to factors which have an impact on the cost side; this can be price of drug and cost of health care services. A difference in organisation and financing of care does influence cost of care [60]. Finally ICERs can differ on account of

methodological factors, like differences in perspective, choice of discount rate, costing method and choice of utility input [60].

When comparing our results with results from other studies, we have chosen to look only at studies conducted on Scandinavian populations. The table shown below is not a complete list of all studies.

Table 16; Findings of other Scandinavian CE-studies

Study	Population norms	Fracture utilities	Drug cost per year	Efficacy	Population	ICER
Zethraeus et al. 2007	Burstrom et al. 2001	Zethraeus et al 2002	SEK 6.000	Assumes that intervention reduces the risk of fracture with 35%	Swedish, 70 year old women with twice the fracture risk of the background population	SEK 260.000
Strom et al. 2007	Lundberg et al. 1999	Zethraeus et al. 2002, Kanis et al 2004	€ 502	FIT	Norwegian women, VFA and CFA	Treatment option was dominate
Johnell et al. 2003		Jonson et al. 1996	SEK 4.322	FIT	Swedish women VFA	 SEK 76.384
Christensen et al. 2005a	Pedersen et al. 2003	Brazier et al. 2002, Oleksik et al. 2000, Dolan et al. 1999	DDK 4.535	FIT	Danish women VFA	 DDK 124.567
Kristiansen et al. 1997		Kristiansen et al. 1997	NOK 4.313	Assumed that alendronate reduces the risk of fracture by 45%	Norwegian women t-score 1.0 t-score 1.5 t-score 2.0 t-score 2.5 t-score 3.0 t-score 3.3	 NOK 698.000 NOK 528.000 NOK 395.000 NOK 291.000 NOK 210.000 NOK 147.000
Jonsson et al. 2003	Lundberg et al. 1999	Jonsson et al. 1998	DDK 3.404	FIT	Danish women VFA CFA	 DDK 13.227 DDK 150.297

In our study, alendronate is dominant for all nine groups, which are in line with the findings of Strom and co-workers [88]. In this article, incidence data for hip fractures is extrapolated from Oslo to the whole of Norway, which will overestimate the Norwegian incidence, as the

incidence in Oslo may be higher than in the rest of the country. This will make their result look more favourable than it really is based on the other input. The ICER is however very sensitive to the price of alendronate, and we have used an even lower price than this study, as the generic competition has reduced the price further.

Christensen and co-workers [13] do not have a dominate result in the base case, but in their sensitivity analysis, alendronate becomes dominant if treatment is extended from three to five years, if alendronate had an offset-time of three years, or if the proportion of patients having severe sequelae was increased or if the intervention group had a risk of fracture which was four times that of the background population. We have in practise fulfilled the three first conditions, so considering this; our findings are in line with these results.

The main reason our result differ from the other analysis can be that we use an annual drug cost which is approximately one fourth of those previously used.

4.3 Policy implications

Our results indicate that treatment with alendronate is more effective and less costly than no treatment for women between 65, 70 and 75 with a t-score between -1.5, -2.0 and -2.5. The sensitivity analysis indicated that the result is robust for changes in all variables. We conclude that treatment of these groups fulfil the cost-effectiveness criterion in the priority setting guidelines. As described in the introduction, the cost effectiveness is however not the only criterion for priority setting. Policy makers must first consider whether or not the severity criterion is fulfilled and whether the effectiveness is sufficiently documented for these groups. It should also be noted that lower price of alendronate will tend to make other osteoporosis treatments less cost-effective than they were before.

Even if we assume that the three first criteria are fulfilled, there are still other things which need to be considered. The programme we have considered here is cost saving. The size of the savings will depend on the size of the target population. This means that the capacity of the health and social sector can be spent on other patients, instead of this patient group.

Second; ethical aspects of giving treatment to more groups of the population have to be considered. Decreasing BMD is a natural consequence of getting older. Low BMD is

asymptomatic, but results in increased fracture risk. It has been argued that treating groups *at risk* of disease represents a medicalisation.

4.4 Conclusion

We conclude that use of alendronate with the current prices is cost-effective in a wide range of patients. The Norwegian guidelines for osteoporosis need to be revised to accommodate the changes in cost-effectiveness.

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Appendix 1: Costs

Table 17; Unit Costs [1, 1, 12, 13, 18, 21, 66-69, 75, 76, 79, 84, 85, 89]

Description	Unit	Unit costs (NOK)	Source / assumptions / comments
GP-visit		125	Fee 2ad: Co-payment (NMA 2006).
		82	In 2006 a GP got NOK 326 from the municipality per patient on his list. These costs come in addition to the patient's co-payment. We assume an average of four visits per year. Thus NOK 326 / 4 = 82 are added for each visit.
		65	Additional fee for specialist in general medicine
	Per visit	**272**	
BMD measurement		250	Fee 870: Measurement of BMD with DXA (NMA 2006)
		200	Fee 899: Co-payment (NMA 2006)
		450	40% of total costs
	Per measurement	**1 125**	Total costs
Alendronate 70 mg			We assume that weekly dose of Alendronate is 70 mg. 12 tablets of Alendronate 70 mg cost NOK 239.20 after the latest price reduction due to the expire of the patent on Alendronate in December 2006 (Physician Desk Reference 2006). Price excluded VAT: NOK 191. Price per year: 191/12*52=829
	Per year	**746**	Reduced costs because of 90% adherence: 829*0.9=746
Biochemical tests			Tests due to treatment with alendronate to follow biochemical markers. NOK 150 per year is an assumption based on the price (DKK 130) used in DOOM
	Per year	**150**	
Nursing home care			Average costs for one year in a public nursing home is NOK 632 229, median costs is 585 903 (Statistics Norway 2007).
	One year	**585 903**	We chose to use the median costs.
Rehabilitation at nursing home			Patients who have rehabilitation in a nursing home are assumed to spend three weeks. We found the price by dividing the median yearly costs by 52 weeks a year, then multiplying by three weeks: (585 903 / 52) * 3 = 33 802.
	Per stay (three weeks)	**33 802**	
Qualified home service			Market price for one hour is NOK 325 including VAT (Oslo Helse og Omsorg AS) 260 when VAT is excluded
	One hour	**260**	
Physiotherapist			Assumption based on fee schedule from NAV and personal communication with the Norwegian Physiotherapist Association
	Per 40 minutes	**250**	
Out-patient clinic visit	Per visit	**265**	Fee 201b: Examination by a specialist (40% of total costs)
		662	Total costs
X-ray	Per examination	200	Fee 202: X-ray, co-payment
		70	Fee PK112: X-ray, no contrast (0.208*335)
		270	Reimbursement + co-payment (40% of total costs)
		675	Total costs
Forearm fracture (emergency room, no replacement)		200	Fee 202: X-ray, co-payment
		70	PK112: X-ray, no contrast (0.208*335)
		229	Fee group 3
		75	Fee B30a: Immobilise, no replacement
		265	Fee 201b: Examination at a specialist
		839	Reimbursement + co-payment (40% of totalt costs)
		2 098	Total costs
Forearm fracture (emergency room, replacement)		200	Fee 202: X-ray, co-payment
		70	PK112: X-ray, no contrast (0.208*335)
		408	Fee group 4
		75	Fee B31g: Immobilise, replacement
		265	Fee 201b: Examination at a specialist
		1 018	Reimbursement + co-payment (40% of totalt costs)
		2 545	Total costs
DRG point	Per point	**31 614**	The price of one DRG point was set to NOK 31 614 in 2006 (SHDIR 2007)

Table 18; Hip fracture costs first year [100]

Age	Total costs	Age	Total costs	Age	Total costs	Age	Total costs
65	174031	75	216959	85	274970	95	348064
66	176352	76	220440	86	279611	96	361986
67	178672	77	223921	87	284252	97	368947
68	180993	78	227401	88	290052	98	377069
69	183313	79	232042	89	303976	99	390992
70	187954	80	239004	90	310936	100	401434
71	194916	81	245965	91	319058		
72	203036	82	252927	92	326019		
73	207678	83	261047	93	332981		
74	212318	84	268009	94	339942		

Table 19; vertebral fracture costs first year

Type of cost	Unit cost	Number of units consumed	Proportion consuming this unit	Total average costs of event	Source / assumptions / comments
GP-visit	272	1	100%	272	
X-ray	675	1	100%	675	
Hospitalisation	18 968	1	25%	4 742	DRG 243: Rygglidelser, traumatiske tilstander og symptomer i ryggen Weight 0.60*31 614=18 968
Out-patient clinic visit	662	1	25%	166	
Physiotherapy	250	12	100%	3 000	
Total				**8 855**	

Table 20; Forearm fracture costs first year

Type of cost	Unit cost	Number of units consumed per year	Proportion consuming this unit	Total average costs	Source / assumptions / comments
Transport	400	1	100%	400	Assuming taxi at a cost of 200 each way
Emergency room (no replacement)	2 098	1	45%	944	45% do not need replacement (Personal communication, Jan Falch)
Emergency room (replacement)	2 545	1	25%	636	25% need replacement (Personal communication, Jan Falch)
Hospitalisation	25 607	1	30%	7 682	DRG 224: Surgery forearm Weight 0.81*31614 30% need surgery (Personal communication, Jan Falch)
GP-visit	272	1	30%	82	
Out patient clinic visit	662	1	100%	662	
Physiotherapy	250	5	30%	375	
Total				**10 781**	

Table 21; Costs of moderate hip fracture sequelae and vertebral fracture sequelae

Type of cost	Unit cost	Number of units consumed per year	Proportion consuming this unit	Total average costs	Source / assumptions / comments
GP-visit	272	2	100%	544	
Physiotherapy	250	12	20%	600	
Qualified home service	260	72	100%	18720	Based on Osnes (2004) we assume that all patients in this group need home nursing care
Total				**19864**	

Table 22; Costs of severe hip fracture sequelae

Type of cost	Unit cost	Number of units consumed per year	Proportion consuming this unit	Total average costs	Source / assumptions / comments
Nursing home	585 903	1	100%	585 903	Based on Osnes (2004) we assume that all patients in this group live in a nursing home
Total				**585 903**	

Table 23; Treatment costs first year

Type of cost	Unit cost	Number of units consumed per year	Total average costs first year	Source / assumptions / comments
Alendronate per year	746	1	746	
GP-visits	272	2	544	
BMD measurement	450	1	1 124	
Biochemical tests	150	1	150	
Total				

Table 24; Treatment costs subsequent years

Type of cost	Unit cost	Number of units consumed per year	Total average costs in the subsequent years	Source / assumptions / comments
Alendronate per year	746	1	746	
GP-visits	272	1	272	
BMD measurement	450	0.5	1125	One BMD measurement every second year (Personal communication, Jan Falch)
Biochemical tests	150	0	0	No biochemical test are needed in following years (Personal communication, Jan Falch)
Total			**2164**	

Appendix 2: Fracture Incidence

Table 25; Incidence of hip fractures [54]

Age	Hip fracture incidence per 10 000, for women in Oslo
65-69	0.00405
70-74	0.00771
75-79	0.01425
80-84	0.02826
85-89	0.04755
90-99	0.06180

Table 26; Incidence of vertebral fractures[46]

Age	Vertebral incidence per 10000, for women in Oslo
65-69	0.00329
70-74	0.00583
75-79	0.00761
80-84	0.00770
85-99	0.01263

Appendix 3: Quality of Life Multipliers

Calculation of multipliers connected to events

Table 27; Calculation of multipliers for fracture events [5, 44, 94, 95]

Fracture event	Quality of life pre-fracture	Quality of life 12 months post-fracture	Multiplier for fracture event	Source
Hip	0.80 (0.77-0.82)	0.67 (0.64-0.70)	0.838	Borgstrom et al. 2006
Vertebral	0.91 (0.88-0.94)	0.80 (0.68-0.91)	0.879	Tosteson et al. 2001
Forearm	1	0.982 (0.978-0.986)	0.982	Dolan et al. 1999

Quality of life post-fracture is divided by quality of life pre-fracture in order in get the multipliers.

Calculation of multipliers for hip sequelae health states

Table 28: Values found in Tosteson et al. 2001 [95]

Fracture type		12-24 months after fracture event	More than 24 months since fracture event
Hip		0.48 (0.32-0.64)	0.85 (0.78-0.93)
Vertebral		0.80 (0.68-0.91)	0.85 (0.78-0.93)
No-fracture	0.91 (0.88-0.94)		

We used the reported quality of life for the people without any fractures as a proxy for the pre-fracture utility. In this study [95] the pre-fracture value was 0.91. The multiplier for moderate sequelae was calculated as the mean utility value after fracture divided with the pre-fracture utility; 0.79/0.91=0.868. We assumed that the 95% confidence intervals reported in the paper was based on a normal distribution. Standard error was calculated as 0.79+1.96*SE=0.92 and 0.79-1.96*SE=0.66, which implied SE=0.0663. We assumed that quality of life for patients in mild sequelae would be one SE above the mean. The multiplier for mild hip sequelae then became (0.79+0.0663)/0.91=0.941. We followed the same approach for severe sequelae and found that the multiplier became (0.79-0.0663)/0.91=0.795.

Appendix 4: Background mortality

Table 29: Background mortality [85]

Age	Mortality rate per 10 000, for women in Norway 2006.
65	0.00886
66	0.00873
67	0.00962
68	0.01035
69	0.01163
70	0.01461
71	0.01327
72	0.01457
73	0.01820
74	0.02005
75	0.02224
76	0.02642
77	0.02856
78	0.03221
79	0.03774
80	0.04106
81	0.04597
82	0.05188
83	0.06011
84	0.06446
85	0.08471
86	0.08857
87	0.09945
88	0.12097
89	0.13281
90	0.14712
91	0.16870
92	0.19006
93	0.18945
94	0.23308
95	0.24759
96	0.27236
97	0.27296
98	0.34527
99	0.34567

Appendix 5: Search strategies

1. Quality of life

EMBASE 1980 to 2007 Week 19

#	Search History	Results
1	"Quality of Life"/	74686
2	Hip Fractures/	6509
3	Spinal Fractures/	2825
4	Osteoporosis/	32015
5	Wrist Injuries/ or Colles' Fracture/ or Radius Fractures/	4029
6	1 and (2 or 3 or 4 or 5)	1361

Ovid MEDLINE(R) 1950 to May Week 1 2007

#	Search History	Results
1	"Quality of Life"/	59111
2	Hip Fractures/	6752
3	Spinal Fractures/	5771
4	Osteoporosis/	23768
5	Wrist Injuries/ or Colles' Fracture/ or Radius Fractures/	8291
6	1 and (2 or 3 or 4 or 5)	368

EMBASE 1980 to 2007 Week 19

#	Search History	Results
1	"Quality of Life"/	74686
2	Hip Fractures/	6509
3	Spinal Fractures/	2825
4	Osteoporosis/	32015
5	Wrist Injuries/ or Colles' Fracture/ or Radius Fractures/	4029
6	Denmark/	8871
7	Sweden/	16220
8	Norway/	7617
9	1 and (2 or 3 or 4 or 5) and (6 or 7 or 8)	13

Ovid MEDLINE(R) 1950 to May Week 1 2007

#	Search History	Results
1	"Quality of Life"/	59111
2	Hip Fractures/	6752
3	Spinal Fractures/	5771
4	Osteoporosis/	23768
5	Wrist Injuries/ or Colles' Fracture/ or Radius Fractures/	8291
6	Denmark/	27873
7	Sweden/	42004
8	Norway/	21322
9	1 and (2 or 3 or 4 or 5) and (6 or 7 or 8)	5

2. Population norms

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	Rating Scale/	44297
2	"Quality of Life"/	74566
3	Population Research/	34501
4	3 and 2 and 1	124
5	DENMARK/	8049
6	SWEDEN/	14932
7	NORWAY/	6992
8	4 and (5 or 6 or 7)	6

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	Rating Scale/	44297
2	"Quality of Life"/	74566
3	Population Research/	34501
4	3 and 2 and 1	124

3. Mortality

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	exp Mortality/	183002
2	SWEDEN/	14932
3	NORWAY/	6992
4	DENMARK/	8049
5	Hip Fracture/	6093
6	1 and 5 and (2 or 3 or 4)	33
7	Vertebra Fracture/	4300
8	Wrist Fracture/	1065
9	1 and 7 and (2 or 3 or 4)	8
10	1 and 8 and (2 or 3 or 4)	2

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	exp Mortality/	183002
2	SWEDEN/	14932
3	NORWAY/	6992
4	DENMARK/	8049
5	Hip Fracture/	6093
6	1 and 5 and (2 or 3 or 4)	33

#	Search History	Results
1	exp Mortality/	183002
2	Fragility Fracture/	2013
3	SWEDEN/	14932
4	NORWAY/	6992
5	DENMARK/	8049
6	1 and 2 and (3 or 4 or 5)	6
7	from 6 keep 1-6	6

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	Bone Density/	21372
2	Mortality/	133363
3	1 and 2	331

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	MORTALITY/	133363
2	Hip Fracture/	6093
3	Vertebra Fracture/	4300
4	Wrist Fracture/	1065
5	OSTEOPOROSIS/ or POSTMENOPAUSE OSTEOPOROSIS/	33564
6	Fragility Fracture/	2013
7	Bone Density/	21372
8	1 and (2 or 3 or 4 or 5 or 6 or 7)	1633
9	1 and (2 or 3 or 4)	788
10	1 and 5	980
11	1 and 6	146
12	1 and 7	331
13	1 and 6 and 5	101

4. Alendronate

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	Alendronate/	4926
2	DRUG EFFECT/	176582
3	Meta Analysis/	30139
4	1 and 2 and 3	24

Ovid MEDLINE(R) 1950 to May Week 1 2007

#	Search History	Results
1	Alendronate/	1527
2	Treatment Outcome/	287448
3	1 and 2	174
4	limit 3 to "review articles"	21

Ovid MEDLINE(R) 1950 to May Week 1 2007

#	Search History	Results
1	Alendronate/	1527
2	*Bone Density/de [Drug Effects]	2704
3	1 and 2	185

5. Costs

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	Hip Fracture/	6093
2	Vertebra Fracture/	4300
3	Forearm Fracture/	829
4	"Health Care Cost"/	51748
5	NORWAY/	6992
6	SWEDEN/	14932
7	DENMARK/	8049
8	(1 or 2 or 3) and 4 and 5	1
9	(1 or 2 or 3) and 4 and (6 or 7)	10
10	OSTEOPOROSIS/	29717
11	4 and 5 and 10	0
12	4 and (5 or 6) and 10	5

6. T and Z-scores

Ovid MEDLINE(R) 1950 to May Week 1 2007

#	Search History	Results
1	Bone Density/	24414
2	Reference Values/	114959
3	Europe/	53225
4	Scandinavia/	3471
5	Norway/	21322
6	Sweden/	42004
7	Denmark/	27873
8	1 and 2 and 5	4

7. Incidence of hip fractures

EMBASE 1988 to 2007 Week 19

#	Search History	Results
1	Hip Fractures/	6093
2	Incidence/	80563
3	Norway/	6992
4	Sweden/	14932
5	Denmark/	8049
6	1 and 2 and (3 or 4 or 5)	39

Ovid MEDLINE(R) 1950 to May Week 1 2007

#	Search History	Results
1	Hip Fractures/	6752
2	Incidence/	106131
3	Norway/	21322
4	Sweden/	42004
5	Denmark/	27873
6	1 and 2 and (3 or 4 or 5)	54

8. Incidence of vertebral fractures

Ovid MEDLINE(R) 1950 to May Week 1 2007

#	Search History	Results
1	Incidence/	106131
2	Norway/	21322
3	Sweden/	42004
4	Denmark/	27873
5	Spinal Fractures/	5771
6	1 and 5 and (2 or 3 or 4)	7