Efficacy and cost-effectiveness of alendronate for the prevention of fractures in postmenopausal women in Norway

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
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Health Technology Assessment (HTA) (Medisinsk metodevurdering)

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Norwegian Knowledge Centre for the Health Services

Background: The Norwegian guidelines for prevention and treatment of osteoporosis and osteoporosis related fractures recommend treatment with bisphosphonates for women with T-score less than -1.6 and previous fractures and also for women with T-score less than or equal to -2.5 without previous fracture. Only women with T-score equal to or less than -2.5 who have previous fractures will have their drug expenses reimbursed. The guideline was last revised in 2005. Since then, the price of alendronate has been reduced by 80%. The University of Oslo has asked the Norwegian Knowledge Centre for the Health Services to evaluate how this price reduction affects the cost-effectiveness of alendronate. **Methods:** We developed a model based economic evaluation with a lifetime perspective. The model follows a hypothetical cohort of women with respect to fractures of the hip, spine and wrist, late effects after fractures and mortality. During the course of the model costs and health effects are accumulated as a result of the fractures. Half of the women receive treatment with a combination of alendronate, calcium and vitamin D. The other half only receives *(continued)*

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(continued from page one) calcium and vitamin D. The estimated efficacy of alendronate in combination with calcium and vitamin D compared to calcium and vitamin D only was based on a systematic review of the literature. **Conclusions:** • Alendronate is likely to be a cost-effective alternative for women aged 65 and 75 years old with a T-score of equal to or less than -2.5 with no previous fracture and for women with a T-score of equal to or less than -2.0 who has suffered a previous fracture. • The scarcity of efficacy data for women with a T-score above -2.5 without a previous fracture makes the inferences for these groups very uncertain.

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Key messages

Background: The Norwegian guidelines for prevention and treatment of osteoporosis and osteoporosis-related fractures recommend treatment with bisphosphonates for women with T-score less than -1.6 and previous fractures and also for women with T-score less than or equal to -2.5 without previous fracture. Only women with T-score equal to or less than -2.5 who have previous fractures will have their drug expenses reimbursed.

The guideline was last revised in 2005. Since then, the price of alendronate has been reduced by 80%. The University of Oslo has asked the Norwegian Knowledge Centre for the Health Services to evaluate how this price reduction affects the cost-effectiveness of alendronate.

Methods: We developed a model based economic evaluation with a lifetime perspective. The model follows a hypothetical cohort of women with respect to fractures of the hip, spine and wrist, late effects after fractures and mortality.

During the course of the model costs and health effects are accumulated as a result of the fractures. Half of the women receive treatment with a combination of alendronate, calcium and vitamin D. The other half only receives calcium and vitamin D. The estimated efficacy of alendronate in combination with calcium and vitamin D compared to calcium and vitamin D only was based on a systematic review of the literature.

Conclusions:

- Alendronate is likely to be a cost-effective alternative for women aged 65 and 75 years old with a T-score of equal to or less than -2.5 with no previous fracture and for women with a T-score of equal to or less than -2.0 who has suffered a previous fracture.

- The scarcity of efficacy data for women with a T-score above -2.5 without a previous fracture makes the inferences for these groups very uncertain.

Executive summary

Background

Norway has one of the highest incidences of osteoporosis-related fractures in the world. Norwegian guidelines for prevention and treatment of osteoporosis and osteoporosis-related fractures recommend treatment with bisphosphonates for women with a T-score less than -1.6 and previous fracture and also for women with T-score equal to or less than -2.5 without previous fracture. Only women with a T-score equal to or less than -2.5 who have suffered a previous fracture will have their drug expenses reimbursed.

The guidelines were last revised in 2005. Since then the price of alendronate, the most widely used bisphosphonates, has declined by 80% due to the introduction of generic competition. The Institute of Health Management and Health Economics at the University of Oslo has asked The Norwegian Knowledge Centre for the Health Services to evaluate the cost-effectiveness of alendronate for post-menopausal women after this price reduction.

Method

We developed a Markov model with three possible fracture events: fracture of the hip, vertebra and wrist. The model also contains four possible sequelae health states: mild, moderate and severe hip fracture sequela and vertebral fracture sequela. We performed analyses for women aged 55, 65 and 75 years old with T-scores of -1.5, -2.0 and -2.5 without previous fracture and T-score -2.0 with a previous fracture. Treatment with 70 mg alendronate per week in combination with calcium and vitamin D was compared to treatment with calcium and vitamin D only. Treatment was assumed to last for five years. The model followed the women from the age at treatment initiation until they all were one hundred years of age or dead.

Efficacy data were based on a review from the Cochrane Collaboration. We updated their literature search and conducted our own meta-analyses in order to obtain efficacy estimates for all of the groups requiring analysis.

In order to assess the robustness of our results, we performed one-way sensitivity analyses, probabilistic sensitivity analyses and we also calculated the expected value of perfect information on groups of parameters.

Results

In the probabilistic sensitivity analysis, the probability that alendronate is cost-effective for women with a T-score of less than -2.0 without previous fractures, varies from 0 % for the 55 years old, to 37 % for the 75 years old. For women with a T-score of less than -2.0 and a previous fracture and women with a T-score of -2.5 and no previous fracture, the likelihood that alendronate can be considered cost-effective varies from just below 10 % for the 55 years old, while it exceeds 90 % for the 65 and 75 years old.

We initially assumed that the Norwegian threshold value was NOK 500 000 per quality adjusted life year. Taking into account that this is not an official threshold, we also assessed how sensitive the conclusions were to this assumption. For women aged 75 years old with a T-score between -2.0 and -2.5, women aged 55 with a T-score less than -2.5 without a previous fracture and for women aged 55 with a T-score of -2.0 and a previous fracture, the conclusion may change if the willingness-to-pay is above NOK 500 000 per QALY.

The conclusions are uncertain for women aged 75 with a T-score between -2.0 and -2.5 without a previous fracture. According to the value of information analysis, the conclusion for this group is most affected by the uncertainty regarding the efficacy estimates. Further research on the efficacy of alendronate for women without previous fractures will reduce the decision uncertainty.

Discussion

The results of this analysis indicate that treatment with alendronate is likely to be cost-effective for women aged 65 and 75 years old with a T-score less than -2.5 without previous fracture and for women aged 65 and 75 years old with a T-score less than -2.0 with a previous fracture.

The conclusions are most uncertain for women aged 75 with a T-score of less than -2.0 and no previous fracture, women aged 55 with a T-score of -2.0 and a previous fracture and women aged 55 with a T-score of less than -2.5 and no previous fracture. Relatively small changes in the efficacy estimates of alendronate or the assumed willingness-to-pay per quality adjusted life year may change the conclusions for these groups.

All models are simplifications of reality and the study results are uncertain due to assumptions made and uncertainty in included parameters. We have only included fractures of the hip, vertebra and wrist as outcomes. In reality low bone mineral

density increases the risk of all types of fractures. This simplification implies an underestimation of the cost-effectiveness of alendronate.

We did not include any side effects of alendronate in the model because there were no differences in the risk of side effects between treatment and control arms in the randomised controlled trials. Randomised controlled trials may however not be the appropriate study design to detect rare side effects, side effects that take long to develop or side effects that are more likely to occur in subpopulations.

Further research on the efficacy of alendronate on women at low risk of fracture may reduce the decision uncertainty for these women.

Conclusion

Alendronate is likely to be a cost-effective alternative for women aged 65 and 75 years old with a T-score of equal to or less than -2.5 with no previous fracture and for women with a T-score of equal to or less than -2.0 who has suffered a previous fracture.

The scarcity of efficacy data for women with a T-score above -2.5 without a previous fracture makes the inferences for these groups very uncertain.

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Directorate of Health, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

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1-side oppsummering (norsk)

Bakgrunn: Norske retningslinjer for forebygging og behandling av osteoporose og osteoporoserelaterte brudd anbefaler behandling med bisfosfonater for kvinner med T-skåre mindre enn -1,6 og tidligere brudd og også for kvinner med T-skåre mindre eller lik -2,5 uten tidligere brudd. Kun kvinner med T-skåre mindre enn -2,5 som har tidligere brudd vil få sine legemiddelutgifter refundert.

Veilederen ble sist revidert i 2005. Siden da har prisen på alendronat blitt redusert med 80 %. Universitetet i Oslo har gitt Nasjonalt kunnskapssenter for helsetjenesten i oppdrag å vurdere hvordan denne prisreduksjonen påvirker kostnadseffektiviteten av alendronat.

Metode: Vi utviklet en modellbasert økonomisk evaluering med et livsløpsperspektiv. Modellen følger en hypotetisk kohort av kvinner med hensyn til brudd i hofte, rygg og håndledd, senskader etter brudd og dødelighet. I løpet av modellens gang registreres kostnader og livskvalitet knyttet til disse hendelsene.

Halvparten av kvinnene får behandling med en kombinasjon av alendronat, kalsium og vitamin D. Den andre halvparten bare får kalsium og vitamin D. Den estimerte effekten av alendronat i kombinasjon med kalsium og vitamin D sammenlignet med kalsium og vitamin D var basert på en systematisk gjennomgang av litteraturen.

Konklusjon:

• Alendronat er sannsynligvis ett kostnadseffektivt alternativ for kvinner som er 65 og 75 år gamle med en T-skåre som er mindre eller lik -2,5 uten tidligere brudd og for kvinner med en T-skåre som er mindre enn -2,0 som har hatt et tidligere brudd.

• Mangelen på effekt data for kvinner med en T-skåre over -2,5 uten tidligere brudd gjør slutninger for disse gruppene svært usikre.

Sammendrag (norsk)

Bakgrunn

Norge ligger på verdenstoppen i forekomst av osteoporotiske brudd. Norske behandlingsretningslinjer for forebygging og behandling av osteoporose og osteoporotiske brudd anbefaler bisfosfonater til kvinner med T-skåre mindre enn -1,6 og tidligere brudd og også til kvinner med T-skåre -2,5 eller mindre uten tidligere brudd. Kun kvinner med T-skåre -2,5 eller mindre og brudd får bisfosfonater på blå resept.

Siste versjon av retningslinjene kom i 2005. Siden den gang har prisen på alendronat, det mest brukte bisfosfonatet, falt med 80 % grunnet generisk konkurranse. Institutt for helseledelse og helseøkonomi ved Universitetet i Oslo har bedt Nasjonalt kunnskapssenter for helsetjenesten å vurdere hvordan dette påvirker kostnadseffektiviteten av alendronat.

Metode

Vi utviklet en Markovmodell med tre mulige bruddhendelser: brudd i hoften, vertebra og håndleddet. Modellen inneholder også fire mulige senskader etter brudd: mild-, moderat- og alvorlig senskade etter lårhalsbrudd og senskade etter vertebralbrudd.

Vi utførte analyser for kvinner 55, 65 og 75 år gamle med T-skåre på -1,5, -2,0 og -2,5 uten tidligere brudd og T-skåre -2,0 med tidligere brudd. Behandling med 70 mg alendronat per uke i kombinasjon med kalsium og vitamin D ble sammenlignet med behandling med kalsium og vitamin D bare. Behandlingen ble antatt å vare i fem år. Modellen fulgte kvinnene fra alder ved behandlingsstart inntil de alle var hundre år gamle eller døde.

Effektdata ble basert på en systematisk kunnskapsoppsummering fra Cochrane gruppen. Vi oppdaterte deres litteratursøk og utførte egne meta-analyser for å få effektestimater for alle gruppene vi planla å analysere.

Vi utførte enveis sensitivitetsanalyse, probabilistisk sensitivitetsanalyse og verdi av forskningsanalyse (EVPPI), for å kvantifisere hvor stor innflytelse usikkerhet i ulike grupper av parametere hadde på konklusjonene.

Resultater

I den probabilistiske sensitivitetsanalysen varierte sannsynligheten for at alendronat var et kostnadseffektivt alternativ for kvinner med T-skåre mellom -2.0 og -2.5 uten tidligere brudd fra 0 % for 55 åringene til 37 % for 75 åringene. For kvinner med T-skåre mindre enn -2.0 med tidligere brudd eller T-skåre mindre en -2.5 varierte sannsynligheten for at alendronat er kostnadseffektiv fra rett under 10 % for 55 åringene til over 90 % for 65 og 75 åringer.

I den probabilistiske sensitivitetsanalysen antok vi at betalingsviljen per kvalitetsjusterte leveår var NOK 500 000. Siden dette ikke er en offisiell norsk grense, undersøkte vi også i hvilken grad konklusjonene var avhengige av denne verdien. Konklusjonene kan endre seg fra at alendronat ikke er kostnadseffektivt til kostnadseffektivt for kvinner 75 år gamle med T-skåre mellom -2.0 og -2.5, kvinner 55 år gamle med T-skår mindre enn -2.5 uten tidligere brudd og kvinner 55 år gamle med T-skåre mindre enn -2.0 med tidligere brudd dersom betalingsviljen per kvalitetsjusterte leveår er høyere enn NOK 500 000.

Konklusjonene er mest usikre for kvinner på 75 år med en T-skåre på mellom -2.0 og -2.5 som ikke har hatt tidligere brudd. I verdi av forskningsanalysen fremkommer det at det er usikkerheten i effektestimatene som har størst innvirkning på konklusjonene for denne gruppen.

Diskusjon

Våre analyser indikerer at alendronat er et kostnadseffektivt alternativ for kvinner som er 65 og 75 år gamle med T-skåre mindre enn -2.5 uten tidligere brudd og for kvinner med T-skår mindre enn -2.0 for kvinner med tidligere brudd.

Konklusjonene er mest usikre for kvinner på 75 år med T-skåre mellom -2.0 og -2.5 uten tidligere brudd, kvinner på 55 år med T-skåre mindre enn -2.0 med tidligere brudd og kvinner på 55 med T-skåre mindre enn -2.5. Relativt små endringer i modellens parameterverdier eller i den antatte betalingsviljen per kvalitetsjusterte leveår kan endre konklusjonene for disse gruppene.

Alle modeller er forenklinger av virkeligheten og det er derfor usikkerhet knyttet til resultatene. Usikkerheten kommer både fra forutsetninger gjort og parameterverdiene.

Vi har kun inkludert brudd i hofte, rygg og håndledd. I realiteten vil lav bentetthet øke risikoen for alle typer brudd. Denne forutsetningen vil tilsi at vi underestimerer kostnadseffektiviteten av alendronat. Mulige bivirkninger av alendronat er ikke ink-

ludert i analysen, ettersom vi ikke fant noen signifikante forskjeller i bivirkninger mellom de som mottok alendronat og de som mottok placebo i de randomiserte kontrollerte studiene. Randomiserte kontrollerte studier er imidlertid ikke den beste studiedesignen for å oppdage sjeldne bivirkninger, bivirkninger som først viser seg etter lang tids bruk eller bivirkninger som har større sannsynlighet for å inntreffe i subpopulasjoner.

Konklusjon

Alendronat er sannsynligvis ett kostnadseffektivt alternativ for kvinner som er 65 og 75 år gamle med en T-skåre som er mindre eller lik -2,5 uten tidligere brudd og for kvinner med en T-skåre som er mindre enn -2,0 som har hatt et tidligere brudd.

Mangelen på effekt data for kvinner med en T-skåre over -2,5 uten tidligere brudd gjør slutninger for disse gruppene svært usikre.

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Abbreviations

Abbreviation	
CI	Confidence interval
RR	Relative risk
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
BMD	Bone mineral density. Often measured in T-score.
NOK	Norwegian kroner
QALY	Quality-adjusted life-year
DXA	Dual energy X-ray absorptiometry
T-score	Measure of bone density relative to the average of young, healthy women. Above or equal to -1.0 is normal. Between -1.0 and -2.5 is osteopenia. Below -2.5 is osteoporosis.
Z-score	Measure of bone density relative to the average in a specific age group
WTP	Willingness-to-pay per QALY. Used as notation for the threshold value.
PSA	Probabilistic (stochastic) sensitivity analysis
MOON	Model for Osteoporotic Outcomes Nor-way
EVPPI	Expected value of perfect information for parameters

Preface

This report was commissioned by the Institute of Health Management and Health Economics at the University of Oslo. The goal of this report is to assess the cost-effectiveness of alendronate in the prevention of fractures in osteopenic and osteoporotic women.

The project group consisted of: Project manager Gunhild Hagen, Torbjørn Wisløff, Ivar Sønbø Kristiansen, Jan Falch, Cathrine Lofthus, Frede Frihagen, Knut-Arne Wensaas, Lars Granum, Janicke Nevjar and Marianne Klemp.

We would like to thank librarian Irene Wiik Langenden, our internal reviewers Kristin Kamilla Linnestad and Brynjar Landmark and our external reviewers Jan Abel Olsen and Jon Magnussen for their help. We would also like to acknowledge Palle Christensen and Christian Kronborg for their work on this model.

Gro Jamtvedt	Marianne Klemp	Gunhild Hagen
Excecutive Director	Research Director	Health Economist Project Manager

Objective

The objective of this report was to assess the efficacy and cost-effectiveness of alendronate in the prevention of fractures in postmenopausal women in Norway.

Background

Current Norwegian treatment guidelines for prevention of osteoporotic fractures (1) recommend treatment with bisphosphonates for women with bone mineral density (BMD) equal to or less than -2.5 with or without previous fracture and with BMD between -1.6 and -2.5 with previous fracture. Treatment is only reimbursed for women with BMD equal to or less than -2.5 and a previous fracture. The hypothesis is that it may now be cost-effective to treat and reimburse a wider group of women given the price reduction that followed the introduction of generic competition in 2005. In other words, it may be rational to update the current guideline. According to the Ministry of Health, national guidelines should be evidence based and consider cost-effectiveness before giving recommendations (2).

OSTEOPOROSIS

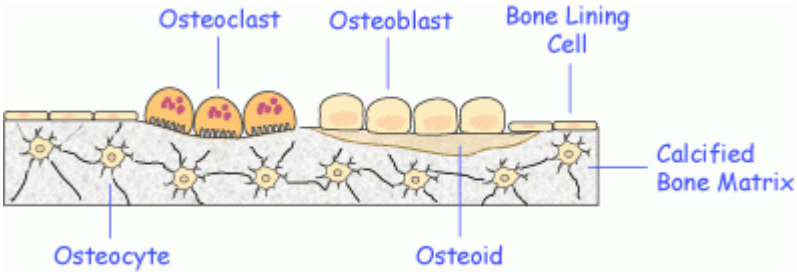
Osteoporosis is asymptomatic until the severity of disease manifest with the occurrence of fractures, particularly fractures of the hip, forearm and spine. It is characterised by low bone mineral density (BMD), which is a measure of bone strength. Low bone mineral density significantly increases the risk of fractures.

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 and endocrine factors, mechanical forces and exposure to risk factors. Bone loss naturally accelerates after the menopause, but may also increase as a result of age-related conditions such as reduced calcium absorption. Certain drugs, for example corticosteroids, and medical conditions can produce so-called secondary osteoporosis (3). Osteoporosis that is caused by "normal ageing" is sometimes referred to as primary osteoporosis, while osteoporosis caused by malabsorbtion of nutrients or by medications is referred to as secondary osteoporosis.

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 which are responsible for bone synthesis and subsequent mineralisation,

and the osteoclasts, which function in resorption of mineralized tissue. These mechanisms are not yet fully understood (4).

Figure 1: Osteoblasts and Osteoclasts (5)

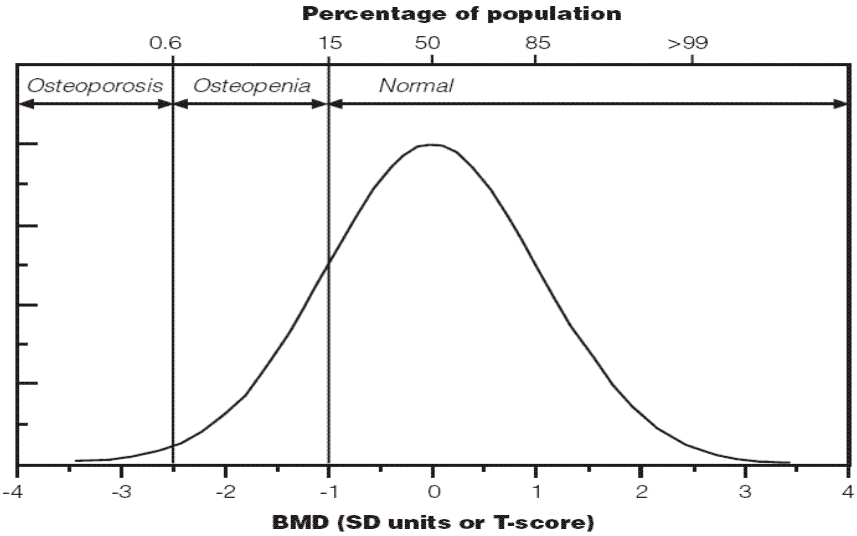


Both men and women, and all age groups are at risk of osteoporosis, but it is most common in postmenopausal women (6). Approximately 30% of all postmenopausal women in Europe have osteoporosis (3).

Clinical definition of osteoporosis

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

Figure 2: Osteoporosis and Osteopenia (5)



Four general diagnostic categories for women, based on BMD values, have been proposed by a WHO Study Group (5):

- Normal BMD: T-score above or equal to -1.0
- Osteopenia: T-score between -1.0 and -2.5
- Osteoporosis: T-score less than or equal to -2.5
- Established osteoporosis: T-score less than or equal to -2.5 and in addition 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 (3).

BMD can be measured in several different ways. The diagnostic criteria suggested by the WHO are based on measurement by dual energy X-ray absorptiometry (DXA).

Assessment of fracture risk – two different approaches

Earlier guidelines were mainly based on T-score and the presence/absence of previous fractures, while guidelines today, to a larger degree, also take clinical risk factors into account. Risk factors for osteoporosis related fractures include age, sex, history of fragility fracture, family history of fracture (maternal hip fracture in particular), physical inactivity, low body mass index, smoking, use of glucocorticoids, alcohol and rheumatoid arthritis (7). The WHO has developed a fracture risk assessment tool (8), and recent guidelines now follow this approach (7;9;10)

SOCIETAL IMPACT OF FRACTURES

Scandinavia has the highest incidence of osteoporotic fractures in Europe (11).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 (12) and health and social care costs (13). There are few studies on prevalence 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 (14).

It has been estimated that there are approximately 9000 hip fractures in Norway each year and that the societal costs of these fractures amount to 1.5 billion NOK (15). In the US osteoporosis related fractures were estimated at $13.8 billion, of which approximately 62% was spent on in-hospital care, 28% on nursing homes and 10% on out-patient care (13). 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, increases (3). The EU has estimated that the treatment costs of osteoporotic fractures will increase by more than 20% by 2020 (16).

ECONOMIC EVALUATION AND PRIORITY SETTING

The rapid technological development in medicine has widened the gap between what health care technologically can offer and what society can afford to pay for (17;18). 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 (19;20).

Three policy documents have specifically addressed the issue of priority setting in the Norwegian health care system; "Guidelines for priority setting in the Norwegian health care service" (21), "Pills, priority setting and policy" (17) and "Priority setting revised" (22). In the Patient Rights Act of 1999, it is stated that a patient is entitled to "necessary treatment" if the patient is expected to benefit from the treatment and if the treatment effects are in a reasonable relationship to the costs (23). According to the priority setting rule (24), a patient is entitled to treatment from the specialised health care system if the following criteria are met:

1. *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 the disease entails in terms of death, disability and discomfort, if treatment is postponed.
2. *The treatment is effective;* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.
3. *The cost-effectiveness of the treatment;* the added costs of the treatment should reasonable compared to the added benefits.

In the recent priority setting guideline for endocrinology issued by the Directorate of Health (25;26;26), all three criteria are explicitly evaluated. The cost-effectiveness of a treatment is investigated through an economic evaluation. Economic evaluation is defined as "the comparative analysis of alternative courses of action in terms of both their costs and consequences" (18). One type of economic evaluation is cost-utility analysis. In a cost-utility analysis, the effect of a treatment is measured in terms of quality-adjusted life-years (QALYs). The QALY attempts to capture both the morbidity and the mortality aspects of a specific disease or condition. An advantage of using a cost-utility analysis and QALYs is that it allows comparison between different treatments and interventions for various diseases and conditions.

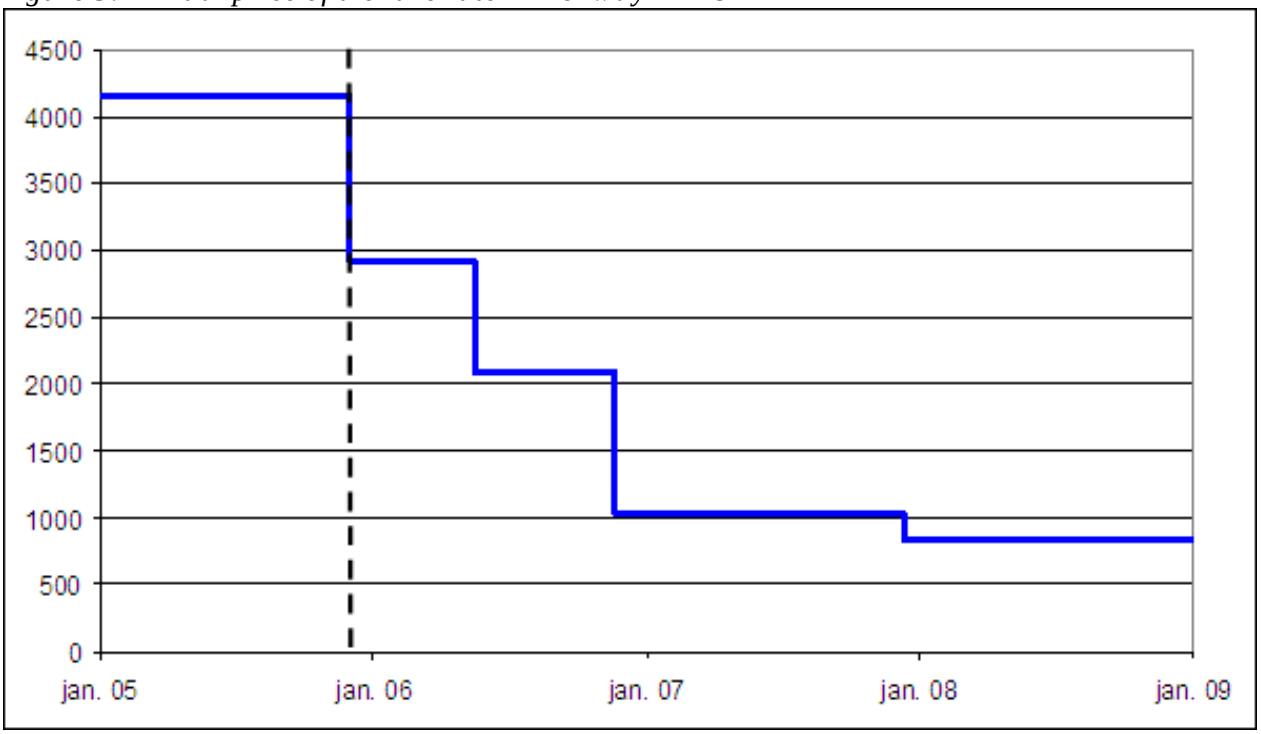
In order to draw conclusions from a cost utility analysis, a limit on the willingness-to-pay per quality-adjusted life-year is in most cases needed, the exceptions are situations where the treatment is both more effective and less costly than the comparator or if the treatment is less effective and more expensive. The policy documents mentioned above give no guidance as to what constitutes a" reasonable" relationship. The Directorate of Health, however, has recently recommended a prelimi-

nary estimate of NOK 500 000 per statistical life year in full health (27). However, there exists no academic consensus regarding this threshold value, nor has it been subject to a political process, and it can therefore be regarded as nothing more than a tentative suggestion.

PRICE OF ALENDRONATE

Since the introduction of generic competition in 2005, the price of alendronate has declined by 80% (Figure 3). The dotted vertical line represents the onset of generic competition and the stepped price model.

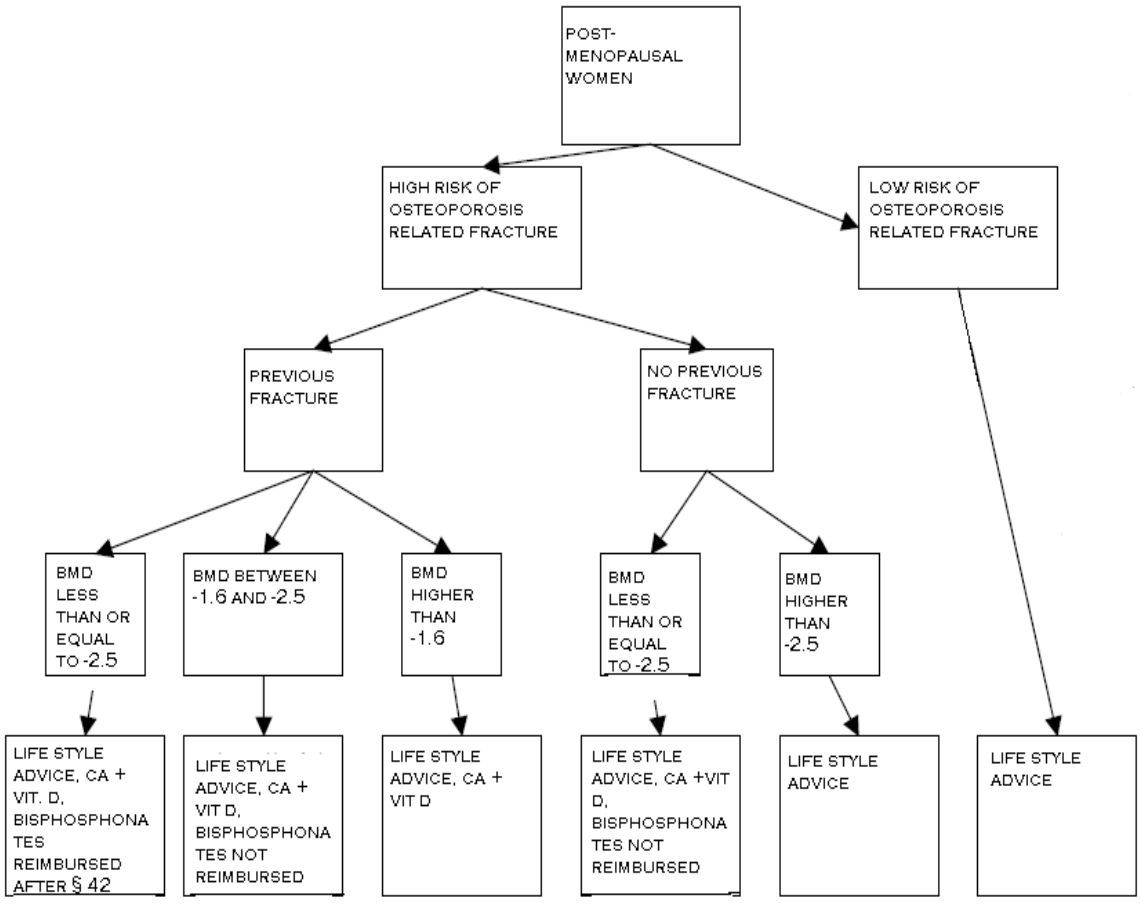
Figure 3: Annual price of alendronate in Norway in NOK



CURRENT NORWEGIAN TREATMENT GUIDELINE

The 2005 Norwegian treatment guidelines for prevention and treatment of osteoporosis and osteoporosis-related fractures (28) recommend that treatment with bisphosphonates be prescribed to postmenopausal women who are considered at high risk. This group consists of 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. However, 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. Alendronate was included in the "stepped pricing model" in December of 2005. Due to the reduction in price, alendronate is likely to be cost-effective for a wider group of individuals than previously was the case. The aim of this economic evaluation was to evaluate the cost-effectiveness of alendronate in the prevention of fractures in osteopenic and osteoporotic women.

Figure 4: Current Norwegian treatment guideline, adapted from (1)



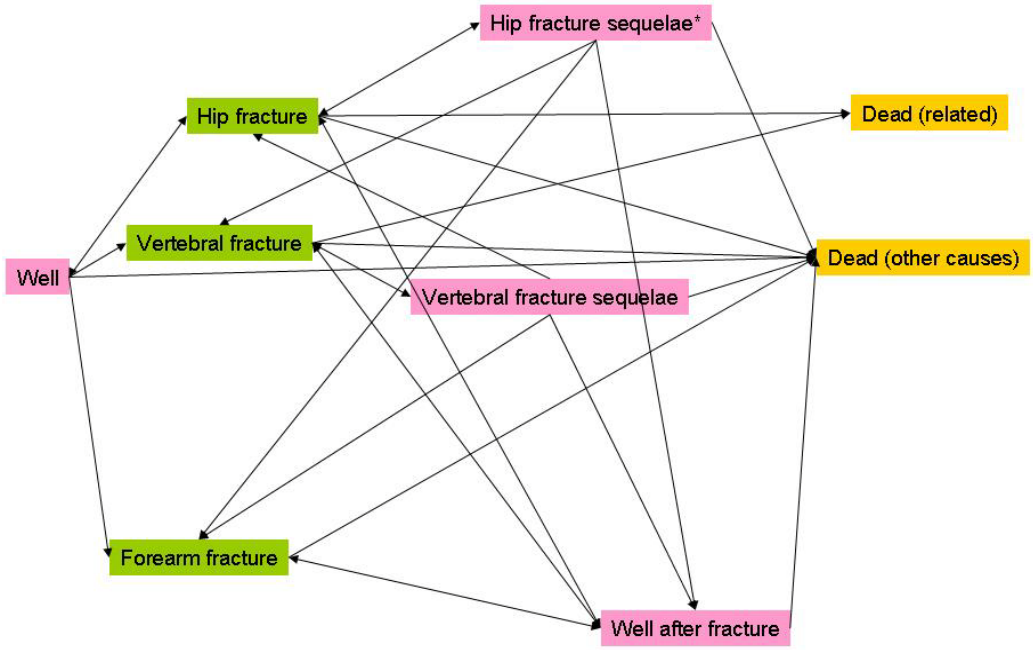
Methods

In this chapter we first present the structure of the model and then the data required to populate it. All health states in the model and many of the transitions have associated costs and quality of life decrements. In addition, the model requires efficacy data and epidemiological data in order to assign probabilities to all of the transitions. Each transition will in most cases require data from more than one source. After presenting the model structure, we describe the data required for transition probabilities including efficacy, quality of life and costs.

MODEL STRUCTURE

We used a Markov model developed in the programme TreeAge Pro® 2009. The model builds upon previous work (29-31). We have named the current version MOON (Model of Osteoporotic Outcomes in Norway). A Markov model is a technique for simulating a hypothetical cohort of patients over time. We start our analysis with a group of 10 000 postmenopausal women. We then follow the women until they are 100 years old or until they die. The model structure is illustrated in Figure 6 and 7. Figure 6 shows a graphical presentation of the model structure, while Figure 7 shows how half of the model (the treatment arm) appears in TreeAge.

Figure 5: Illustration of Model Structure MOON

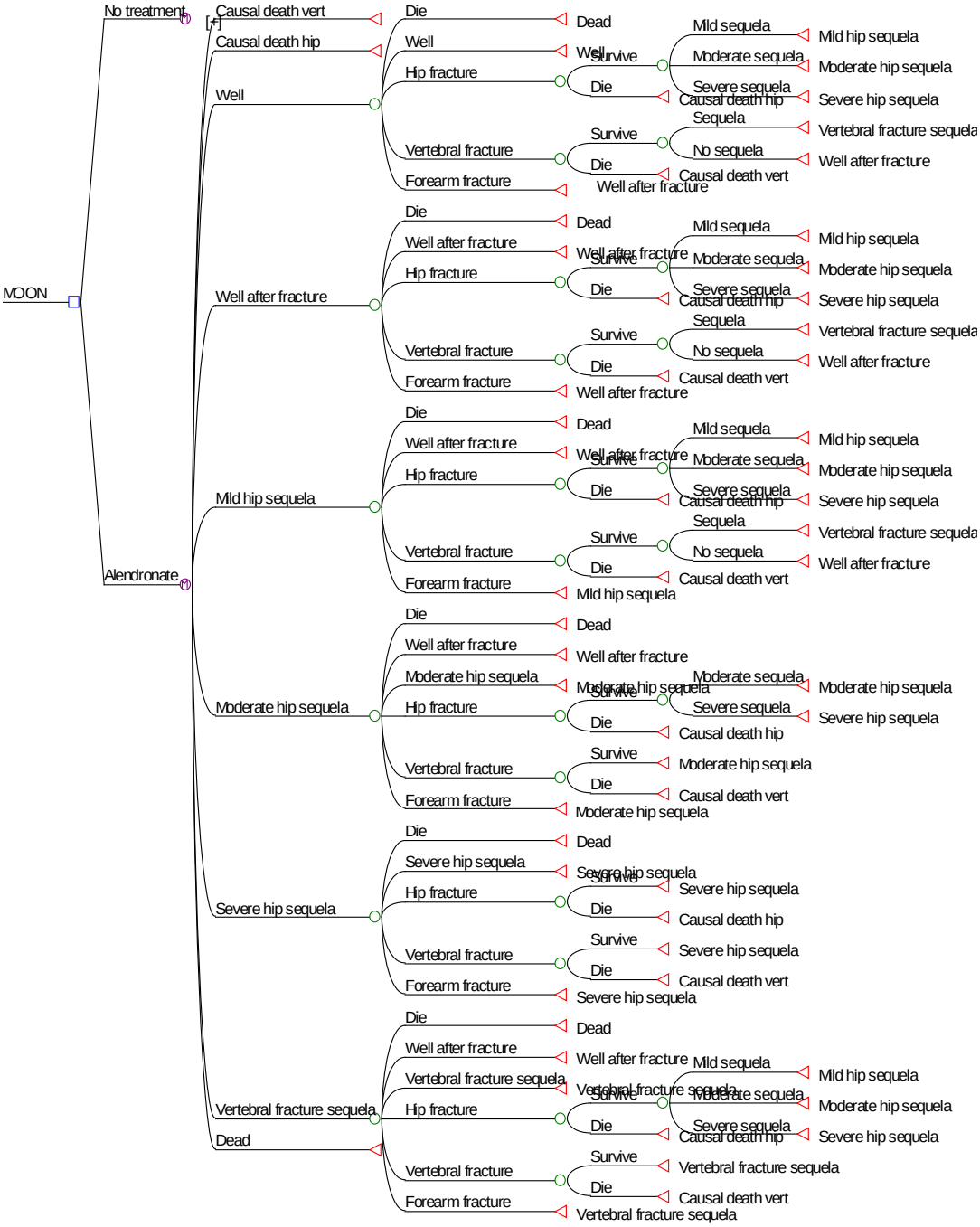


*Hip fracture sequela is divided into; mild, moderate and severe

The model contains eight health states and three possible fractures, *i.e.* fracture of the hip, wrist and vertebra. We start the analysis with a cohort of 10 000 women in the "well" health state. By well, we mean with or without previous fracture, but otherwise average compared to other women in the Norwegian population at given ages. Half the women receive alendronate and supplemental calcium and vitamin D. The others receive only supplemental calcium and vitamin D. During the course of the model, a woman can remain well or she may suffer a fracture of the hip, wrist or spine or she may die.

The probability of a fracture occurring is based on estimates of incidence and risk connected to having a low BMD and a previous fracture. If a woman has a fracture, there is a cost connected to this event, *i.e.* cost of operation, GP visit etc. Suffering a fracture may have long term effects on mobility and functional level. After a fracture, some women will therefore move into one of the sequelae health states. It is also possible to recover from a fracture event or from the vertebral sequela, mild hip sequela and moderate hip sequela health states and move back to the well state after fracture health state. For the health state severe hip sequela we assumed that recovery is not possible. Each health state and fracture event has associated costs and a health profile in terms of QALYs.

Figure 6: Model structure MOON in TreeAgePro 2009, treatment arm only



EFFICACY OF ALENDRONATE

PICO

Population: postmenopausal women
Intervention: alendronate with supplementation of calcium and vitamin D
Comparator: calcium and vitamin D
Outcome: fracture of hip, vertebra and wrist

Literature search

Data on the effect of alendronate was based on a recent Cochrane-review (32).
Our librarian updated the systematic search, in order to identify any studies published after the last search done by the Cochrane group. Details about the search can be found in Appendix 1. Our updated search resulted in no additional relevant randomised controlled trials (RCTs).

We excluded five studies included in the Cochrane review. Three (33-35) studies were excluded based on choice of outcome (use of surrogates) and two because they did not contain enough information to determine whether the included women had or had not suffered previous fractures (36;37).

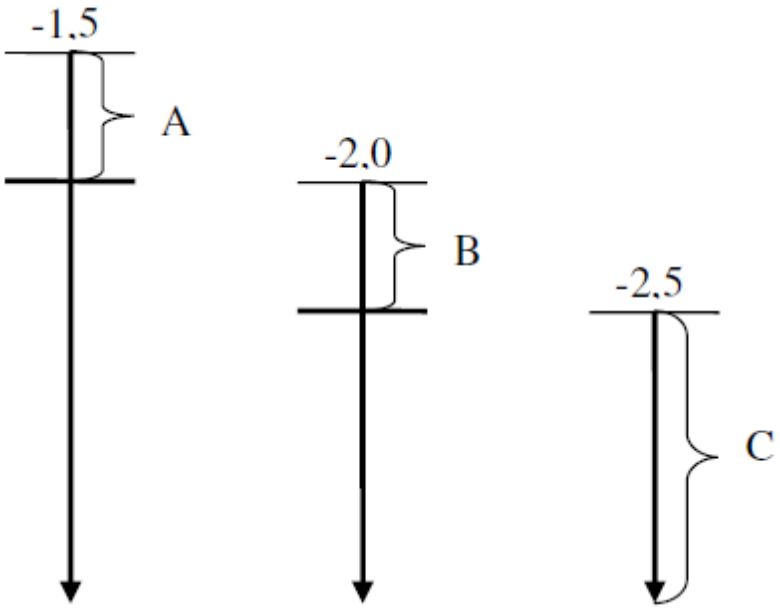
Meta-analyses

Because our project had a different objective than the Cochrane review, we subdivided the studies into more groups. The objective of our analysis was to analyse 6 different groups: three with a previous vertebral fracture and three with no previous fracture. For patients without former fracture, we intended to analyse BMD less than -2.5, BMD between -2.5 and -2.0 and BMD between -2.0 and -1.5, Because a fracture itself imposes an important risk, we planned to analyse groups with somewhat higher T-score for those with prevalent fracture (less than -2.0, between -2.0 and -1.0 and between -1.0 and 0.0).

Studies were divided into groups of BMD based on T-scores specified as inclusion criteria in each trial. Results from studies that distinguished between different T-scores, were included only in meta-analyses for the corresponding T-scores. The grouping of the efficacy results are illustrated in Figure 7 and 8.

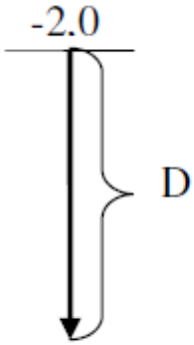
When we in this report refer to women with a T-score of -1.5 with no previous fracture, efficacy data are based on interval A in Figure 7, *i.e.* the interval between -2.0 to -1.5. Similarly, efficacy data for women with a T-score of -2.0 with no previous fracture are based on interval B, the interval between -2.5 and -2.0. For women with a T-score of -2.5, the efficacy data are based on women with a T-score of -2.5 or less, represented by interval C.

Figure 7: Division of efficacy data into groups of T-score for women without previous fracture



For women with a T-score of -2.0 and a previous fracture, efficacy estimates are based on interval D in Figure 8, *i.e.* a T-score of -2.0 or less.

Figure 8: Division of efficacy into groups of T-score for women with a previous fracture



All analyses were performed on the intention-to-treat (ITT) populations. The meta-analyses were performed in Review Manager 5 with the random effects model. Details on included studies can be found in Appendix 2. Meta-analyses of efficacy data can be found in Appendix 3. Pooled results from the meta-analysis are shown in Table 1.

Table 1: Efficacy estimates of alendronate used in the model, expressed as RR with 95 % CI in parentheses

	With prevalent vertebral fracture		Without prevalent vertebral fracture			
T- score	**0**	**-1.0**	**-2.0**	**-1.5**	**-2.0**	**-2.5**
Hip	*	*	**0.49** (0.24 to 1.01)	**1**	**1**	**0.44** (0.19 to 1.01)
Vertebral	*	*	**0.55** (0.43 to 0.7)	**0.83** (0.33 to 2.10)	**0.53** (0.27 to 1.03)	**0.50** (0.31 to 0.80)
Wrist	*	*	**0.53** (0.32 to 0.88)	**1.91** (0.95 to 3.82)	**1.32** (0.75 to 2.33)	**0.89** (0.56 to 1.39)

*Not estimable based on included studies.

For hip fractures we were not able to distinguish between the -1.5 and the -2.0 group, the joint point estimate was 1.85 (95% CI 0.69-4.98). The quality of the evidence on hip fractures was graded to be very low for these two groups. In the base case analysis we therefore assumed a relative risk of one for both these groups, in other wordswe assumed that for these groups, alendronate would have no effect on hip fracture risk. In the tornado diagram we varied the efficacy estimate from the lower to the upper end of the 95 % confidence interval.

Because studies that included patients with a previous fracture had a T-score of -2.0 as their inclusion criteria, it was not possible to conduct meta-analyses for T-scores of 0 and -1. Due to this lack of data on efficacy in these groups, we excluded them from the model. Also, there was not sufficient efficacy data to include upper arm fractures in the model.

The analysis was performed in steps; we started with the group that had the highest risk of fracture. If treatment was cost-effective for this group, we continued to the next. The order of our analyses were first the category with previous fracture (T-score less than -2.0), because patients with previous fracture have a higher risk of new fractures than patients without a previous fracture. Because there is a higher risk of fracture with decreasing T-score, the second group we analysed was the group with T-score -2.5 and below. If alendronate was cost-effective also in that strategy, we would continue to analyse the group with T-score between -2.0 and -2.5 and finally the group with T-score between -1.5 and -2.0.

GRADEing the evidence

We evaluated the quality of the evidence for each outcome using the GRADE methodology (38). GRADEing involves assessing the level of confidence we have in the results of the studies based on the current documentation. Each outcome measured in the studies was assessed according to five criteria: type of study, possible limitations in the study design (allocation concealment, blinding and loss to follow up), inconsistency (agreement between studies, heterogeneity), indirectness (transferability to our settings and populations), imprecision (length and placement of confidence interval) and publication bias. More in depth information about the GRADE methodology can be found at the webpage of the Grade working group (39). We based our GRADEing on the study information in Appendix 2 and the meta-analyses found in Appendix 3. GRADE summary of findings tables for the included studies are presented in Appendix 4.

We further incorporated the GRADE assessment into the model by assigning probability distributions related to the quality of the evidence, with a wider spread for the lower quality documentation, *c.f.* probability distributions for efficacy parameters in Appendix 11 and 12.

Compliance

Compliance with the treatment was based on the numbers reported in the RCT's and results from a Danish survey (40).

Safety of alendronate

Based on our review of the literature and our meta-analyses, we did not find any evidence that patients receiving alendronate were more likely to experience side effects than those receiving placebo, *c.f.* Appendix 5.

Duration of treatment

In the base case we modelled five years of treatment. We assumed that the treatment effect would decrease after discontinuation over a period of three years.

EPIDEMIOLOGICAL DATA

For some of the epidemiological data we have performed systematic searches of the literature. Literature searches for epidemiological data can be found in Appendix 6. The epidemiological data was used to determine incidence, mortality and long term health effects of fractures (sequelae). When selecting the epidemiological input data we emphasized the appropriateness of the study design, transferability to Norwegian conditions and control with confounding factors.

Incidence of fractures

Incidence of hip-, vertebral- and wrist-fractures were calculated based on two studies from Oslo and one from Malmo, respectively (41-43). Since incidence of fractures have been shown to vary between urban and rural areas (44-46), we adjusted these estimates using a study from Trøndelag (47). Tables with estimated number of fractures can be found in Appendix 7. Below average bone mineral density will increase the risk of fractures. The associated risk increase with low BMD was based on a review of the literature (48). Women who have experienced a previous fracture will also be at increased risk of new fractures (7). The fracture risk equations were applied to population structure data from Statistics Norway (49).

Mortality

Increased mortality has been observed after both hip- (50-59) and vertebral fractures (52;57;60-64). We chose the study by Vestergaard et al. (53) as input for the excess mortality after both hip and vertebral fractures. As the study had controlled for a number of confounding variables, all excess mortality was assumed to be causally related to the fracture incident. Many studies also reported increased mortality associated with low BMD (65-69). We chose a study from Rotterdam as input for our model (68). The risk equations were applied to data from Statistics Norway (70).

Sequelae

Many people will suffer a permanently impaired functional level after a hip fracture (hip sequela). In our analysis we modelled three kinds of hip sequelae; mild, moderate and severe. A study from Oslo, Norway, analysed sequela after hip fracture (71). In this study the authors reported that among patients without prior sequela, 17% were in nursing home and 56% had reduced walking ability one year after hip fracture. Other publications have similar findings (50;72). We modelled the probability of hip sequelae to vary with age; *c.f.* calculations in Appendix 8. We assumed that 1/3 of the patients would suffer sequela after a vertebral fracture.

Table 2: Baseline epidemiological data for women aged 65

Parameter	Variable name	Variable value	Source
Incidence of hip fracture	tHip	0.00405[1]	Loftus et al. (41)
Adjustment for geographical variation in incidence	RR_hip_Trondelag_vs_Oslo	0.935[1]	Finsen et al. (47) and Loftus et al. (41)
Risk increase associated with low BMD	bmdfr	1.38[1]	Johnell et al. (48)
Risk increase associated with previous fracture	RR_former_fx	1.62	Kanis et al. (7)
Estimated incidence of hip fracture	*tHip*bmdfr*RR_hip_Trondelag_vs_Oslo*RR_former_fx*		
Mortality increase associated with hip fracture	hfrm	1.95	Vestergaard et al. (53)
Mortality causally related to hip or vertebral fracture	Cd	100%	
Mortality increase associated with low BMD	bmdr	1.04	Van der Klift et al. (68)
Age and gender specific mortality	Background_mort	0.00765	Statistics Norway (73)
Estimated mortality after hip fracture	*Background_mort*bmdr*hfrm*Cd*		
Incidence of vertebral fracture	tVertebral	0.00329[1]	Kanis et al. (42)
Incidence of wrist fracture	tWrist	0.01295[1]	Lofthus et al. (43)
Mortality increase associated with vertebral fracture	vfrm	1.95	Vestergaard et al. (53)
Probability of severe hip sequela	pHipSevereSequela_I	0.03549[1]	Osnes et al. (71) and calculations in Appendix 8.
Probability of moderate hip sequela	pHipModerateSequela_I	0.1159[1]	Osnes et al. (71) and calculations in Appendix 8.
Probability of mild hip sequela	1 – pModerate - pSevere		

[1]Varies with age. Value displayed is for the age of 65.

COSTS

Costs in the model are connected to health states and events (transitions). In order to cost the health states and events, we needed to know what actually happens to these patients. Sometimes several treatment options are possible; a patient may for example receive rehabilitation in one of several different places. We then needed to find the probability of the different options, unit price for the different options and in some instances the number of units, for example number of days or number of visits. Costs were therefore collected through a mix of expert opinion, published literature, national tariffs and other sources. Admissions to hospital for different procedures were costed by the DRG system (74). While we used a fee schedule to cost GP visits (75).

Cost of hip fracture event

The cost of a hip fracture event includes costs connected to the surgical procedure, transportation to and from hospital and rehabilitation. In hospital costs were estimated based on the relevant Diagnosis Related Groups (DRG's) and input from expert on the likelihood of the different operations. Re-operations were included. We also costed transportation to and from hospital.

Some hip fracture patients will receive rehabilitation in a hospital. This rehabilitation was costed by expert opinion (76). We assumed that this in hospital rehabilitation would last for 17 days. Others will have rehabilitation a nursing home (77); we assumed that this stay would last for one month. Yet others will receive rehabilitation in a rehabilitation centre. We costed this stay by a report from SINTEF (78) and assumed that this rehabilitation would last for three weeks. All patients are offered physiotherapy after a hip fracture, but we assumed that only one third would actually attend. For this third we assumed 24 visits with a unit cost of NOK 250. Transport to and from physiotherapy was also costed.

Cost of hip fracture sequelae

Moderate sequela was costed by assuming one hour of home help and half an hour of nurse time per week. We costed this based on a study from Trondheim (79). Severe sequela was costed by the cost of nursing home stay (77). Based on a report from the Norwegian Board of Health Supervision (Helsetilsynet) we assumed that patients would spend on average three years in a nursing home before they died (80).

Costs of vertebral fracture

The proportion of vertebral fractures requiring hospitalisation was estimated based on data from the Norwegian patient registry on number of admissions in 2007 coded as DRG 239. Seeing that DRG 239 includes neoplasms, these admissions

were excluded based on the main- and additional diagnoses coded for the fracture admissions. We also excluded all men and all persons below the age of 55 from the dataset. Our estimate is that 28% patients will require hospitalisation after a vertebral fracture. Patients admitted to the hospital were costed by the DRG weight. Patients not hospitalized were assumed to visit their GP.

Cost of wrist fracture

For wrist fractures we assumed that 20% would require surgery. Surgery was costed by DRG 224. The remaining 80% were assumed to visit the emergency room, with 45 % of these requiring replacements. Loss of production was included if the fracture event came before pension age.

Cost of treatment with alendronate

In the base case estimates, we assumed that the BMD was known when treatment was initiated. We have thus not included cost of the initial BMD measurement in the base case estimates. Cost of treatment during the first year only includes drug cost. In the years following treatment initiation, we have also included GP visits and BMD measurements (monitoring the effect of treatment). Costs were discounted at a rate of 4%.

Table 3: Cost of model events, women aged 65

Event	Costs (NOK)
Hip fracture	165 181
Vertebral fracture	18 048
Wrist fracture	9 007

Table 4: Costs of model health states

Health state	Costs (NOK)
Mild hip sequela	324
Moderate hip sequela	22 100
Severe hip sequela	666 138
Vertebral fracture sequela	19 864

Table 5: Costs of treatment with alendronate

Components	Costs (NOK)
Drug cost	832
Cost of GP visit	274
Cost of DXA measurement	450

More details on costs can be found in Appendix 9.

QUALITY OF LIFE

Multipliers connected to Health States and Transition Rewards

We used QALY weights from a recent systematic review by Peasgood et al. (81).

Table 6: QALY weights

	Fracture event	Sequela	Mild sequela	Moderate sequela	Severe sequela
Hip fracture	0.70		0.882**	0.80**	0.66**
Vertebral fracture	0.59	0.934*			
Wrist fracture	0.956				

*Assumption.

**We assumed that the quality of life in the moderate sequela health state would be equal to the mean quality of life in subsequent years after fracture as reported in Peasgood et al. 2009. Mild hip sequela was assumed to be the higher end of the 95% confidence interval and severe sequela the lower end.

Population values

We did not have access to pre-fracture quality of life values for women with osteopenia, osteoporosis and established osteoporosis so we decided to use population values of health related quality of life (HRQL) as an estimate for these variables. We were able to identify two sets of HRQL population values from Sweden (82;83). We chose to use the dataset from Burstrom et al. (74) as this was based on the EQ-5D, the same instrument as the QALY multipliers. Using population values as a proxy for pre-fracture QoL may introduce some bias into our analysis, as "our" group of women may have a lower QoL than the general population due to possible presence of co-morbidity.

Health effects were discounted at a rate of 4% per year.

SENSITIVITY ANALYSES

Most parameters in MOON are uncertain in the sense that we are not confident that they represent the true value. In order to assess the impact of this uncertainty on the results, we conducted a variety of sensitivity analyses.

One-way sensitivity analysis

In a one-way sensitivity analysis, one parameter is changed at a time and the incremental cost-effectiveness ratio (ICER) is recalculated using the possible upper and lower values for the parameter. The upper and lower values can be taken from the upper and lower ends of a 95% confidence interval or by increasing and decreasing the value by a percentage. A tornado diagram is a graphical representation of a range of one-way sensitivity analyses.

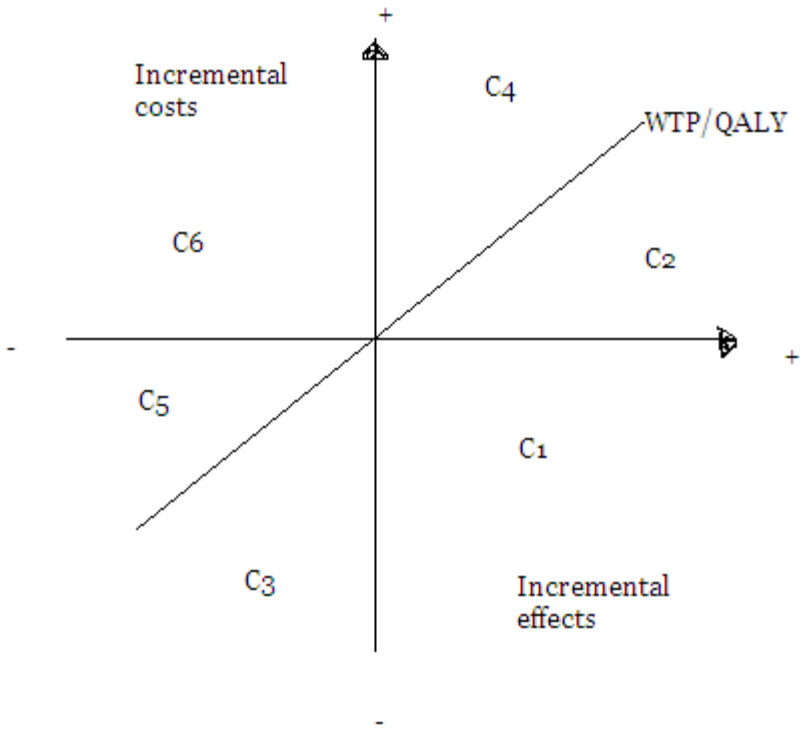
Probabilistic sensitivity analysis

In a probabilistic sensitivity analysis (PSA) the uncertain parameters in the model are represented by distributions and not fixed values. As opposed to one-way sensitivity analysis (like the tornado diagram), all parameters are changed simultaneously in a PSA. We assigned distributions to the parameters according to the methodology described by Briggs et al. (84). Details of the distributions used in MOON can be found in Appendix 11. In Monte Carlo simulations, the computer draws values for each parameter and runs the model for each set of parameters. This is typically done 1 000 or 10 000 times, depending on the number of parameters. Because MOON has several parameters, we chose to use 10 000 iterations. The results of these Monte Carlo simulations can be used to calculate the probability that specific interventions that are cost-effective, if willingness-to-pay (WTP) is given.

For each draw, the ICER is recalculated and plotted on the cost-effectiveness plane (Figure 9). To identify cost-effective points, a component labelling system is used. C1 is where the treatment (here alendronate) is dominant ('superior'), *i.e.* more effective and less costly than the comparator (here calcium and vitamin D). C2 is where the treatment is more costly and more effective, but lies below the WTP. C3 is where the treatment is less costly and less effective, but lies below the WTP. C4 is where the treatment is more costly, and lies above the WTP. C5 is where the treatment is less costly and less effective, and lies above the WTP. C6 is where the treatment is dominated ('inferior'), *i.e.* less effective and more expensive.

Cost-effective points for "alendronate" lie below the WTP line, in components 1-3. The sum of the percentage of points in components C1-C3 is the likelihood that choosing to treat with alendronate in combination with calcium and vitamin D is the cost-effective alternative compared to treatment with calcium and vitamin D alone. The sum of the percentages in components C4-C6 is the likelihood that treatment with calcium and vitamin D is cost-effective compared to treatment with alendronate, calcium and vitamin D.

Figure 9: The cost-effectiveness plane



Value of information

The use of value of information analysis has increased over the last years. The aims of such analyses are to explore which parameters have the largest influence on the conclusions and also parameters for which it might be worth conducting further research. When analyzing the expected value of perfect information for parameters (EVPPI), we grouped parameters in efficacy, compliance, costs, probabilities and utilities. For each of these 5 groups, we first performed 1 000 simulations of the parameters in that group, and for each iteration, we then performed Monte Carlo simulations with 1 000 iterations to calculate expected value of perfect information. It is also possible to do EVPPI on single parameters, but we have not done that in this report because of time constraints.

Budget impact

To estimate the budget impact, we calculated the number of women in each risk group. To calculate the number of women with a given T-score, we used the conversion from Z-score to T-score in Appendix 12 for patients without fracture. For each age group, the T-scores were applied to a standard normal distribution to give a value of the probability of being in that group. These probabilities were multiplied by the size of the female population in the relevant age group to give number of women with the specified T-score.

To get an estimate of the number of osteopenic women with fracture, we multiplied the population by 10 % based on numbers from HUBRO (a health survey from Oslo)

The estimated number of women in each group were multiplied by the annual medication cost of alendronate (NOK 832,-), to give an estimate of how much this would affect the budget. We also calculated additional costs when the cost of one DXA measurement per patient was added (NOK 450,-).

To give an impression of the total impact on health care costs, we also conducted analyses in which we multiplied the number of women in each group by the incremental cost in that group taken from our analyses of cost-effectiveness.

Results

BASE CASE RESULTS

Base case results are presented in Table 7. The results for women with a T-score of -2.0 and no previous fracture are based on an assumption that alendronate has no effect on hip fractures, *c.f.* Table 1.

Table 7: Base case results, costs (in NOK) and QALYs per patient

		No previous fracture				**Previous fracture**	
		Femoral neck T-score					
		-2.0		**-2.5**		**-2.0**	
Age		**No drug**	**Drug**	**No drug**	**Drug**	**No drug**	**Drug**
55	Costs	155 543	159 766	198 789	201 740	188 994	191 917
	QALYs	12.6674	12.6673	12.5877	12.5902	12.6016	12.6048
	ICER	-31 696 092 *(dominated)*		1 143 281		902 539	
65	Costs	181 492	185 938	233 499	231 255	232 546	230 444
	QALYs	9.8901	9.8914	9.8002	9.8146	9.8018	9.8171
	ICER	3 466 358		-156 416 *(dominant)*		-137 561 *(dominant)*	
75	Costs	180 308	184 518	234 172	213 213	246 081	226 395
	QALYs	6.5826	6.5878	6.4801	6.5390	6.4621	6.5207
	ICER	814 292		-355 860 *(dominant)*		-335 514 *(dominant)*	

For patients at the lowest risk of fractures (55 years, T-score -2.0, no previous fracture), alendronate results in somewhat lower QALYs than no alendronate and higher costs, this makes alendronate a dominated strategy. For patients at the highest risk of fracture (75 years, T-score -2.0, with previous fracture), alendronate both in-

creases QALYs and decreases costs compared to no alendronate, which makes alendronate a dominant strategy for patients in this group.

The incremental QALYs of using alendronate increase with age and with increasing risk within the same age group in most cases. In other words, alendronate is more likely to be considered cost-effective for older women and women with higher fracture risk.

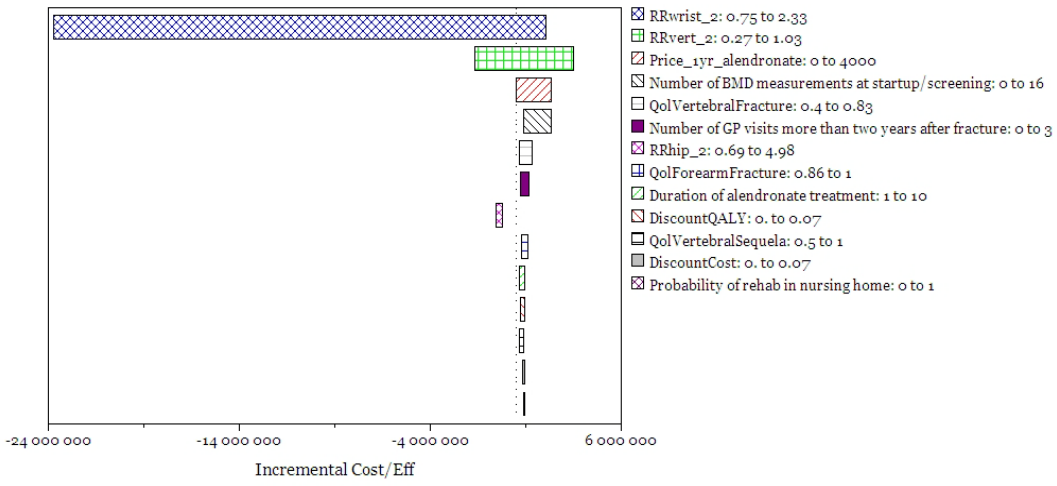
DETERMINISTIC SENSITIVITY ANALYSES

Tornado diagram

A tornado diagram illustrates the impact of a series of one way sensitivity analyses, *i.e.* one parameter is changed at a time. The bars are ordered according to the impact the parameter change has on the ICER. In Figure 10, the vertical dotted line represents the assumed willingness-to-pay per QALY of NOK 500 000. Bars that cross the dotted line represent uncertainty that changes the decision. The ordering of the parameters is sensitive to the upper and lower values chosen for the different variables.

We chose to perform a tornado analysis on women aged 75 with a T-score of -2.0 and no previous fracture. The reason for this is that this is the group where the conclusion, whether or not alendronate can be considered cost-effective, seems to be most uncertain because the base case ICER is closest to the WTP (NOK 844 292). The result of the sensitivity analysis is illustrated in Figure 10.

Figure 10: Tornado diagram for women aged 75, with a T-score of -2.0 and no previous fracture



As illustrated in Figure 10 the results for this group are most sensitive to changes in the efficacy estimates of alendronate on hip-, wrist- and vertebral fractures. This is perhaps not surprising, since all efficacy estimates for this group are insignificant. The lower end of the confidence interval thus represents a situation where alendro-

nate reduces the risk of fracture while the upper end represents a situation where alendronate will increase fracture risk.

Although all changes in input parameters will have some impact on the estimated ICER, only changes in the efficacy parameters have the potential to change the conclusion for this group.

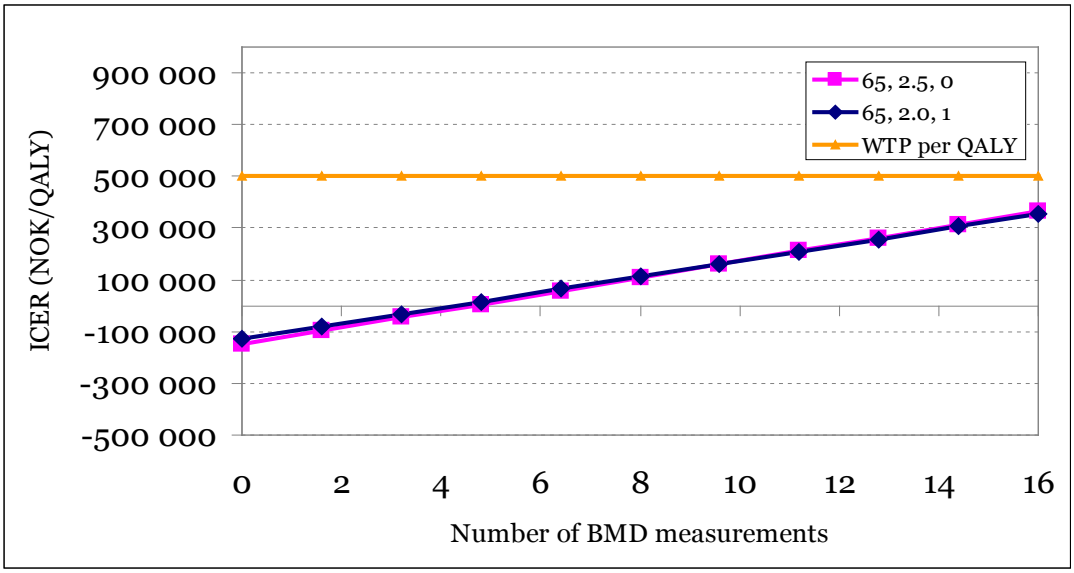
In Figure 10, the sensitivity of the ICER for changes in the efficacy on hip fractures is underrepresented. The reason for this is that varying the input from the lower to the upper end of the 95% confidence interval has a dramatic effect on the ICER. For the lower end (RR=0.69) alendronate will be dominant (i.e. more effective and cost-saving) and for the upper end (RR=1.44) alendronate will be dominated (i.e. less effective and more expensive). In other words both ICERs are negative, but they represent two opposite situations, *c.f.* Figure 9 and the difference between quadrant C1 and quadrant C6.

One-way sensitivity analyses

On the number of BMD measurements per woman treated

If the guideline for osteoporosis is changed to include women with lower risk of fractures, it is possible that GPs will request more BMD tests. In our initial analysis, we assumed that all testing of women is independent of what is stated in guidelines. If we however assume that number of women tested is dependent on what the guidelines say, and in addition, guidelines are directly based on our guidelines. Then we would have to include an increased use of BMD measurements in our model. In figure 11, we have varied the number of BMD measurements taken from 0 to 16 per woman treated. These sensitivity analyses indicate that the conclusions were robust because no lines crossed assumed WTP line.

Figure 11: One-way sensitivity on number of BMD measurements per woman treated



In calculating the base case we assumed that the women were already fully evaluated before they entered the model, so the base-case input is 0. We only included in the plot the groups that were likely to be sensitive, *e.g.* when the conclusion did not change for the 65 years old, we knew that the results for the 55 years old would also be robust.

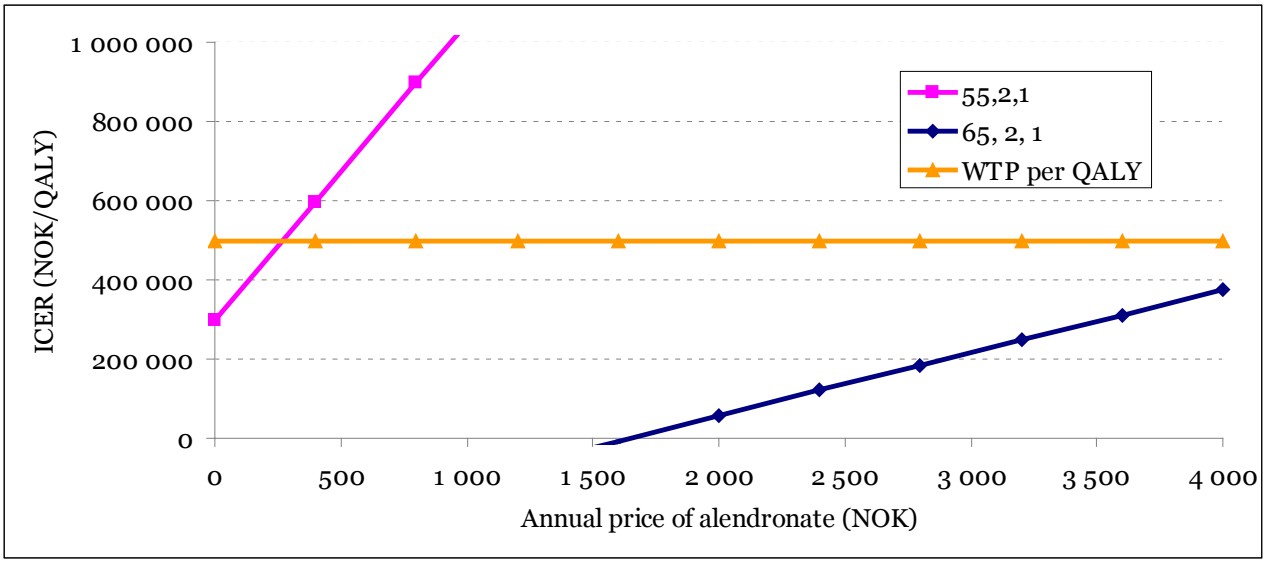
Women aged 55 were not included in the plot as they were unlikely to be considered cost-effective in the base case. The same reasoning applied to women with a T-score of -2.0 and a previous fracture.

On the price of alendronate

We also conducted sensitivity analyses on the annual price of alendronate.
The price was varied from 0 and up to the price of alendronate before the introduction of generic competition. The results are illustrated in Figure 12. The analysis indicates that alendronate would be cost-effective for women aged 55 with a T-score of -2.0 with a previous fracture if the price of alendronate was reduced further.

The analysis also indicates that alendronate was cost-effective for 65 years old with a T-score of -2.0 with a previous fracture even before the price reduction.

Figure 12: One way sensitivity on the annual price of alendronate for women with a T-score of -2.0 with a previous fracture



PROBABILISTIC SENSITIVITY ANALYSIS

Incremental cost-effectiveness scatter plots

The results presented in Table 8 to 10 are based on an assumed willingness-to-pay per quality-adjusted life-year (QALY) of NOK 500 000. Components C1-C6 in the tables corresponds to the quadrants in the cost-effectiveness plane (Figure 9). C1-C3 is situations in which alendronate in combination with calcium and vitamin D is cost-effective compared to calcium and vitamin D alone.

Results for women aged 55, 65 and 75 years old with a T-score of -2.0 and no previous fracture

Table 8 displays the results of the Monte Carlo simulation for women aged 55, 65 and 75 years old with a T-score of -2.0 with no previous fracture.

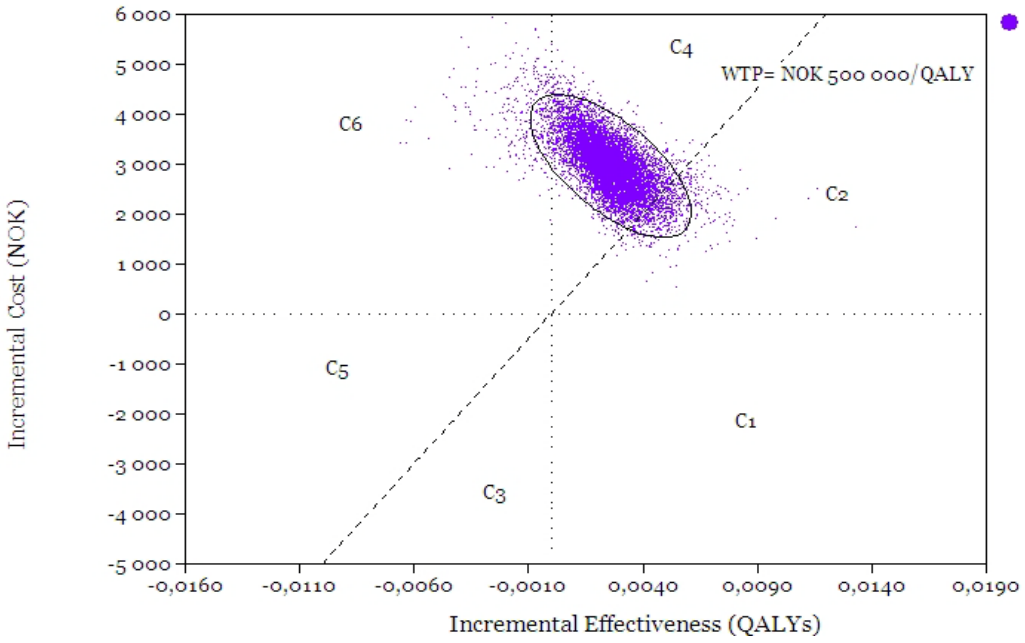
Table 8: Results for women with a T-score of -2.0 and no previous fracture

Component	Incr. Eff.	Incr. Cost	ICER	55- years old	65- years old	75- years old
C1	IE>0	IC<0	Dominant	0 %	0 %	0.06%
C2	IE>0	IC>0	<500 000	0.01%	7.67%	36.85%
C3	IE<0	IC<0	>500 000	0 %	0 %	0 %
C4	IE>0	IC>0	>500 000	54.98%	61.59%	46.89%
C5	IE<0	IC<0	<500 000	0 %	0 %	0 %
C6	IE<0	IC>0	Dominated	45.01%	30.74%	16.2%
∑ C1-C3	**Percentage alendronate cost-effective**			**0%**	**8 %**	**37%**

For women aged 55 there is a 45 % probability that alendronate will be dominated, *i.e.* be more expensive and less effective than calcium and vitamin D. The reason for this is that wrist fractures, the most incident fracture in this age group, in fact have a negative efficacy estimate for this group (RR=1.32, 95 % CI= 0.75-2.33). The estimated efficacy on vertebral fractures is however positive, so as the incidence of these fractures increases with age, the probability that alendronate will be cost-effective will also increase.

For women with a T-score of -2.0 with no previous fracture, the probability that alendronate is cost-effective compared to calcium and vitamin D varies from 0 % for women aged 55 years old to 37 % for women aged 75 years old, assuming a willingness-to-pay of NOK 500 000 per QALY. Figure 11 gives a graphical presentation of the simulated points on the cost-effectiveness plane for women aged 75 years old.

Figure 13: Cost-effectiveness scatter plot for women aged 75 with no previous fracture



Results for women aged 55, 65 and 75 years old with a T-score of -2.5 and no previous fracture

Results for women with a T-score of -2.5 are shown in Table 9. For women with a T-score of -2.5, the probability that alendronate is cost-effective for women aged 55 is 7 %. In 90 % of the simulations alendronate is more effective and more expensive than the comparator for this group, but the ICER is above the assumed willingness-to-pay per QALY of NOK 500 000.

Table 9: Women with a T-score of -2.5 and no previous fracture

Component	Incr. Eff.	Incr. Cost	ICER	55- years old	65- years old	75- years old
C1	IE>0	IC<0	Dominant	0 %	79.04%	93.09%
C2	IE>0	IC>0	<500 000	6.64%	13.73%	2.3%
C3	IE<0	IC<0	>500 000	0 %	0 %	0 %
C4	IE>0	IC>0	>500 000	89.87%	4.98%	1.41%
C5	IE<0	IC<0	<500 000	0 %	0 %	0 %
C6	IE<0	IC>0	Dominated	3.49%	2.25%	3.2%
∑ C1-C3	**Percentage alendronate cost-effective**			**7 %**	**93 %**	**95 %**

For women aged 65, alendronate has a probability of 93 % of being cost-effective. In 79 % of the simulations alendronate is both more effective and less expensive than the comparator for this group.

For women aged 75, alendronate has a 95 % probability of being cost-effective. In 93 % of these cases, alendronate is both more effective and less costly than calcium and vitamin D. In 2 % of the cases alendronate is more expensive than calcium and vitamin D, but the estimated ICERs are below the assumed willingness-to-pay.

Results for women aged 55, 65 and 75 years old with a T-score of -2.0 with a previous fracture

Results for women with a T-score of -2.0 with a previous fracture are shown in Table 10. For women aged 55 years old, with a T-score of -2.0 who has suffered a previous fracture, alendronate has a 9 % probability of being cost-effective. For women aged 65 years old, alendronate has a probability of 94 % of being cost-effective. In 78 % of these cases, alendronate is both more effective and less expensive than calcium and vitamin D.

Table 10: Women with a T-score of -2.0 with a previous fracture

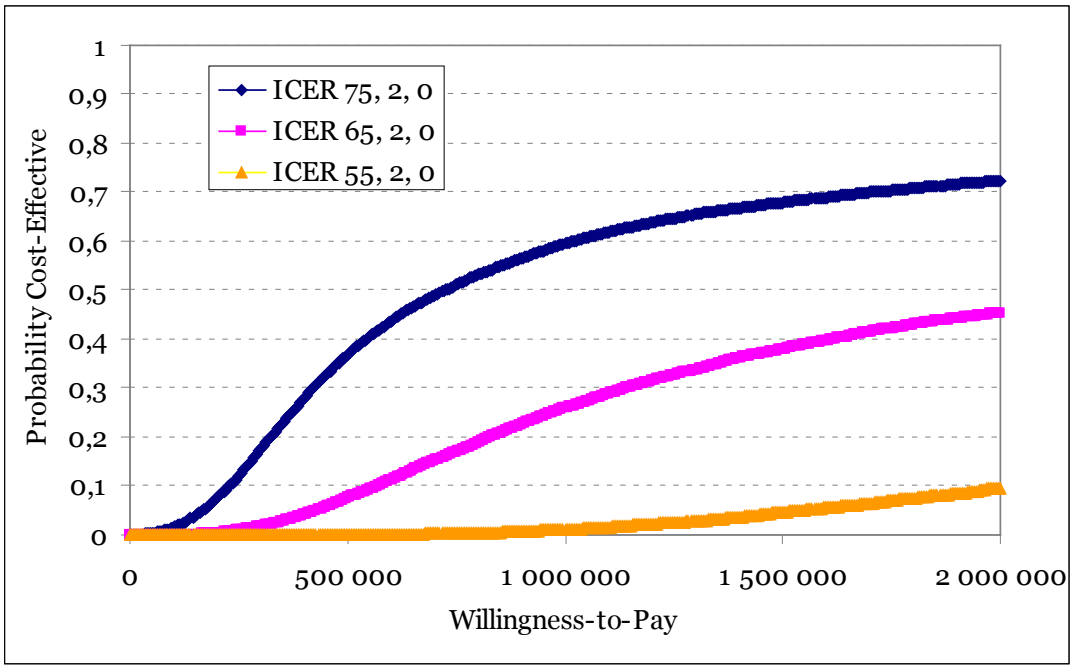
Component	Incr. Eff.	Incr. Cost	ICER	55-years old	65-years old	75-years old
C1	IE>0	IC<0	Dominant	0 %	77.55%	93.03%
C2	IE>0	IC>0	<500 000	8.93%	16.46%	2.67%
C3	IE<0	IC<0	>500 000	0 %	0 %	0 %
C4	IE>0	IC>0	>500 000	90.08%	4.37%	1.64%
C5	IE<0	IC<0	<500 000	0 %	0 %	0 %
C6	IE<0	IC>0	Dominated	0.99%	1.62%	2.66%
∑ C1-C3	**Percentage alendronate cost-effective**			**9 %**	**94 %**	**96 %**

Cost-effectiveness acceptability curves

In Tables 8-10 we assumed that the willingness-to-pay per QALY is NOK 500 000. We also assessed to what degree the conclusions were sensitive to changes in willingness-to-pay by varying this from NOK 0 to NOK 2 000 000.

Figure 14 illustrates the effect of changing the willingness-to-pay per QALY on the estimated ICERs for women with a T-score of -2.0 and no previous fracture.

Figure 14: Cost-effectiveness acceptability curves for women aged 55, 65 and 75 years old with a T-score of -2.0 and no previous fracture

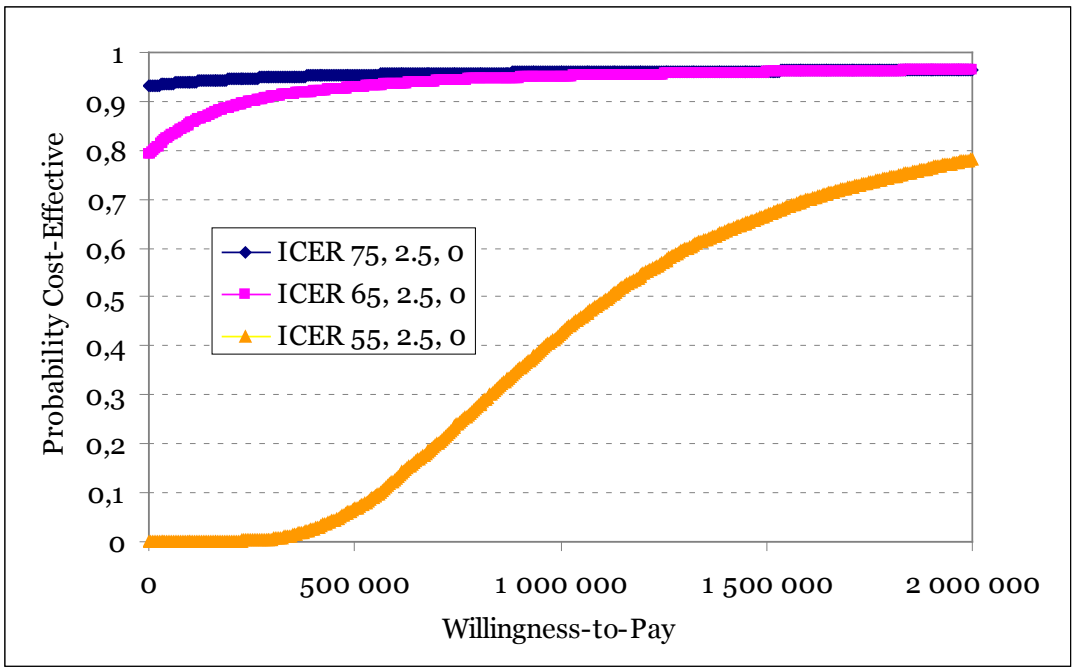


For women aged 55 with T-scores of -2.0 and no previous fracture, the conclusion is not changed by varying the willingness-to-pay. Varying the willingness-to-pay per QALY from NOK 0 to NOK 2 000 000 will only increase the likelihood that alendronate is cost-effective from 0 to 10 % for this group. For women aged 65, the probability that alendronate is a cost-effective strategy varies from 10 % to 45 % when the willingness-to- pay increases from NOK 500 000 per QALY to NOK 2 000 000 per QALY. For women aged 75, the probability that alendronate is cost-effective increases from 37 % at a willingness-to-pay of NOK 500 000, to 72 % at a WTP of NOK 2 000 000.

Figure 15 illustrates the effect of changing the willingness-to-pay per QALY on the estimated ICERs for women with a T-score of -2.5 and no previous fracture. For women aged 65 and 75, the conclusion is insensitive to changes in the willingness-to-pay. The reason for this is that alendronate for these groups is a dominant strategy (with a likelihood of 79 % of being cost-effective for the 65 years old and 93 % for

the 75 years old), since alendronate is cost-saving, the decision is independent of WTP, *c.f.* quadrant C1 in Figure 9.

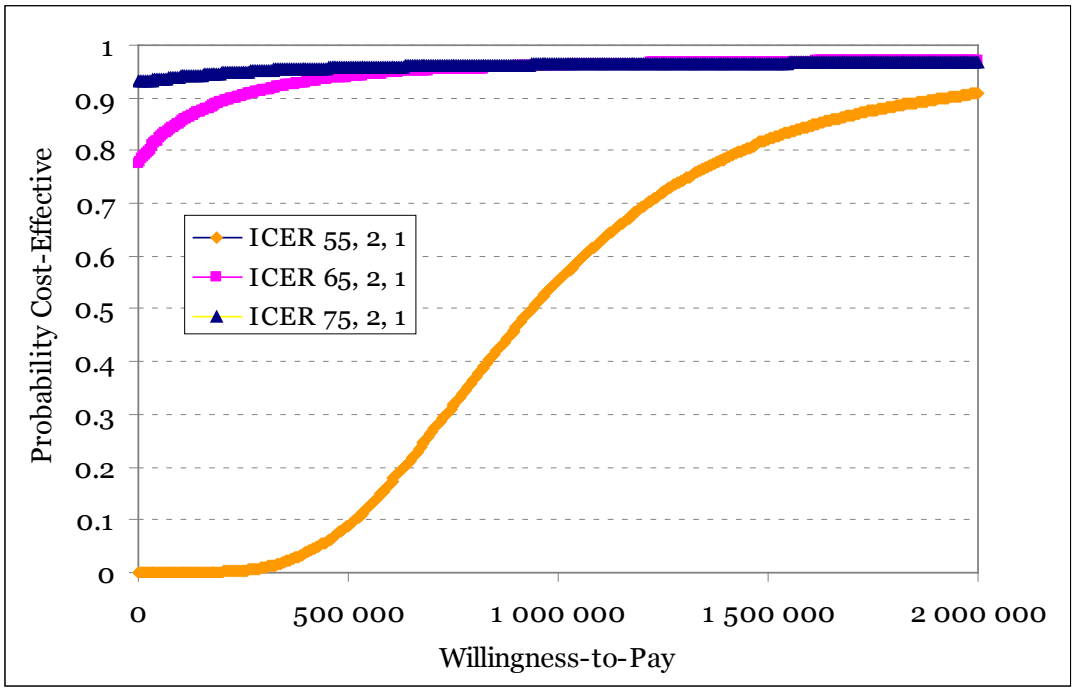
Figure 15: Cost-effectiveness acceptability curves for women aged 55, 65 and 75 years old with a T-score of -2.5.



For women aged 55 with a T-score of -2.5, the conclusion is highly sensitive to changes in WTP. As the WTP is increased from NOK 500 000 to NOK 2 000 000 the probability that alendronate is cost-effective increases from 7 % to 78 %.

Figure 16 illustrates the effect of changing the willingness-to-pay per QALY on the estimated ICERs for women with a T-score of -2.0 and a previous fracture. The pattern here is very similar to the one for women with T-score of -2.5. For women aged 65 and 75 the conclusion is insensitive to changes in the WTP, although the percentages changes a little. For women aged 55 years old, however, the decision is highly sensitive to the assumed willingness-to-pay per QALY. When the WTP is varied from NOK 500 000 to NOK 2 000 000, the likelihood that alendronate is a cost-effective option increases from 9 % to 92 %.

Figure 16: Cost-effectiveness acceptability curves for women aged 55, 65 and 75 years old with a T-score of -2.0 with a previous fracture



BUDGET IMPACT

Our budget impact analyses indicate that it would cost NOK 62.5 million to treat all groups of women that are cost-effective according to our analyses (shaded in table 11). This analysis is only based on medication cost (value added tax included) of one year of alendronate.

Table 11: Budget impact based on 2009 numbers (drug cost only).

	Number of women in thousands			Yearly alendronate costs per group in thousands (NOK)		
	With no previous fracture		With a previous fracture	With no previous fracture		With a previous fracture
T-score / Age group	(-2.0,-2.5)	(-2.5,->)	(-2.0,-2.5)	(-2.0,-2.5)	(-2.5,->)	(-2.0,-2.5)
55-64	18	15	9	14 600	12 500	7 500
65-74	9	13	12	7 800	10 900	9 700
75,->	14	30	21	12 000	24 700	17 200

In Table 12, we have calculated expected costs of alendronate AND one DXA measurement per patient. The costs of treating the same groups of women would then be NOK 96.3 million.

Table 12: Budget impact based on 2009 numbers (alendronate and one DXA measurement per one woman treated).

	Number of women in thousands			Yearly alendronate costs per group (in thousands NOK)		
	With no previous fracture		With a previous fracture	With no previous fracture		With a previous fracture
T-score / Age group	(-2.0,-2.5)	(-2.5,->)	(-2.0,-2.5)	(-2.0,-2.5)	(-2.5,->)	(-2.0,-2.5)
55,->	18	15	9	22 500	28 400	11 600
65,->	9	13	12	12 000	16 800	14 900
75,->	14	30	21	18 400	38 100	26 500

In addition to budget impact analyses based only on alendronate costs, we also performed analyses based on results from cost-effectiveness analyses (Table 13). Based on these analyses, treatment with alendronate seems to reduce health care costs by several million kroner, particularly in older age groups (shaded groups cost-effective or dominant compared to no treatment).

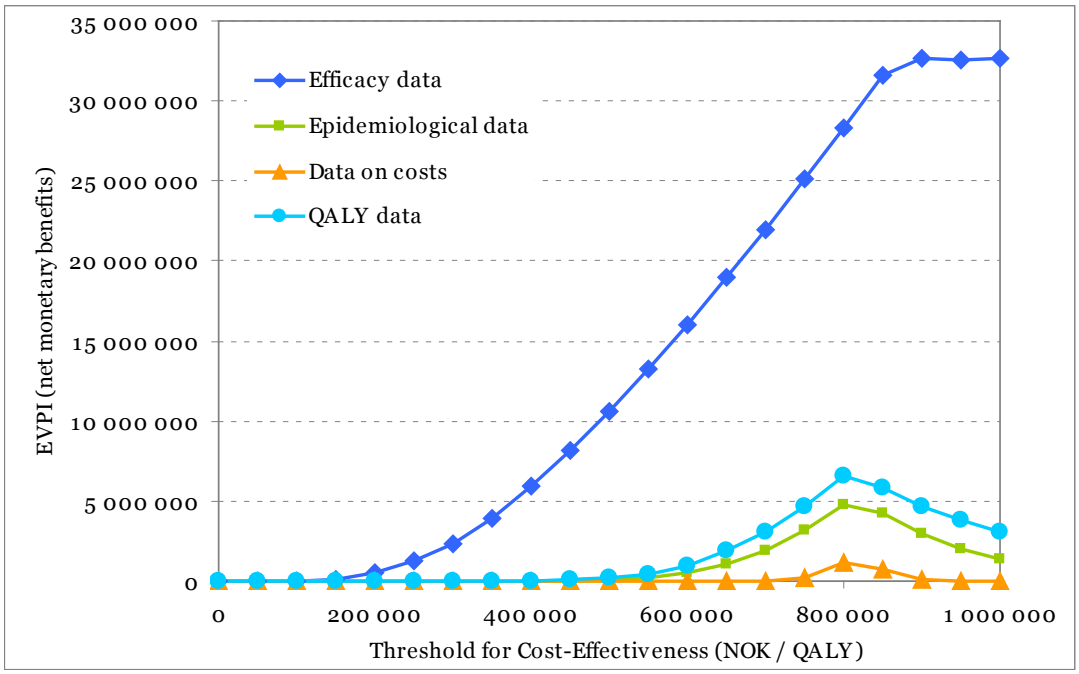
Table 13 :Budget impact based on cost-effectiveness analyses

	Number of women (in thousands)			Incremental costs per age group (in thousands NOK)		
	With no previous fracture		With a previous fracture	With no previous fracture		With a previous fracture
Age	**(-2.0,-2.5)**	**(-2.5,->)**	**(-2.0,-2.5)**	**(-2.0,-2.5)**	**(-2.5,->)**	**(-2.0,-2.5)**
55-64	18	15	9	74 000	44 200	26 500
65-74	9	13	12	41 600	-27 500	-26 100
75,->	14	30	21	-60 600	-622 900	-406 300

VALUE OF INFORMATION ANALYSIS

We performed EVPPI to explore whether it was worth spending money on further research. Analyses were performed with 1 000 x 1 000 Monte Carlo simulations. In Figure 17 population EVPPI is plotted against the assumed Norwegian threshold for cost-effectiveness (NOK 500 000 per QALY). The calculation of population EVPPI is based on the assumption that alendronate will be the most effective generic drug for another four years. The population numbers used are calculated on the basis of numbers shown in Table 11.

Figure 17: EVPPI for women aged 75 years old with a T-score of -2.0 and no previous fracture



From Figure 17 it is evident that efficacy is the group of parameters that would benefit most from more research. The net benefit of eliminating the uncertainty related to the efficacy of alendronate for this group is NOK 10.6 million, assuming a willingness-to-pay per quality-adjusted-life-year of NOK 500 000. Further research on costs, utilities and epidemiological factors are unlikely to be beneficial for this group at this level of WTP.

The results from the EVPPI can also be read as an estimate of which group of parameters the decision is most sensitive to. In this case the decision is most sensitive to the efficacy parameters.

Discussion

We have conducted a systematic review and a model based economic evaluation of alendronate for the prevention of fractures in postmenopausal women in Norway.

SUMMARY OF RESULTS

According to our analysis, treatment with alendronate is likely to be cost-effective for women aged 65 and 75 with a T-score of -2.5 without a previous fracture and -2.0 with a previous fracture. For these groups alendronate is not only cost-effective, but also dominant, *i.e.* treatment with alendronate yields larger health gains than no treatment and is also cost-saving.

The conclusions are most uncertain for women aged 75 with T-score -2.0 and no previous fracture and women aged 55 with a T-score of -2.0 with a previous fracture, assuming a Norwegian willingness-to-pay per QALY of NOK 500 000. Relatively small changes in the input parameters or in the threshold value can change the conclusion for these groups. Conclusions for women aged 55 with a T-score of -2.5 with no previous fracture and -2.0 with a previous fracture are very sensitive to the threshold value. Assuming a WTP of NOK 500 000 it is unlikely that treating these groups can be considered cost-effective, but the probability that treatment is likely to be considered cost-effective increases rapidly with increasing WTP.

According to the analysis of perfect information on parameters, the conclusion for women aged 75 with a T-score of -2.0 and no previous fracture is very sensitive to the efficacy estimates of alendronate. For these women, efficacy estimates on wrist fractures are non-significant and we also did not have enough information to assign an efficacy estimate on hip fractures. Further research on the clinical efficacy of alendronate for this group of women will have a large impact on the conclusion.

We find alendronate to be dominant, *i.e.* more effective and cost saving for the women analysed aged 75 and for women aged 65 with a T-score -2.0 and a previous fracture and for 65 year old women with a T-score of -2.5 without a previous fracture. Treating these groups has the potential to result in large savings for the Norwegian health care system.

Whether or not to treat women aged 55 with a T-score of -2.5 without a previous fracture or with a T-score of -2.0 with a previous fracture (here the results from the clinical efficacy part of our review implies that alendronate is efficacious) or women aged 75 with a T-score of -2.0 and no previous fracture is dependent on how much society is willing to pay for a quality adjusted life year. It is unlikely that treating these groups can be considered cost-effective assuming a willingness-to-pay of NOK 500 000. However at a willingness-to-pay of 1 million, these conclusions are more uncertain.

It should also be noted that the age intervals between cost-effective- and non cost-effective groups in our analysis is 10 years which can be regarded as a wide time interval. When reimbursement agencies will decide which patient groups to reimburse in Norway, they are advised to interpolate the recommended thresholds for medical intervention if the person's age is close to the next (or former) age category. This means the treatment guidance and information on when a treatment is cost-effective cannot be considered as absolute for the age- and risk groups included in our analysis.

LIMITATIONS

Transferability of efficacy data

There may be a question as to whether the efficacy data are transferrable to a Norwegian setting. Given that the incidence of fractures is higher in Norway than in other countries, we find it likely that the efficacy of alendronate is transferable to a Norwegian setting, but possibly underestimated based on the RCTs. Vertebral fracture efficacy is based on a mix of morphometric and clinical fractures.

In the FIT studies, women were treated with 5 mg alendronate daily for 24 months (average follow up 2.9 years). The dosage was then changed when it became apparent that 10 mg had a higher effect than 5 mg. Due to the low initial dosage, alendronate may be somewhat more efficacious than shown in the FIT study.

The quality of the efficacy documentation

We find it very likely that alendronate is cost-effective for women aged 65 and 75 with a T-score of less than -2.5 and no previous fracture and for women with a T-score of less than -2.0 without a previous fracture. For these groups, only the documentation of efficacy on vertebral fractures is of high quality. For women with a T-score of less than -2.5 without a previous fracture, only the efficacy on vertebral fractures is statistically significant. For women with a T-score of less than -2.0 with a previous fracture, efficacy estimates on vertebral and wrist fractures are statistically significant, but not the ones on hip fractures.

We have therefore included the whole range of the confidence interval in the model and also the quality of the efficacy documentation as assessed with GRADE. The cost-effective groups are cost-effective in spite of the fact that alendronate only has low quality documentation and statistically insignificant effect on hip fractures, which is the fracture that has the largest impact on both costs and health outcomes in our model.

For women with a T-score above -2.5 with no previous fracture, the efficacy documentation is of low or very low quality. All results for these groups are statistically insignificant. Alendronate only has a positive point estimate on vertebral fractures for the group with a T-score between -2.0 and -2.5 (RR=0.53, 95% CI 0.27-1.03). Due to the lack of demonstrated clinical efficacy for these groups, alendronate is unlikely to be a cost-effective alternative. The one possible exception is women aged 75 with a T-score between -2.0 and -2.5. For this group the possible effect on vertebral fractures can make alendronate cost-effective, but only if society is willing to pay more than commonly assumed for health gains.

Fractures included in the analysis

We have only modelled three types of fractures, *i.e.* the hip, wrist and spine. In reality low bone mineral density will increase the risk of many types of fractures; we may therefore have underestimated the health effects of treatment with alendronate. We have for example not included fractures of the upper arm. A complicated fracture of the upper arm costs NOK 84 105 in the first year after fracture and might have given other cost-effectiveness results if included in our model-analysis (85).

Safety of alendronate

We did not include any health effects or costs associated with side effects in the model. One reason for this was that we were not able to find any evidence of side effects in the included randomised controlled trials (see meta-analyses of side effects in Appendix 5). Randomised controlled trials are an appropriate study design for common, anticipated side effects, but not necessarily for rare side effects, side effects that are more likely to occur in subpopulations or side effects that take long to develop (86). There have been reports from observational studies that long term use of alendronate induces an increased risk of subtrochanteric stress fractures (87-90). Alendronate has also been reported to be associated with an increased risk of osteonecrosis of the jaw (91-99).

Side effects can also be related to poor compliance, *i.e.* failing to take the drug in the prescribed manner. Alendronate has a very strict intake regime involving not laying down for thirty minutes, drinking a minimum amount of water, intake while fasting etc. Compliance with alendronate is higher in patients receiving adequate informa-

tion and motivation by their doctor. It is therefore likely that patients in the RCT's were more compliant than the average patient will be in "real life".

Case finding

We have not included risk factors other than BMD, age and previous fracture in our model. Inclusion of risk factors such as maternal hip fracture, smoking and low body mass index is possible at a later time. Although we have done sensitivity analyses on the number of women screened per one woman treated, this evaluation is not a "screen and treat" analysis.

COMPARISON WITH RECENT ECONOMIC EVALUATIONS OF ALENDRONATE

A large amount of studies have been published on the cost-effectiveness of alendronate. A full review of all published studies on the cost-effectiveness of alendronate for the prevention of fractures in postmenopausal women is outside the scope of this project, below we present the conclusions from a few other studies from Scandinavia and one from Minnesota.

Strøm et al. assessed the cost-effectiveness of alendronate vs. dietary supplements in nine European countries, Belgium, Denmark, France, Germany, Italy, Spain, UK , Sweden and Norway (100). They analysed the intervention for women with BMD equal to or less than -1.6 and prior vertebral fracture and women with BMD equal to or less than -2.4 and no prior fracture. They found alendronate to be cost saving (dominant) in Norway for both groups using an annual price of alendronate of € 502.

A recent review of the literature by Fleurence et al. (101) identified two studies (30;102) on the cost-effectiveness of alendronate in postmenopausal women in a Scandinavian population. The study by Johnell et al. found alendronate to be cost-effective for women aged 71 with low BMD and a previous fracture (102). Christensen et al. found alendronate to be cost-effective for women aged 71 with a fracture risk twice that of the average Danish population (30).

A study from Minnesota analysed the cost-effectiveness of alendronate for women 55, 65 and 75 years old without previous fractures and with T-scores -1.5, -2.0 and -2.5 (103). They found alendronate not to be cost-effective in a US setting. Their calculatios were however based on an annual price of alendronate of $ 842 (approximately NOK 5 052), a price higher than what we have included in our sensitivity analyses on price.

NEED FOR FURTHER RESEARCH

Based on our EVPPI analyses, it would be rational to conduct an RCT of alendronate vs. no treatment in 75-year old postmenopausal women with T-score of -2.0 and no previous fracture if research would cost less than NOK 10.6 million. We conclude that the value of further research on the clinical efficacy of alendronate in low risk groups is still high.

QALY weights were the next group of parameters that might be worthwhile to research further, followed by epidemiological data.

Conclusions

Assuming a willingness-to-pay per QALY of NOK 500 000, alendronate is likely to be cost-effective for women with a T-score of -2.5 without fracture and with a T-score of -2.0 and a previous fracture, for women aged 65 and 75.

The lack of efficacy data for women with a T-score above -2.5 without a previous fracture makes the inferences for these groups uncertain.

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Appendices

APPENDIX 1: SEARCH FOR EFFICACY

Search 1: Efficacy of alendronate

Oppdateringssøk for Cochraneoversikt fra 2008

Wells GA, Cranney A, Peterson J, Boucher M, Shea B, Robinson V, Coyle D, Tugwell P. Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD001155. DOI: 10.1002/14651858.CD001155.pub2.

Database: Ovid MEDLINE(R) <1950 to February Week 3 2008>

Search for: limit 36 to yr="2007 - 2008"
Results: 76 stk RCT 'er (markert som SOK: Cochrane review oppdateringssøk_RCT)
Results: 4 stk systematiske oversikter (markert som SOK: Cochrane review oppdateringssøk_rev)

---

1 osteoporosis, postmenopausal/
2 osteoporosis/
3 osteoporosis.tw.
4 exp bone density/
5 bone loss$.tw.
6 (bone adj2 densit$).tw.
7 or/2-6
8 menopause/
9 post-menopaus$.tw.
10 postmenopaus$.tw.
11 or/8-10
12 7 and 11
13 1 or 12
14 alendronate/
15 alendronate.tw,rn.

16 fosamax.tw.
17 aminohydroxybutane bisphosphonate.tw.
18 or/14-17
19 13 and 18
20 meta-analysis.pt,sh.
21 (meta-anal: or metaanal:).tw.
22 (quantitativ: review: or quantitativ: overview:).tw.
23 (methodologic: review: or methodologic: overview:).tw.
24 (systematic: review: or systematic: overview).tw.
25 review.pt. and medline.tw.
26 or/20-25 (48635)
27 19 and 26 (55)
28 clinical trial.pt.
29 randomized controlled trial.pt.
30 tu.fs.
31 dt.fs.
32 random$.tw.
33 (double adj blind$).tw.
34 placebo$.tw.
35 or/28-34
36 19 and 35 (812)
37 limit 36 to yr="2007 - 2008" (76) RCT (er markert som: i RefMan)
38 limit 27 to yr="2007 - 2008" (4) SO (er markert som: i RefMan)

Cochrane Library:

1 osteoporosis, postmenopausal/
2 osteoporosis/
3 osteoporosis:ti,ab,kw
4 exp bone density/
5 bone next loss*:ti,ab,kw
6 bone NEAR/2 densi*:ti,ab,kw
7 or/2-6
8 menopause/
9 post-menopaus$.tw.
10 postmenopaus$.tw.
11 or/8-10
12 7 and 11
13 1 or 12
14 alendronate/
15 alendronate.tw,rn.
16 fosamax.tw.
17 aminohydroxybutane bisphosphonate.tw.
18 or/14-17
19 13 and 18

Restricted to 2007-2008

Fant 10 referanser i Clinical Trials

Søk 1 (utført den 170308)

Database: Cochrane Library (Issue 1, 2008)
Sok: 1

#1 MeSH descriptor Osteoporosis, this term only 1060
#2 MeSH descriptor Bone Density explode all trees 2535
#3 (bone next loss* or osteoporosis):ti,ab,kw or (bone near/2 densi*):ti,ab,kw 5425
#4 (#1 OR #2 OR #3) 5425
#5 MeSH descriptor Alendronate, this term only 363
#6 (alendronate or fosamax):ti,ab,kw or "aminohydroxybutane bisphosphonate":ti,ab,kw 445
#7 (#5 OR #6) 445
#8 (#4 AND #7) 399
#9 (men or man or males or male):ti,ab,kw
#10 (#8 AND #9) 95

Treff:
CR: 1 stk (CochraneReviews170308)
Other Reviews: 1 stk (Otherreviews170308)
Clinical Trials: 91 stk (ClinicalTrials170308)
Methods Studies: 0 stk
Technology Assessments 0 stk
Economic Evaluations 2 stk (EconomicEvaluations170308)

Tilsammen 95 treff i Cochrane Library

Søk 1 i Medline (140308):
Database: Medline140308
Sok: 1

1. osteoporosis/
2. osteoporosis.tw.
3. exp bone density/
4. bone loss*.tw.
5. (bone adj2 densi*).tw.
6. or/1-5

7. alendronate/
8. alendronate.tw.
9. fosamax.tw.
10. (aminohydroxybutane adj bisphosphonate).tw.
11. or/7-10
12. 6 and 11
13. men.tw.
14. male.tw.
15. Male/
16. (man or males).tw.
17. 13 or 14 or 15 or 16
18. 12 and 17
19. Animals/
20. Humans/
21. 19 not (19 and 20)
22. 18 not 21

APPENDIX 2: SUMMARY INFORMATION ON INCLUDED EFFICACY STUDIES

Table 14: Summary information on included efficacy studies

Study	Country	Population size (n)	Allocation concealment	Blinding	Follow-up period
Black et al. 1996 (FIT) (104)	USA	Treatment=1022 Control=1005 Total=2027	Adequate-A	Double blind identical placebo	3 yr
Cummings et al. 1998 (FIT) (105)	USA	Treatment=2214 Control=2218 Total=4432	Adequate-A	Double blind	4 yr
Liberman et al. 1995 (106)	US Australia Canada Europe Israel Mexico New Zeland South America	Treatment=597 Control=397 Total=994	Unclear-B	Double blind	3 yr

APPENDIX 3: META-ANALYSES OF EFFICACY

Figure 18: Efficacy of alendronate on vertebral fractures

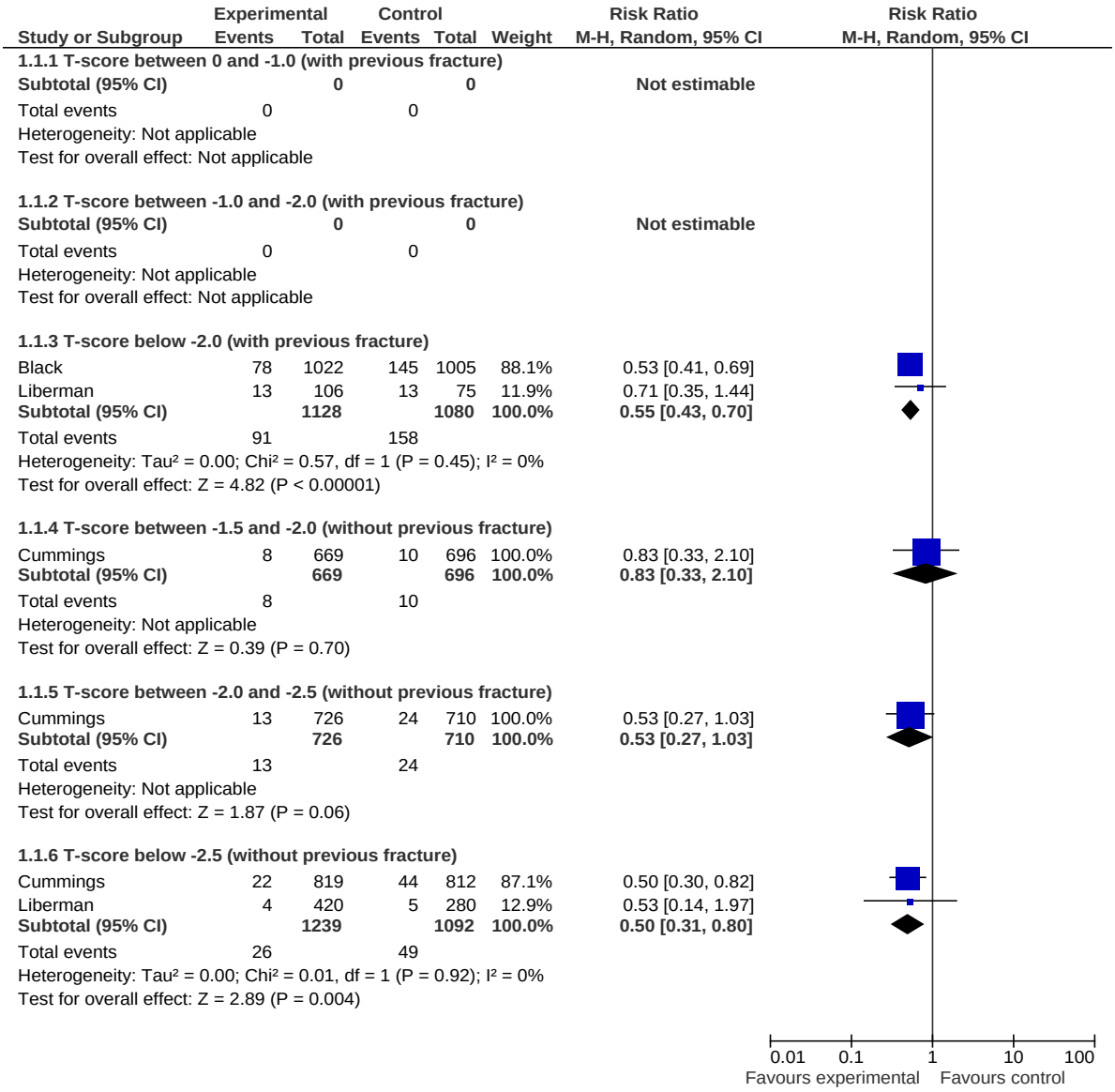


Figure 19: Efficacy of alendronate on hip fractures

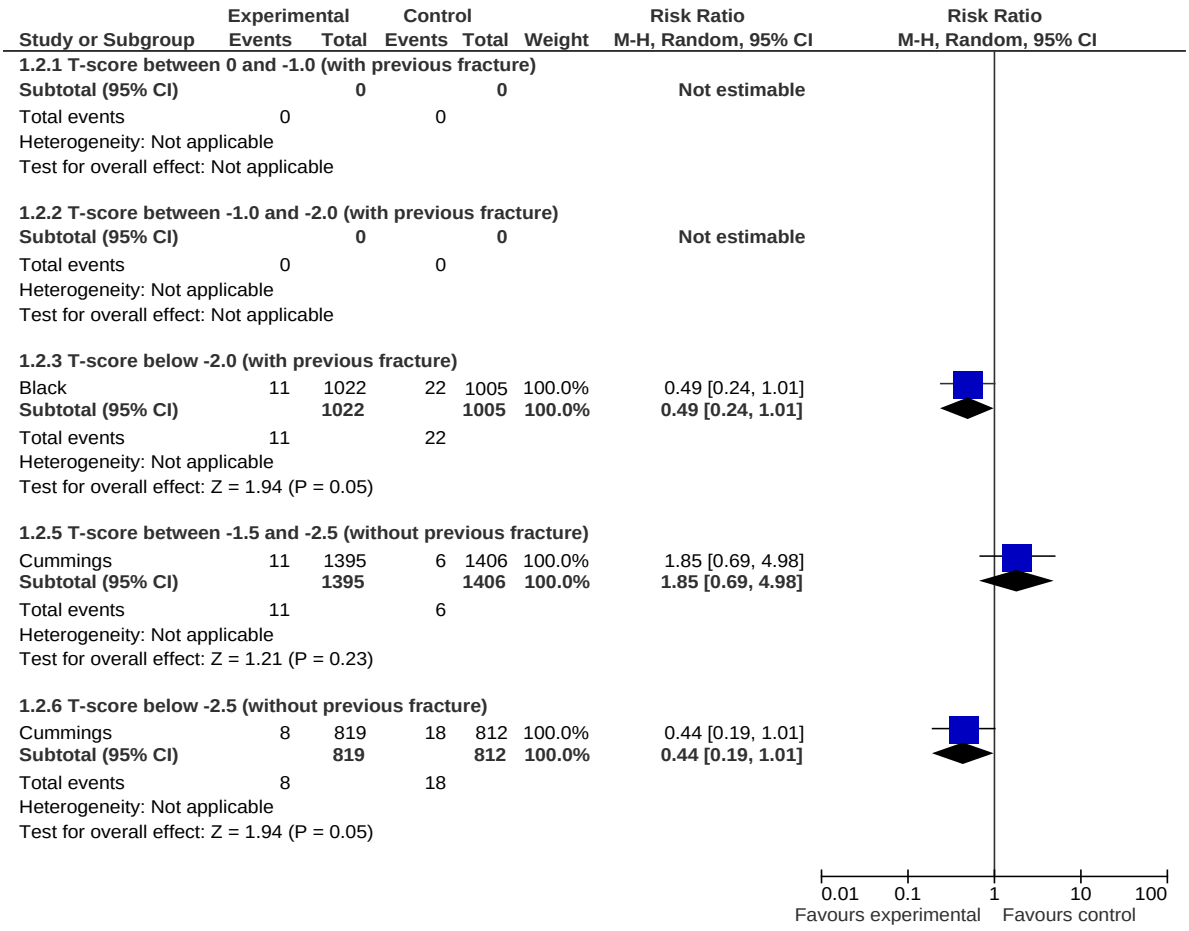
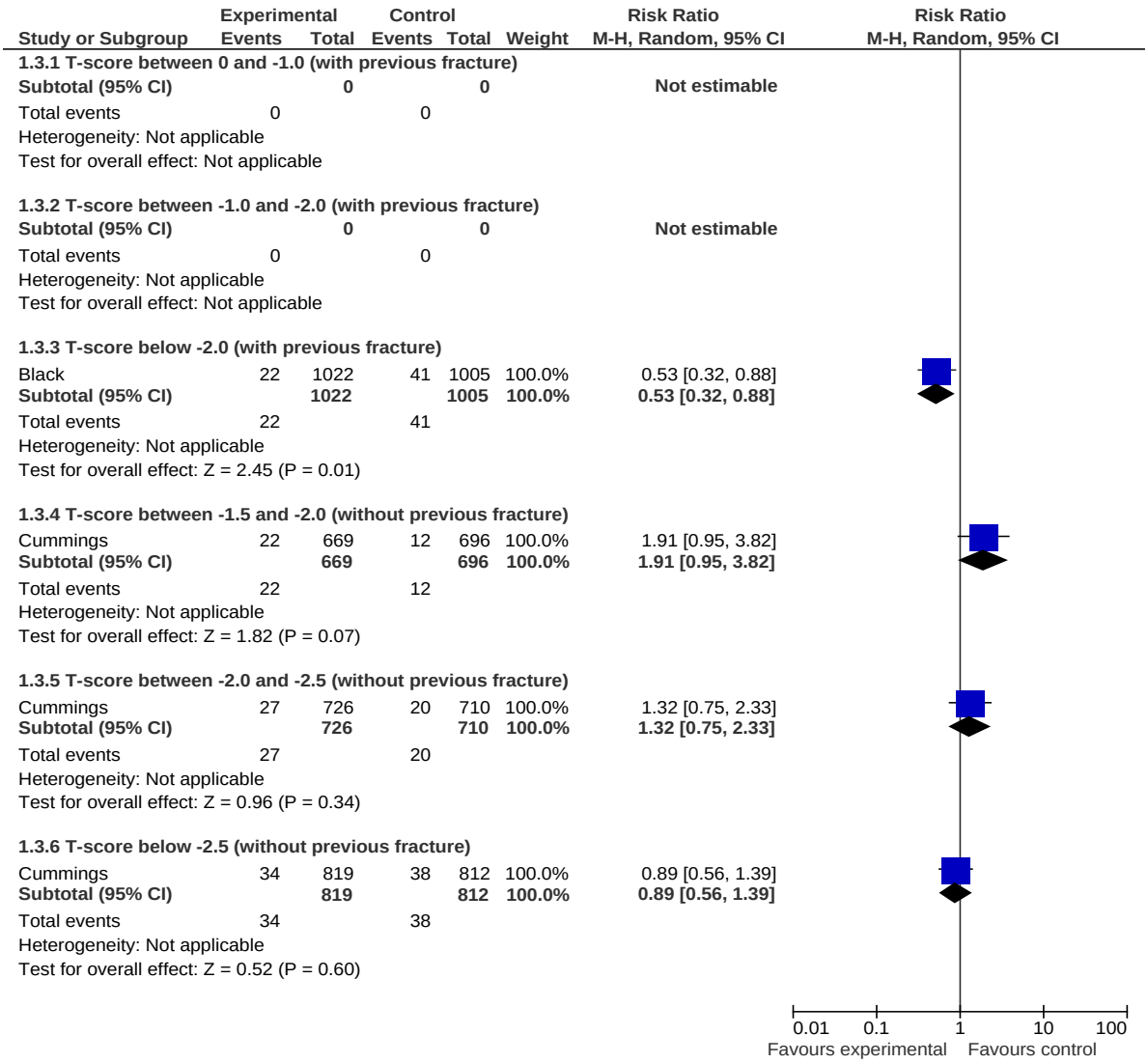


Figure 20: Efficacy of alendronate on wrist fractures



APPENDIX 4: GRADE EVIDENCE TABLES

The aggregated quality of the evidence is described in the following terms:
High quality*:* Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality*:* Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Author(s): GH + TW
Date: 2010-06-24
Question: Should alendronate vs be used in women with T-score less than -2.5 and no previous fracture?
Settings:
Bibliography: Cummings et al. 1998 Liberman et al. 1995

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Alendronate		Relative (95% CI)	Absolute	
Vertebral fracture (follow-up 3-4 years; assessed with: Radiograph)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	26/1239 (2.1%)	49/1092 (4.5%)	RR 0.50 (0.31 to 0.8)	22 fewer per 1000 (from 9 fewer to 31 fewer)	⊖⊖⊖⊖ HIGH
Hip fracture (follow-up 4 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/819 (1%)	18/812 (2.2%)	RR 0.44 (0.19 to 1.01)	12 fewer per 1000 (from 18 fewer to 0 more)	⊖⊖OO LOW
Wrist fractures (follow-up 4 years)											
1	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[3]	none	34/819 (4.2%)	38/812 (4.7%)	RR 0.89 (0.56 to 1.39)	5 fewer per 1000 (from 21 fewer to 18 more)	⊖⊖OO LOW

[1] Only one study
[2] 95 % CI covers 0.75 and 1
[3] CI covers both 0.75, 1 and 1.25

Author(s): GH + TW
Date: 2010-06-24
Question: Should alendronate vs no treatment be used in women with T-score between -2 and -2.5 and no previous fracture?
Settings:
Bibliography: Cummings et al. 1998

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Alendronate	No treatment	Relative (95% CI)	Absolute	
Vertebral fracture (follow-up 4 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/726 (1.8%)	24/710 (3.4%)	RR 0.53 (0.27 to 1.03)	9 fewer per 1000 (from 17 more to 2 more)	⊖⊖OO LOW
Wrist fracture (follow-up 4 years)											
1	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[3]	none	27/726 (3.7%)	20/710 (2.8%)	RR 1.32 (0.75 to 2.33)	9 more per 1000 (from 7 fewer to 37 more)	⊖⊖OO LOW

[1] Only one study
[2] CI covers both 0.75 and 1
[3] CI covers both 0.75 1 and 1.25

Author(s): GH +TW
Date: 2010-06-24
Question: Should alendronate vs no treatment be used in women with T-score between -1.5 and -2.0 and no previous fracture?
Settings:
Bibliography: Cummings et al. 1998

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Alendronate	No treatment	Relative (95% CI)	Absolute	
Vertebral fracture (follow-up 4 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/669 (1.2%)	10/696 (1.4%)	RR 0.83 (0.33 to 2.1)	2 fewer per 1000 (from 10 fewer to 16 more)	⊖⊖OO LOW
Wrist fracture (follow-up 4 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22/669 (3.3%)	12/696 (1.7%)	RR 1.91 (0.95 to 3.82)	16 more per 1000 (from 1 fewer to 49 more)	⊖⊖OO LOW

[1] Only one study
[2] CI covers both 0.75, 1 and 1.25
[3] CI covers both 1 and 1.25

Author(s): GH + TW
Date: 2010-06-24
Question: Should alendronate vs no treatment be used in women with T-score less than -2 and previous fracture?
Settings:
Bibliography: Black et al. 1996 Liberman et al. 1995

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Alendronate	No treatment	Relative (95% CI)	Absolute	
Vertebral fracture (follow-up 3-4 years; assessed with: Radiograph)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	91/1128 (8.1%)	158/1080 (14.6%)	RR 0.55 (0.43 to 0.7)	66 fewer per 1000 (from 44 fewer to 83 fewer)	⊖⊖⊖⊖ HIGH
Hip fracture (follow-up mean 3 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/1022 (1.1%)	22/1005 (2.2%)	RR 0.49 (0.24 to 1.01)	11 fewer per 1000 (from 17 fewer to 0 more)	⊖⊖OO LOW
Wrist fracture (follow-up mean 3 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/1022 (2.2%)	41/1005 (4.1%)	RR 0.53 (0.32 to 0.88)	19 fewer per 1000 (from 5 fewer to 28 fewer)	⊖⊖⊖O MODERATE

[1] Only one study
[2] CI covers both 0.75 and 1

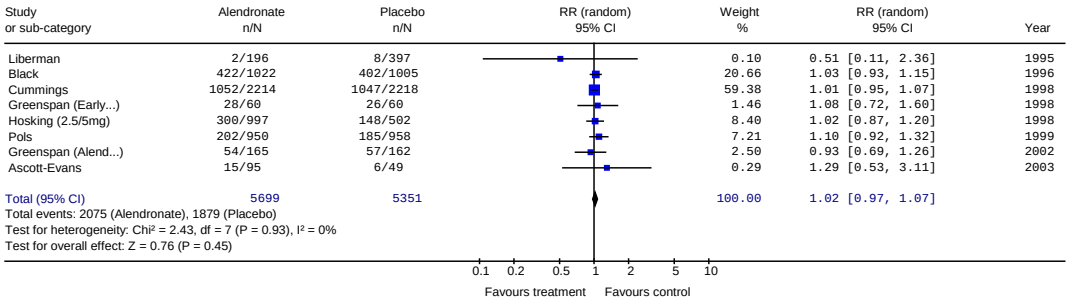
Author(s): GH + TW
Date: 2010-06-24
Question: Should alendronate vs no treatment be used in postmenopausal women with T-score between -1.5 and -2.0 without previous fracture?
Settings:
Bibliography: Cummings et al. 1998

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Alendronate	No treatment	Relative (95% CI)	Absolute	
Hip fracture (follow-up mean 4 years)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/1395 (0.8%)	6/1406 (0.4%)	RR 1.85 (0.69 to 4.98)	4 more per 1000 (from 1 fewer to 17 more)	⊖OOO VERY LOW
								0%		-	

[1] Only one study
[2] 95 % CI covers 0.75, 1 and 1.25

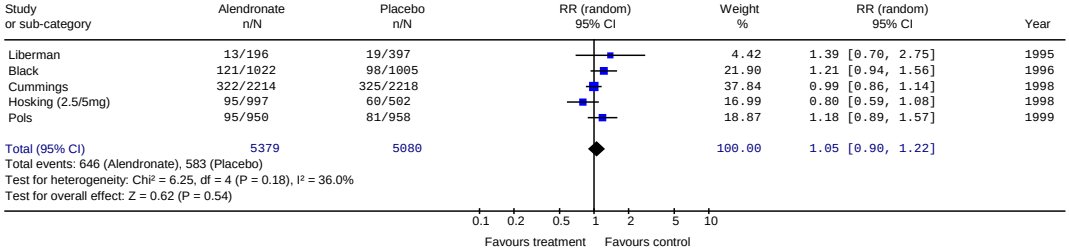
APPENDIX 5: META-ANALYSIS OF SIDE EFFECTS

Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 01 Upper GI event



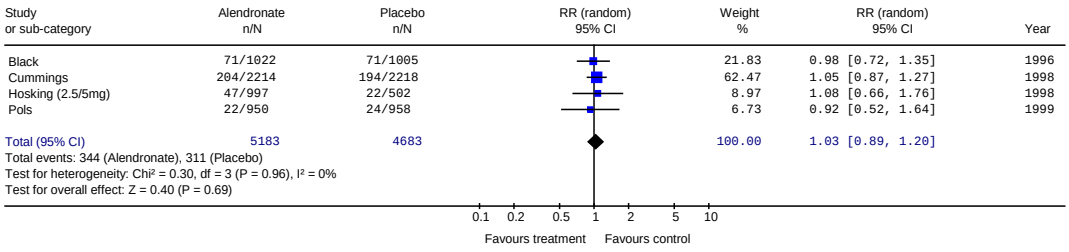
Total events: 2075 (Alendronate), 1879 (Placebo)
Test for heterogeneity: Chi² = 2.43, df = 7 (P = 0.93), I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)

Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 02 Abdominal pain



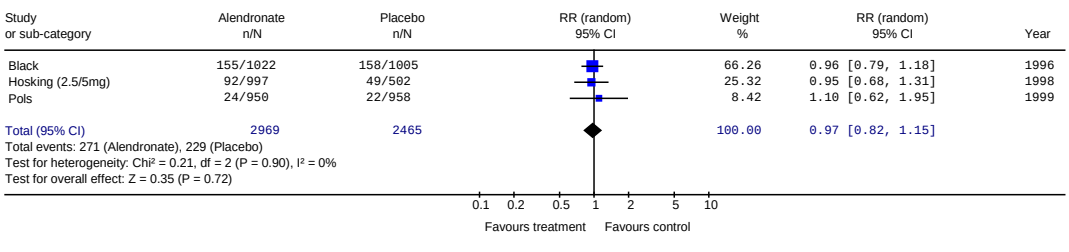
Total events: 646 (Alendronate), 583 (Placebo)
Test for heterogeneity: Chi² = 6.25, df = 4 (P = 0.18), I² = 36.0%
Test for overall effect: Z = 0.62 (P = 0.54)

Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 03 Acid regurgitation



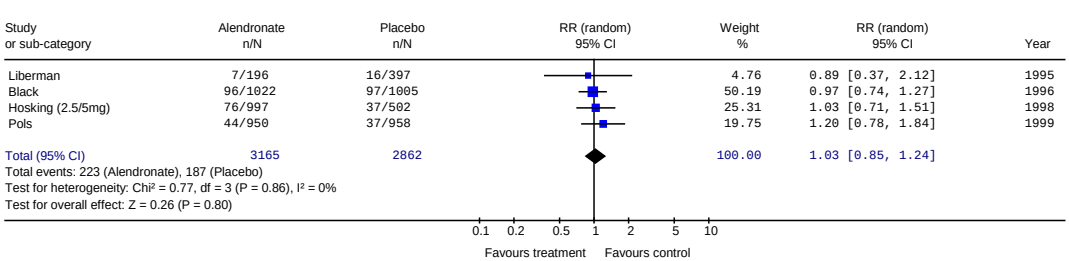
Total events: 344 (Alendronate), 311 (Placebo)
Test for heterogeneity: Chi² = 0.30, df = 3 (P = 0.96), I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 04 Dyspepsia



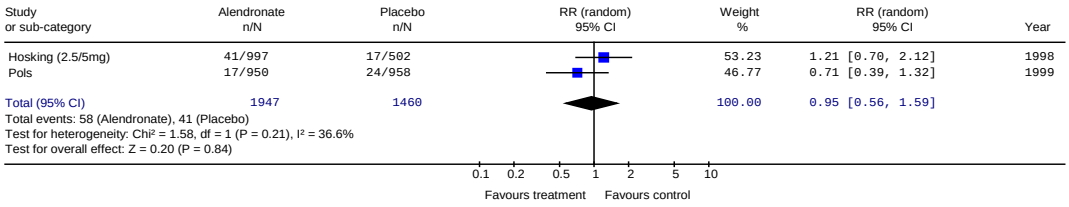
Total events: 271 (Alendronate), 229 (Placebo)
Test for heterogeneity: Chi² = 0.21, df = 2 (P = 0.90), I² = 0%
Test for overall effect: Z = 0.35 (P = 0.72)

Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 05 Nausea

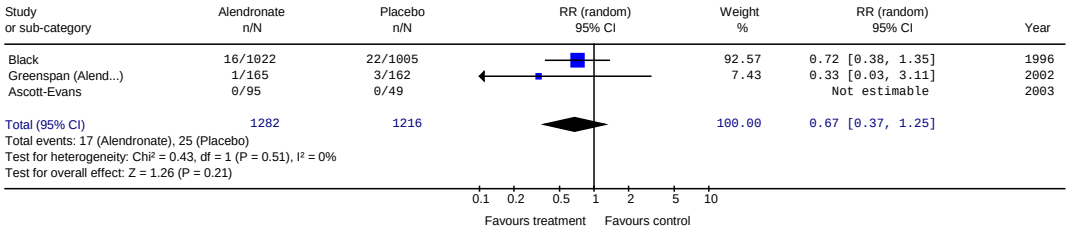


Total events: 223 (Alendronate), 187 (Placebo)
Test for heterogeneity: Chi² = 0.77, df = 3 (P = 0.86), I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

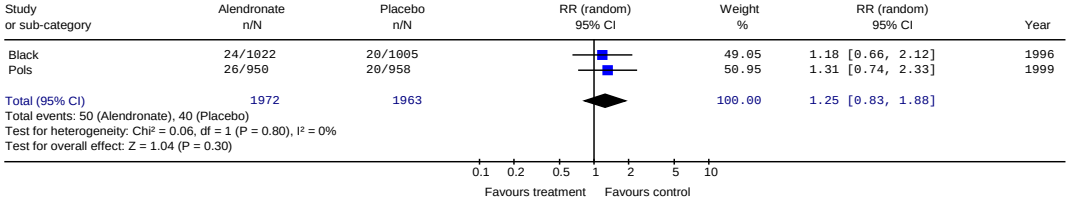
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 06 Vomiting



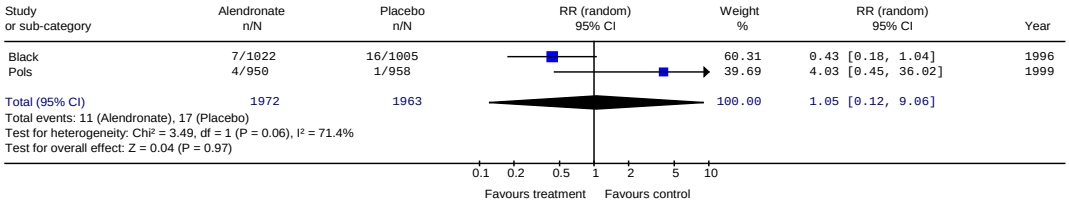
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 07 Serious upper GI event



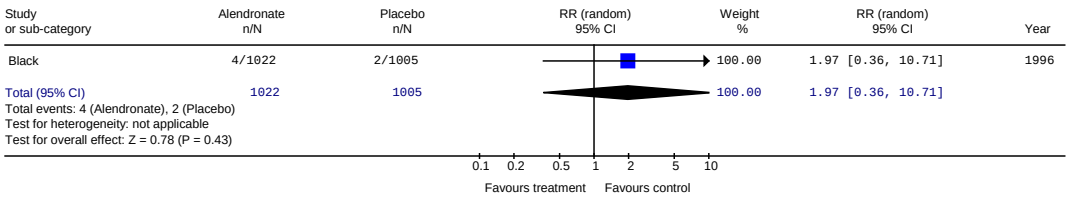
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 08 Gastritis/gastroenteritis



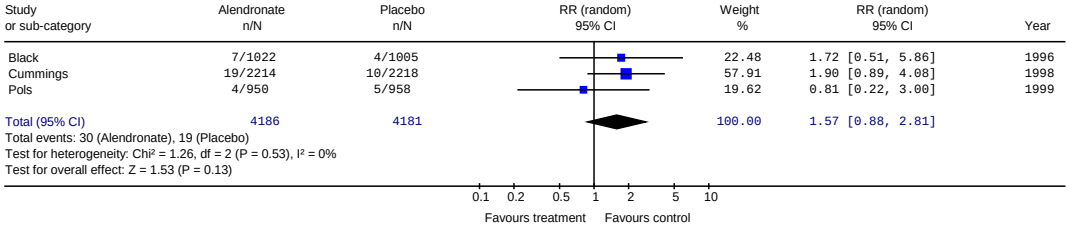
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 09 Gastric ulcer



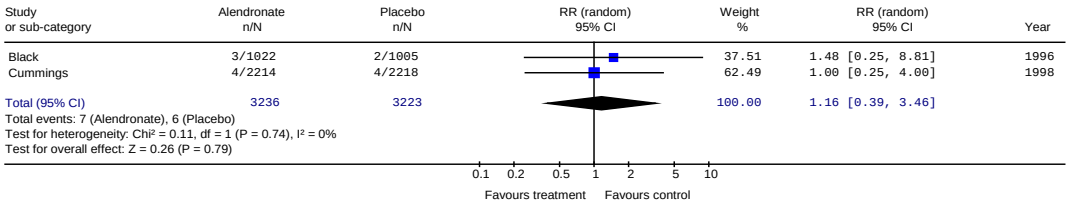
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 10 Other gastric



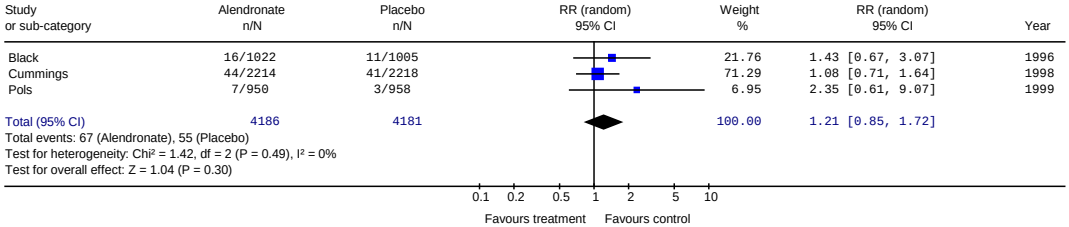
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 11 Oesophagitis



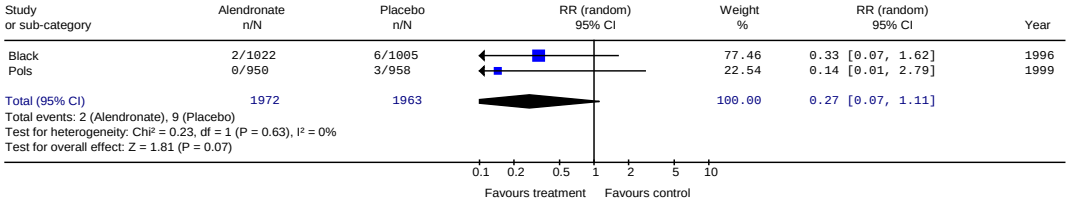
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 12 Oesophageal ulcer



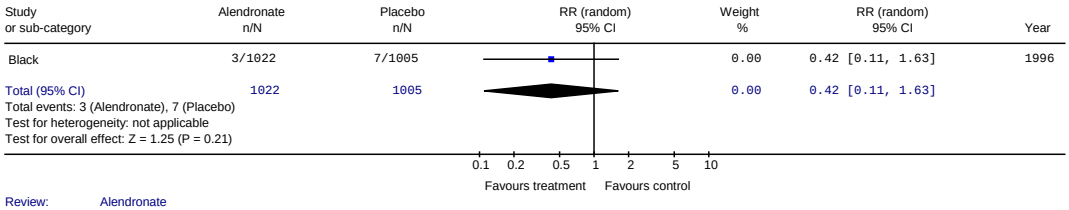
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 13 Other oesophageal



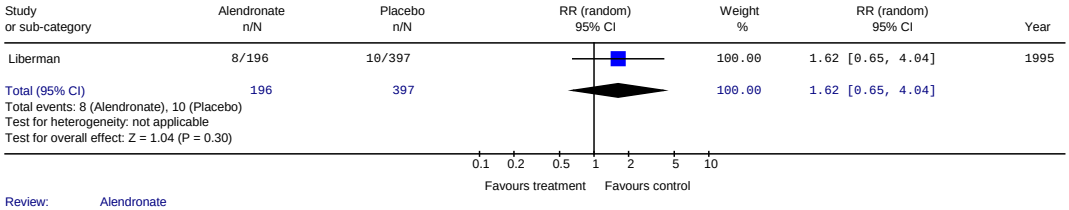
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 14 Duodenal ulcer



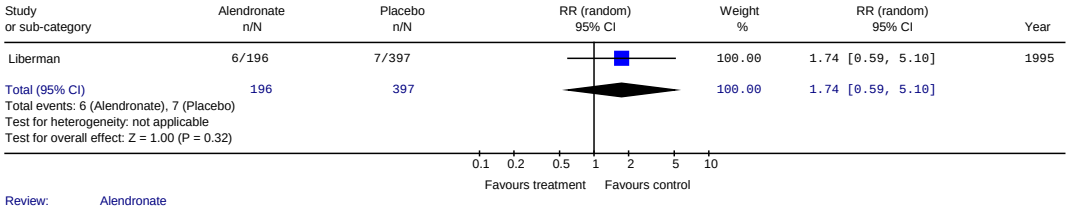
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 15 Peptic ulcer



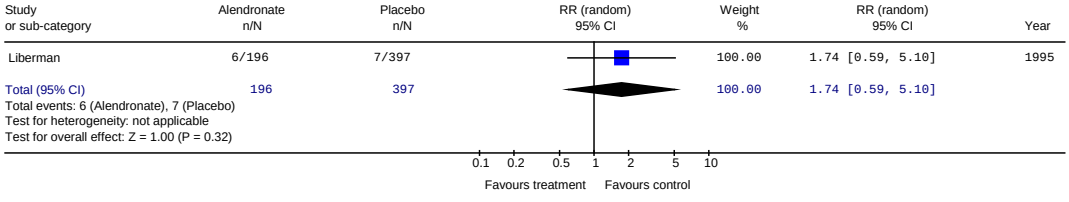
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 16 Musculoskeletal pain



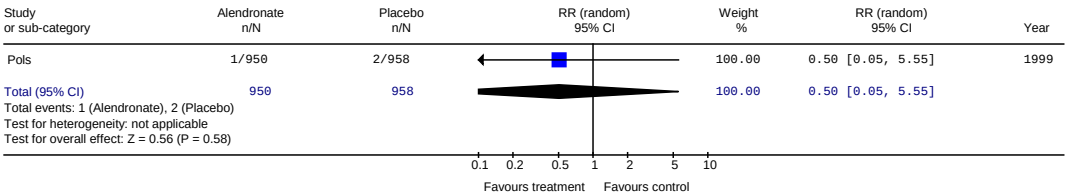
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 17 Constipation



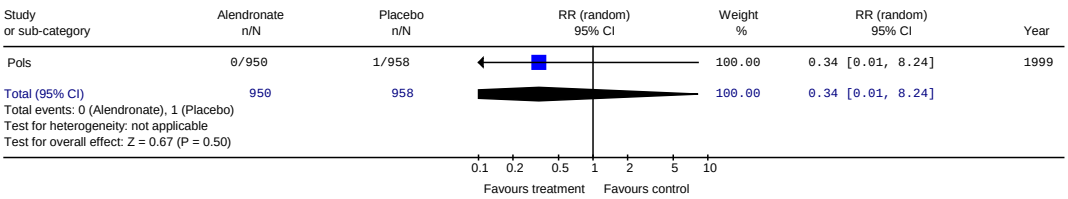
Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 18 Diarrhea



Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 19 Dysphagia



Review: Alendronate
Comparison: 01 Alendronate vs control (side effects)
Outcome: 20 Odynophalgia



APPENDIX 6: SEARCHES FOR EPIDEMIOLOGICAL DATA

Search 2a: Vertebral sequelae, specific search

Database: Helsebiblioteket Ovid MEDLINE(R) <1950 to Present>

Dato: 26. mai, 2008.
Utfører: Irene W. Langengen
Antall treff: 456
RefMan: Userdef 1: Medline260508
Userdef 2: 2a
Filter: "prognosis (sensitivity)"

---

1 Spinal Fractures/ (6598)
2 (vertebra* adj3 fracture*).tw. (4813)
3 (spinal adj3 fracture*).tw. (1414)
4 (thoracic adj3 fracture*).tw. (549)
5 (lumbar adj3 fracture*).tw. (694)
6 (spine adj3 fracture*).tw. (1689)
7 1 or 2 or 3 or 4 or 5 or 6 (11132)
8 osteoporosis/ (25892)
9 Osteoporosis, Postmenopausal/ (7974)
10 Bone Density/ (27060)
11 osteoporoses.tw. (92)
12 osteoporotic.tw. (6768)
13 (bone loss or bmd).tw. (21379)
14 bone losses.tw. (78)
15 (bone adj3 density).tw. (21785)
16 (bone adj3 densities).tw. (662)
17 (fragil* adj2 bone*).tw. (769)
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (60293)
19 7 and 18 (4392)
20 Activities of Daily Living/ (36350)
21 Time Factors/ (783910)
22 Walking/ (9804)
23 Mobility Limitation/ (498)
24 Pain/ or Kyphosis/ (91832)
25 Back pain/ (12242)
26 Home Care Services/ (23060)
27 Home Nursing/ (7351)
28 Morbidity/ (18907)
29 Fatal Outcome/ (34104)
30 Long-Term Care/ (18362)

31 Nursing Homes/ (24045)
32 Bed rest/ (2902)
33 Length of Stay/ (39320)
34 Physical Therapy Modalities/ (20333)
35 (Mobility or walk* or (limit* adj3 activ*) or (active* adj3 daily adj3 living) or (active* adj3 daily adj3 life) or adl or ambulation or morbidity or nursing home* or (home adj3 help) or home care or homecare or home help or home nursing or home health care or physical therapy or physiotherap*).tw. (298807)
36 (home rehabilitation or institutional care or institutional* or long term care or long term therapy or long term treatment or domiciliary care or adverse outcomes or function effects or bed rest or bedrest or bedridden or pain or back pain or backpain or back ache or suffering).tw. (373148)
37 (mobilization or independent living or self care or breathing difficulties or mortality or death rate or death or fatal* or sick leave or kyphosis or kyphoses or vertebral deforma* or length of hospital* stay or length of stay or sequel* or disabilit*).tw. (707446)
38 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (2062487)
39 7 and 18 and 38 (1581)
40 comment.pt. (357722)
41 letter.pt. (626507)
42 editorial.pt. (221024)
43 animal/ (4265686)
44 human/ (10405832)
45 43 not (43 and 44) (3215231)
46 or/40-42,45 (4081923)
47 39 not 46 (1554)
48 limit 47 to "prognosis (sensitivity)" (456)

Search 2b: vertebral sequelae, without prognostic filter

Database: Helsebiblioteket Ovid MEDLINE(R) <1950 to Present>

Dato: 26. mai, 2008.
Utfører: Irene W. Langengen
Antall treff: 1098
RefMan: Userdef 1: Medline260508
Userdef 2: 2b

Spinal Fractures/ (6598)
2 (vertebra* adj3 fracture*).tw. (4813)
3 (spinal adj3 fracture*).tw. (1414)
4 (thoracic adj3 fracture*).tw. (549)
5 (lumbar adj3 fracture*).tw. (694)
6 (spine adj3 fracture*).tw. (1689)
7 1 or 2 or 3 or 4 or 5 or 6 (11132)
8 osteoporosis/ (25892)
9 Osteoporosis, Postmenopausal/ (7974)
10 Bone Density/ (27060)
11 osteoporoses.tw. (92)
12 osteoporotic.tw. (6768)
13 (bone loss or bmd).tw. (21379)
14 bone losses.tw. (78)
15 (bone adj3 density).tw. (21785)
16 (bone adj3 densities).tw. (662)
17 (fragil* adj2 bone*).tw. (769)
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (60293)
19 7 and 18 (4392)
20 Activities of Daily Living/ (36350)
21 Time Factors/ (783910)
22 Walking/ (9804)
23 Mobility Limitation/ (498)
24 Pain/ or Kyphosis/ (91832)
25 Back pain/ (12242)
26 Home Care Services/ (23060)
27 Home Nursing/ (7351)
28 Morbidity/ (18907)
29 Fatal Outcome/ (34104)
30 Long-Term Care/ (18362)
31 Nursing Homes/ (24045)
32 Bed rest/ (2902)
33 Length of Stay/ (39320)
34 Physical Therapy Modalities/ (20333)

35 (Mobility or walk* or (limit* adj3 activ*) or (active* adj3 daily adj3 living) or (active* adj3 daily adj3 life) or adl or ambulation or morbidity or nursing home* or (home adj3 help) or home care or homecare or home help or home nursing or home health care or physical therapy or physiotherap*).tw. (298807)
36 (home rehabilitation or institutional care or institutional* or long term care or long term therapy or long term treatment or domiciliary care or adverse outcomes or function effects or bed rest or bedrest or bedridden or pain or back pain or backpain or back ache or suffering).tw. (373148)
37 (mobilization or independent living or self care or breathing difficulties or mortality or death rate or death or fatal* or sick leave or kyphosis or kyphoses or vertebral deforma* or length of hospital* stay or length of stay or sequel* or disabilit*).tw. (707446)
38 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (2062487)
39 7 and 18 and 38 (1581)
40 comment.pt. (357722)
41 letter.pt. (626507)
42 editorial.pt. (221024)
43 animal/ (4265686)
44 human/ (10405832)
45 43 not (43 and 44) (3215231)
46 or/40-42,45 (4081923)
47 39 not 46 (1554)
48 limit 47 to "prognosis (sensitivity)" (456)
49 47 not 48 (1098)

Search 3: mortality after vertebral fractures

Database: Helsebiblioteket EMBASE <1980 to Present>

Dato: 21. mai, 2008.
Utfører: Irene W. Langengen
Antall treff: 447
RefMan: Userdef 1: Embase210508
Userdef 2: 3

---

1 Spine Fracture/ep [Epidemiology] (113)
2 "Mortality"/ (161485)
3 fatality/ (40896)
4 (mortality or mortalities or death rate* or fatality rate* or fatal*).mp. or death*.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (581843)
5 2 or 3 or 4 (581843)
6 (vertebra* adj3 fracture*).tw. (4472)
7 (spinal adj3 fracture*).tw. (1111)
8 (spin adj3 fracture*).tw. (3)
9 spine fracture/ or vertebra fracture/ (7700)
10 (thoracic adj3 fracture*).tw. (440)
11 (lumbar adj3 fracture*).tw. (635)
12 6 or 7 or 8 or 9 or 10 or 11 (9816)
13 Osteoporosis/ (35089)
14 Postmenopause, Osteoporosis/ (5378)
15 Primary Osteoporosis/ (58)
16 Secondary Osteoporosis/ (116)
17 Bone Density/ (24130)
18 (osteoporosis or osteoporoses or osteoporotic or bone loss or bmd or bone losses or (bone adj3 density) or (bone adj3 densities) or (fragil* adj2 bone*)).tw. (47145)
19 13 or 14 or 15 or 16 or 17 or 18 (63769)
20 5 and 12 and 19 (420)
21 1 and 19 (60)
22 20 or 21 (468)
23 editorial.pt. (210345)
24 letter.pt. (413808)
25 Animal/ (18239)
26 Nonhuman/ (3062352)
27 25 or 26 (3068134)
28 Human/ (6119665)
29 27 not (27 and 28) (2586272)
30 or/23-24,29 (3188122)
31 22 not 30 (447)

Database: Helsebiblioteket Ovid MEDLINE(R) <1950 to Present>

Dato: 21. mai, 2008.

Utfører: Irene W. Langengen

Antall treff: 258

RefMan: Userdef 1: Medline210508

Userdef 2: 3

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1 Spinal Fractures/ (6589)
2 (vertebra* adj3 fracture*).tw. (4807)
3 (spinal adj3 fracture*).tw. (1411)
4 (thoracic adj3 fracture*).tw. (549)
5 (lumbar adj3 fracture*).tw. (692)
6 (spine adj3 fracture*).tw. (1687)
7 1 or 2 or 3 or 4 or 5 or 6 (11119)
8 osteoporosis/ (25857)
9 Osteoporosis, Postmenopausal/ (7964)
10 Bone Density/ (27013)
11 osteoporoses.tw. (92)
12 osteoporotic.tw. (6752)
13 (bone loss or bmd).tw. (21340)
14 bone losses.tw. (78)
15 (bone adj3 density).tw. (21746)
16 (bone adj3 densities).tw. (661)
17 (fragil* adj2 bone*).tw. (769)
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (60208)
19 7 and 18 (4384)
20 mortality/ or fatal outcome/ (62900)
21 (mortality or mortalities or death rate* or fatality rate* or fatal* or death*).tw. (603064)
22 20 or 21 (639318)
23 19 and 22 (261)
24 Spinal Fractures/mo [Mortality] (74)
25 18 and 24 (21)
26 23 or 25 (264)
27 comment.pt. (357185)
28 letter.pt. (625940)
29 editorial.pt. (220698)
30 animal/ (4262655)
31 human/ (10397158)
32 30 not (30 and 31) (3213354)
33 or/27-29,32 (4079082)
34 26 not 33 (258)

Search 4: Mortality after hip fractures

Database: Helsebiblioteket Ovid MEDLINE(R) <1950 to June Week 1 2008>

Dato: 17. juni, 2008.
Utfører: Irene W. Langengen
Antall treff: 426
RefMan: Userdef 1: Medline170608
Userdef 2: 4

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1 Hip Fractures/ (7629)
2 Femoral Neck Fractures/ (6063)
3 Femoral Fractures/ (10740)
4 (acetabulofemoral fracture* or acetabulum fracture* or hip fracture* or intertrochanteric fracture*).tw. (6466)
5 (subtrochanteric fracture* or trochanteric fracture* or femoral neck fracture*).tw. (3289)
6 (femur neck fracture* or femur fracture* or femoral fracture*).tw. (3636)
7 1 or 2 or 3 or 4 or 5 or 6 (25436)
8 osteoporosis/ (26012)
9 Osteoporosis, Postmenopausal/ (8007)
10 Bone Density/ (27227)
11 osteoporoses.tw. (93)
12 osteoporotic.tw. (6811)
13 (bone loss or bmd).tw. (21512)
14 bone losses.tw. (78)
15 (bone adj3 density).tw. (21926)
16 (bone adj3 densities).tw. (667)
17 (fragil* adj2 bone*).tw. (778)
18 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (60618)
19 7 and 18 (3876)
20 mortality/ or fatal outcome/ (63435)
21 (mortality or mortalities or death rate* or fatality rate* or fatal* or death*).tw. (608151)
22 20 or 21 (644742)
23 19 and 22 (398)
24 Hip Fractures/mo [Mortality] (555)
25 Femoral Fractures/mo [Mortality] (146)
26 Femoral Neck Fractures/mo [Mortality] (296)
27 or/24-26 (913)
28 18 and 27 (81)
29 23 or 28 (426)

30 comment.pt. (360625)
31 letter.pt. (630827)
32 editorial.pt. (223075)
33 animal/ (4280762)
34 human/ (10463793)
35 33 not (33 and 34) (3223695)
36 or/30-32,35 (4097036)
37 29 not 36 (418)

Database: EMBASE <1980 to 2008 Week 24>

Dato: 17. juni, 2008.
Utfører: Irene W. Langengen
Antall treff: 1041
RefMan: Userdef 1: Embase170608
Userdef 2: 4

---

1 "Mortality"/ (162684)
2 fatality/ (41002)
3 (mortality or mortalities or death rate* or fatality rate* or fatal*).mp. or death*.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (585173)
4 1 or 2 or 3 (585173)
5 hip fracture/ (7282)
6 acetabulum fracture/ (988)
7 femur intertrochanteric fracture/ (542)
8 femur neck fracture/ (2831)
9 femur pertrochanteric fracture/ or femur subtrochanteric fracture/ or femur trochanteric fracture/ (1201)
10 (acetabulofemoral fracture* or acetabulum fracture* or hip fracture* or intertrochanteric fracture* or subtrochanteric fracture* or trochanteric fracture* or femoral neck fracture* or femur neck fracture* or femur fracture* or femoral fracture*).tw. (9803)
11 5 or 6 or 7 or 8 or 9 or 10 (15036)
12 Osteoporosis/ (35295)
13 Postmenopause, Osteoporosis/ (5413)
14 Primary Osteoporosis/ (58)
15 Secondary Osteoporosis/ (117)
16 Bone Density/ (24330)
17 (osteoporosis or osteoporoses or osteoporotic or bone loss or bmd or bone losses or (bone adj3 density) or (bone adj3 densities) or (fragil* adj2 bone*)).tw. (47440)
18 12 or 13 or 14 or 15 or 16 or 17 (64182)

19 4 and 11 and 18 (619)
20 Hip Fracture/ep or Acetabulum Fracture/ep or femur intertrochanteric fracture/ep or Femur Pertrochanteric Fracture/ep or Femur Subtrochanteric Fracture/ep or Femur Trochanteric Fracture/ep (1155)
21 18 and 20 (654)
22 19 or 21 (1131)
23 editorial.pt. (211581)
24 letter.pt. (416447)
25 Animal/ (18242)
26 Nonhuman/ (3073061)
27 25 or 26 (3078843)
28 Human/ (6147228)
29 27 not (27 and 28) (2593851)
30 or/23-24,29 (3199495)
31 22 not 30 (1041)
32 from 31 keep 1-1041 (1041)

Search 5: Mortality connected to low BMD

Database: Ovid MEDLINE(R) <1950 to June Week 3 2008>
Antall: 298 stk
Dato: 270608
Filter: Ovid “prognosis (sensitivity)"
---
1 mortality/ or fatal outcome/ (63586)
2 (mortality or mortalities or death rate* or fatality rate* or fatal* or death*).tw. (609780)
3 1 or 2 (646454)
4 osteoporosis/ (26077)
5 Osteoporosis, Postmenopausal/ (8022)
6 Bone Density/ (27297)
7 osteoporoses.tw. (93)
8 osteoporotic.tw. (6823)
9 (bone loss or bmd).tw. (21568)
10 bone losses.tw. (78)
11 (bone adj3 density).tw. (21976)
12 (bone adj3 densities).tw. (668)
13 (fragil* adj2 bone*).tw. (780)
14 or/4-13 (60769)
15 3 and 14 (1701)
16 limit 15 to "prognosis (sensitivity)" (505)
17 limit 15 to "prognosis (specificity)" (152)
18 limit 15 to "prognosis (optimized)" (779)

19 Spinal Fractures/ (6633)
20 (vertebra* adj3 fracture*).tw. (4847)
21 (spinal adj3 fracture*).tw. (1422)
22 (thoracic adj3 fracture*).tw. (550)
23 (lumbar adj3 fracture*).tw. (698)
24 (spine adj3 fracture*).tw. (1694)
25 19 or 20 or 21 or 22 or 23 or 24 (11193)
26 osteoporosis/ (26077)
27 Osteoporosis, Postmenopausal/ (8022)
28 Bone Density/ (27297)
29 osteoporoses.tw. (93)
30 osteoporotic.tw. (6823)
31 (bone loss or bmd).tw. (21568)
32 bone losses.tw. (78)
33 (bone adj3 density).tw. (21976)
34 (bone adj3 densities).tw. (668)
35 (fragil* adj2 bone*).tw. (780)
36 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (60769)
37 25 and 36 (4418)
38 mortality/ or fatal outcome/ (63586)
39 (mortality or mortalities or death rate* or fatality rate* or fatal* or death*).tw. (609780)
40 38 or 39 (646454)
41 37 and 40 (265)
42 Spinal Fractures/mo [Mortality] (74)
43 36 and 42 (21)
44 41 or 43 (268)
45 comment.pt. (361648)
46 letter.pt. (631823)
47 editorial.pt. (223715)
48 animal/ (4287246)
49 human/ (10480715)
50 48 not (48 and 49) (3227844)
51 or/45-47,50 (4102964)
52 44 not 51 (262)
53 Hip Fractures/ (7639)
54 Femoral Neck Fractures/ (6066)
55 Femoral Fractures/ (10746)
56 (acetabulofemoral fracture* or acetabulum fracture* or hip fracture* or intertrochanteric fracture*).tw. (6481)
57 (subtrochanteric fracture* or trochanteric fracture* or femoral neck fracture*).tw. (3292)
58 (femur neck fracture* or femur fracture* or femoral fracture*).tw. (3643)
59 53 or 54 or 55 or 56 or 57 or 58 (25464)

60 osteoporosis/ (26077)
61 Osteoporosis, Postmenopausal/ (8022)
62 Bone Density/ (27297)
63 osteoporoses.tw. (93)
64 osteoporotic.tw. (6823)
65 (bone loss or bmd).tw. (21568)
66 bone losses.tw. (78)
67 (bone adj3 density).tw. (21976)
68 (bone adj3 densities).tw. (668)
69 (fragil* adj2 bone*).tw. (780)
70 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 (60769)
71 59 and 70 (3884)
72 mortality/ or fatal outcome/ (63586)
73 (mortality or mortalities or death rate* or fatality rate* or fatal* or death*).tw. (609780)
74 72 or 73 (646454)
75 71 and 74 (399)
76 Hip Fractures/mo [Mortality] (557)
77 Femoral Fractures/mo [Mortality] (146)
78 Femoral Neck Fractures/mo [Mortality] (296)
79 or/76-78 (915)
80 70 and 79 (81)
81 75 or 80 (427)
82 comment.pt. (361648)
83 letter.pt. (631823)
84 editorial.pt. (223715)
85 animal/ (4287246)
86 human/ (10480715)
87 85 not (85 and 86) (3227844)
88 or/82-84,87 (4102964)
89 81 not 88 (419)
90 52 or 89 (570)
91 15 not 90 (1157)
92 limit 91 to "prognosis (sensitivity)" (298)
93 limit 91 to "prognosis (specificity)" (74)
94 limit 91 to "prognosis (optimized)" (546)

Database: EMBASE <1980 to 2008 Week 25>

Utført av Irene W. Langenge

Dato: 270608

Filter: Ovid "prognosis (specificity)"

Antall: 338 stk

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1 "Mortality"/ (163034)

2 fatality/ (41024)

3 (mortality or mortalities or death rate* or fatality rate* or fatal*).mp. or death*.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (586147)

4 1 or 2 or 3 (586147)

5 Osteoporosis/ (35345)

6 Postmenopause, Osteoporosis/ (5422)

7 Primary Osteoporosis/ (59)

8 Secondary Osteoporosis/ (117)

9 Bone Density/ (24375)

10 (osteoporosis or osteoporoses or osteoporotic or bone loss or bmd or bone losses or (bone adj3 density) or (bone adj3 densities) or (fragil* adj2 bone*)).tw. (47506)

11 or/5-10 (64282)

12 4 and 11 (3329)

13 limit 12 to "prognosis (sensitivity)" (2653)

14 limit 12 to "prognosis (specificity)" (398)

15 limit 12 to "prognosis (optimized)" (1138)

16 Spine Fracture/ep [Epidemiology] (114)

17 "Mortality"/ (163034)

18 fatality/ (41024)

19 (mortality or mortalities or death rate* or fatality rate* or fatal*).mp. or death*.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (586147)

20 17 or 18 or 19 (586147)

21 (vertebra* adj3 fracture*).tw. (4517)

22 (spinal adj3 fracture*).tw. (1119)

23 (spin adj3 fracture*).tw. (3)

24 spine fracture/ or vertebra fracture/ (7777)

25 (thoracic adj3 fracture*).tw. (441)

26 (lumbar adj3 fracture*).tw. (639)

27 21 or 22 or 23 or 24 or 25 or 26 (9906)

28 Osteoporosis/ (35345)

29 Postmenopause, Osteoporosis/ (5422)

30 Primary Osteoporosis/ (59)

31 Secondary Osteoporosis/ (117)

32 Bone Density/ (24375)
33 (osteoporosis or osteoporoses or osteoporotic or bone loss or bmd or bone losses or (bone adj3 density) or (bone adj3 densities) or (fragil* adj2 bone*)).tw. (47506)
34 28 or 29 or 30 or 31 or 32 or 33 (64282)
35 20 and 27 and 34 (423)
36 16 and 34 (60)
37 35 or 36 (471)
38 editorial.pt. (212059)
39 letter.pt. (417113)
40 Animal/ (18243)
41 Nonhuman/ (3076365)
42 40 or 41 (3082147)
43 Human/ (6155100)
44 42 not (42 and 43) (2596189)
45 or/38-39,44 (3202947)
46 37 not 45 (449)
47 "Mortality"/ (163034)
48 fatality/ (41024)
49 (mortality or mortalities or death rate* or fatality rate* or fatal*).mp. or death*.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (586147)
50 47 or 48 or 49 (586147)
51 hip fracture/ (7295)
52 acetabulum fracture/ (989)
53 femur intertrochanteric fracture/ (542)
54 femur neck fracture/ (2831)
55 femur pertrochanteric fracture/ or femur subtrochanteric fracture/ or femur trochanteric fracture/ (1201)
56 (acetabulofemoral fracture* or acetabulum fracture* or hip fracture* or intertrochanteric fracture* or subtrochanteric fracture* or trochanteric fracture* or femoral neck fracture* or femur neck fracture* or femur fracture* or femoral fracture*).tw. (9812)
57 51 or 52 or 53 or 54 or 55 or 56 (15052)
58 Osteoporosis/ (35345)
59 Postmenopause, Osteoporosis/ (5422)
60 Primary Osteoporosis/ (59)
61 Secondary Osteoporosis/ (117)
62 Bone Density/ (24375)
63 (osteoporosis or osteoporoses or osteoporotic or bone loss or bmd or bone losses or (bone adj3 density) or (bone adj3 densities) or (fragil* adj2 bone*)).tw. (47506)
64 58 or 59 or 60 or 61 or 62 or 63 (64282)
65 50 and 57 and 64 (620)

66 Hip Fracture/ep or Acetabulum Fracture/ep or femur intertrochanteric fracture/ep or Femur Pertrochanteric Fracture/ep or Femur Subtrochanteric Fracture/ep or Femur Trochanteric Fracture/ep (1155)
67 64 and 66 (654)
68 65 or 67 (1132)
69 editorial.pt. (212059)
70 letter.pt. (417113)
71 Animal/ (18243)
72 Nonhuman/ (3076365)
73 71 or 72 (3082147)
74 Human/ (6155100)
75 73 not (73 and 74) (2596189)
76 or/69-70,75 (3202947)
77 68 not 76 (1041)
78 46 or 77 (1239)
79 12 not 78 (2576)
80 limit 79 to "prognosis (sensitivity)" (1981)
81 limit 79 to "diagnosis (optimized)" (199)
82 limit 79 to "prognosis (specificity)" (338)

APPENDIX 7: ESTIMATED NUMBER OF FRACTURES

Table 15: Estimated number of hip fractures in Norway

Age	Number of women in the relevant age groups (107)	RR Trøndelag vs Oslo, based on (41;47)	Age and gender specific incidence in Oslo (41)	Estimated number of fractures
55-59	144 519	0.70159925	0.00114	116
60-64	130 357	0.93043465	0.00161	195
65-69	93 263	0.86396708	0.00405	326
70-74	79 949	0.87963564	0.00771	542
75-79	77 813	0.97077733	0.01425	1 076
80-84	70 574	0.82458309	0.02826	1 645
85-89	48 223	0.72501896	0.04755	1 663
90 and older	23 981	0.72192749	0.0618	1 070
Total	668 679	0.81094672		6 633

Table 16: Estimated number of clinical vertebral fractures in Norway

Age	Number of individuals (35)	RR Trøndelag vs Oslo, based on (32;34)	Age and gender specific incidence in Malmo (42)	Estimated number of fractures (42)
55-59	144 519	0.810947	0.00253	297
60-64	130 357	0.810947	0.00339	358
65-69	93 263	0.810947	0.00459	347
70-74	79 949	0.810947	0.00628	407
75-79	77 813	0.810947	0.00865	546
80-84	70 574	0.810947	0.01204	689
85-89	48 223	0.810947	0.01688	660
90 and older	23 981	0.810947	0.01688	328
Total	668 679			3 633

Table 17: Estimated number of wrist fractures in Norway

Age	Number of individuals (108)	RR Trøndelag Vs Oslo (41;47)	Age and gender specific incidence in Oslo (43)	Estimated number of fractures
55-59	144519	0.810946717	0.00732	858
60-64	130357	0.810946717	01116	1 180
65-69	93263	0.810946717	0.01295	979
70-74	79949	0.810946717	0.01317	854
75-79	77813	0.810946717	0.01387	875
80-84	70574	0.810946717	0.01501	859
85-89	48223	0.810946717	0.0151	591
90 and older	23981	0.810946717	0.01397	272
Total	668679			6 467

APPENDIX 8: CALCULATION OF PROBABILITY OF SEQUELAE AFTER HIP FRACTURES

Table 18: Probability of sequelae after hip fracture

Age	RR	P severe, without RR	P moderate, with RR	Input P, severe	Input P, moderate
100	16	2.72	8.96	0.949271797	0.999998026
95	8	1.36	4.48	0.774770777	0.998595178
90	4	0.68	2.24	0.52541679	0.96251904
85	2	0.34	1.12	0.3111	0.8064
80	1	0.17 (71)	0.56 (71)	0.17 (71)	0.56 (71)
75	0.5	0.085	0.28	0.088956642	0.336675042
70	0.25	0.0425	0.14	0.045514087	0.18555236
65	0.125	0.02125	0.07	0.023022051	0.097532472
60	0.0625	0.010625	0.035	0.011578051	0.05001709
55	0.03125	0.0053125	0.0175	0.00580588	0.025329333

APPENDIX 9: COSTS

Table 19: Expected costs hip fracture event

	DRG weight	DRG Unit price	Costs per unit	Number of units	Probability	Expected cost per patient (NOK)
-DRG 209A	4.51	32 490			0.430025	63 012
-DRG 210	2.5	32 490			0.1435	11 656
-DRG 211	1,67	32 490			0.1435	7 786
-DRG 236	1.11	32 490			0.0835	3 011
-DRG 230	0.66	32 490			0.06225	1 335
Ambulance to hospital			10 000		1.0	10 000
Ambulance from hospital			10 000		0.8	8 000
Taxi from hospital			500		0.2	100
Expected cost of OP per patient						*105 560*
Rehabilitation in hospital	0.107 per diem (109)	32 490		17 (110)	0.3423 (111)	31 956
Other rehabilitation *			1 726 (78)	21*	0.0811 (112)	2 939
Rehabilitation in nursing home	0.06 (113)	32 490		30*	0.4595 (114)	26 870
Physiotherapy			250	24*	0.3333 (115)	2 000
Taxi to & from physiotherapy			500 (116)	48*	0.33*	8 000

Expected cost of rehabilitation	*71 765*
Expected cost og hip fracture event	*177 325*

*Assumptions.

Table 20: Expected cost of sequelae per patient

	Cost per annum	Number of units	Expected cost per patient in NOK
Severe hip sequela	666 138 (77)	3	1 998 414
Moderate hip sequela	23 140 (79)	1	23 140

Table 21: Expected cost of vertebral fracture

	Unit cost	Number of units	Proportion of patients incuring this cost	Expected cost per patient in NOK
GP visit	274	1	100 %	274
X-ray+outpatient visit	680	1	100 %	680
Hospitalisation DRG 239	1.14*32 490	1	28 %	10 371
Outpatient check up	700	1	25 %	175
Physiotherapy	252	16	1/3	1 331

Table 22: Cost of vertebral fracture sequela

	Unit cost	Number of units	Proportion of patients incuring this cost	Expected cost per patient in NOK
GP	274	2	1/3	181
Physio.	252	6	1/3	499
				13 511

Table 23: Expected cost of wrist fracture

	Unit cost	**Number of units**	**Proportion of patients incuring this cost**	**Expected cost per patient in NOK**
Emergency room, no replacement	2 114	1	45 %	951
Emergency room, replacement	2 564	1	35 %	897
Hospitalisation DRG 224	0.83 * 32 490	1	20%	5 393
Physioterapy	252	5	30 %	375
Transport/taxi to from emergency or hospital	500	2	67 %	667
Loss of production/societal cost of sick leave	32 300/4 *1.45	8 weeks	36 % of fractures under pension age Assume that 45% of these women are employed	15 175
GP visit	274	1	30 %	82
Outpatient check up (polyclinic)	700	1	100 %	700
				24 240

Table 24: Cost of initiating treatment

	Unit price	Number of units	Expected costs in NOK
Cost of one year treatment with alendronate	832 (117)	1	832
			832

Table 25: Cost of treatment the year after initiation

	Unit price	Number of units	Expected costs in NOK
Cost of one year treatment with alendronate	832	1	832
DXA measurement	450	1	450
GP visit	274	1	274
Biochemical tests	47	1	47
			1 600

Table 26: Treatment costs in the following years

	Unit price	Number of units	Expected costs in NOK
Cost of one year treatment with alendronate	832		832
GP visit every second year	274	1*½	124
			953

Appendix 10: Probability distributions used in the PSA

Table 27: Distributions used in PSA

Name	Parameters/Info
dist_RRwrist_2_vfx	Log-Normal, u (mean of logs) = Ln(0.53), sigma (std dev of logs) = (Ln(0.88)-Ln(0.32))/(2*GRADE_high_quality); Expected value: 0,547944971
dist_RRwrist_2	Log-Normal, u (mean of logs) = Ln(1.32), sigma (std dev of logs) = (Ln(2.33)-Ln(0.75))/(2*GRADE_low_quality); Expected value: 1,400731077
dist_RRwrist_2_5	Log-Normal, u (mean of logs) = Ln(0.89), sigma (std dev of logs) = (Ln(1.39)-Ln(0.56))/(2*GRADE_low_quality); Expected value: 0,924640441
dist_RRhip_2_vfx	Log-Normal, u (mean of logs) = Ln(0.49), sigma (std dev of logs) = (Ln(1.01)-Ln(0.24))/(2*GRADE_moderate_quality); Expected value: 0,539052735
dist_RRhip_2_5	Log-Normal, u (mean of logs) = Ln(0.44), sigma (std dev of logs) = (Ln(1.01)-Ln(0.19))/(2*GRADE_moderate_quality); Expected value: 0,500558182
dist_RRvert_2_vfx	Log-Normal, u (mean of logs) = Ln(0.55), sigma (std dev of logs) = (Ln(0.70)-Ln(0.43))/(2*GRADE_high_quality); Expected value: 0,554266027
dist_RRvert_2	Log-Normal, u (mean of logs) = Ln(0.53), sigma (std dev of logs) = (Ln(1.03)-Ln(0.27))/(2*GRADE_moderate_quality); Expected value: 0,57576208
dist_RRvert_2_5	Log-Normal, u (mean of logs) = Ln(0.50), sigma (std dev of logs) = (Ln(0.80)-Ln(0.31))/(2*GRADE_high_quality); Expected value: 0,514838384
dist_hfrm	Log-Normal, u (mean of logs) = Ln(1.95), sigma (std dev of logs) = (Ln(1.97)-Ln(1.94))/(1.96*2); Expected value: 1,950014942
distr_bmdr	Log-Normal, u (mean of logs) = Ln(1.04), sigma (std dev of logs) = (Ln(1.19)-Ln(0.91))/(2*1.96); Expected value: 1,042438173
dist_days_of_other_rehab	Gamma, alpha = (21^2)/(3.5^2), lambda = 21/(3.5^2); Expected value: 21
Distr_DRGweight_209A	Gamma, alpha = (4.51^2)/((4.51*DRG_spread_factor)^2), lambda = 4.51/((4.51*DRG_spread_factor)^2); Expected value:

	4,51
Distr_DRGweight_210	Gamma, alpha = (2.5^2)/((2.5*DRG_spread_factor)^2), lambda = 2.5/((2.5*DRG_spread_factor)^2); Expected value: 2,5
Distr_DRG_weight_211	Gamma, alpha = (1.67^2)/((1.67*DRG_spread_factor)^2), lambda = 1.67/((1.67*DRG_spread_factor)^2); Expected value: 1,67
Distr_DRG_weight_230	Gamma, alpha = (0.66^2)/((0.66*DRG_spread_factor)^2), lambda = 0.66/((0.66*DRG_spread_factor)^2); Expected value: 0,66
Distr_DRGweight_236	Gamma, alpha = (1.11^2)/((1.11*DRG_spread_factor)^2), lambda = 1.11/((1.11*DRG_spread_factor)^2); Expected value: 1,11
Distr_DRGweight_rehab_hospital	Gamma, alpha = (0.107^2)/((0.107*DRG_spread_factor)^2), lambda = 0.107/((0.107*DRG_spread_factor)^2); Expected value: 0,107
Distr_rehab_nursinghome	Gamma, alpha = (0.06^2)/((0.06*DRG_spread_factor)^2), lambda = 0.06/((0.06*DRG_spread_factor)^2); Expected value: 0,06
Distr_DRGweight_239	Gamma, alpha = (1.14^2)/((1.14*DRG_spread_factor)^2), lambda = 1.14/((1.14*DRG_spread_factor)^2); Expected value: 1,14
Distr_DRGweight_224	Gamma, alpha = (0.83^2)/((0.83*DRG_spread_factor)^2), lambda = 0.83/((0.83*DRG_spread_factor)^2); Expected value: 0,83
Distr_days_of_rehab_hospital	Gamma, alpha = (17^2)/(7^2), lambda = 17/(7^2); Expected value: 17
Distr_days_rehab_nursing	Gamma, alpha = (30^2)/(14^2), lambda = 30/(14^2); Expected value: 30
Distr_n_taxi_wrist	Gamma, alpha = (1^2)/(0.5^2), lambda = 1/(0.5^2); Expected value: 1
Distr_p_DRG_209A	Beta, Real-numbered parameters, alpha = ((0.430025^2)*(1-0.430025)/((0.430025*0.2)^2)), beta = (0.430025*(1-0.430025)/((0.430025*0.2)^2))-((0.430025^2)*(1-0.430025)/((0.430025*0.2)^2)); Expected value: 0,430025
Distr_p_DRG_210	Beta, Real-numbered parameters, alpha = ((0.1435^2)*(1-0.1435)/((0.1435*0.2)^2)), beta = (0.1435*(1-

	0.1435)/((0.1435*0.2)^2))-((0.1435^2)*(1-0.1435)/((0.1435*0.2)^2)); Expected value: 0,1435
Distr_p_DRG_211	Beta, Real-numbered parameters, alpha = ((0.1435^2)*(1-0.1435)/((0.1435*0.2)^2)), beta = (0.1435*(1-0.1435)/((0.1435*0.2)^2))-((0.1435^2)*(1-0.1435)/((0.1435*0.2)^2)); Expected value: 0,1435
Distr_p_DRG_224	Beta, Real-numbered parameters, alpha = ((0.21^2)*(1-0.21)/((0.21*0.2)^2)), beta = (0.21*(1-0.21)/((0.21*0.2)^2))-((0.21^2)*(1-0.21)/((0.21*0.2)^2)); Expected value: 0,21
Distr_p_DRG_230	Beta, Real-numbered parameters, alpha = ((0.06225^2)*(1-0.06225)/((0.06225*0.20)^2)), beta = (0.06225*(1-0.06225)/((0.06225*0.20)^2))-((0.06225^2)*(1-0.06225)/((0.06225*0.20)^2)); Expected value: 0,06225
Distr_p_DRG_236	Beta, Real-numbered parameters, alpha = ((0.0835^2)*(1-0.0835)/((0.0835*0.20)^2)), beta = (0.0835*(1-0.0835)/((0.0835*0.20)^2))-((0.0835^2)*(1-0.0835)/((0.0835*0.20)^2)); Expected value: 0,0835
Distr_p_ER_repl__wrist	Beta, Real-numbered parameters, alpha = ((0.35^2)*(1-0.35)/((0.35*0.2)^2)), beta = (0.35*(1-0.35)/((0.35*0.2)^2))-((0.35^2)*(1-0.35)/((0.35*0.2)^2)); Expected value: 0,35
distr_p_ER_no_repl_wrist	Beta, Real-numbered parameters, alpha = ((0.45^2)*(1-0.45)/((0.45*0.2)^2)), beta = (0.45*(1-0.45)/((0.45*0.2)^2))-((0.45^2)*(1-0.45)/((0.45*0.2)^2)); Expected value: 0,45
distr_p_GP_wrist	Beta, Real-numbered parameters, alpha = ((0.3^2)*(1-0.3)/((0.3*0.20)^2)), beta = (0.3*(1-0.3)/((0.3*0.20)^2))-((0.3^2)*(1-0.3)/((0.3*0.20)^2)); Expected value: 0,3
Distr_p_DRG_239	Beta, Real-numbered parameters, alpha = ((0.38^2)*(1-0.38)/((0.38*0.20)^2)), beta = (0.38*(1-0.38)/((0.38*0.20)^2))-((0.38^2)*(1-0.38)/((0.38*0.20)^2)); Expected value: 0,38
distr_p_other_rehab	Beta, Real-numbered parameters, alpha = ((0.081081081^2)*(1-0.081081081)/((0.081081081*0.20)^2)), beta = (0.081081081*(1-0.081081081)/((0.081081081*0.20)^2))-((0.081081081^2)*(1-0.081081081)/((0.081081081*0.20)^2)); Expected value: 0,081081081

Distr_cost_of_ER_no_replacement	Normal, Mean = 2114, Std Dev = 2114*0.1; Expected value: 2114
distr_p_physio_hip	Beta, Real-numbered parameters, alpha = ((0.33^2)*(1-0.33)/((0.33*0.20)^2)), beta = (0.33*(1-0.33)/((0.33*0.20)^2))-((0.33^2)*(1-0.33)/((0.33*0.20)^2)); Expected value: 0,33
distri_p_physio_wrist	Beta, Real-numbered parameters, alpha = ((0.3^2)*(1-0.3)/((0.3*0.20)^2)), beta = (0.3*(1-0.3)/((0.3*0.20)^2))-((0.3^2)*(1-0.3)/((0.3*0.20)^2)); Expected value: 0,3
distr_p_rehab_hosp	Beta, Real-numbered parameters, alpha = ((0.342342342^2)*(1-0.342342342)/((0.342342342*0.20)^2)), beta = (0.342342342*(1-0.342342342)/((0.342342342*0.20)^2))-((0.342342342^2)*(1-0.342342342)/((0.342342342*0.20)^2)); Expected value: 0,342342342
distr_p_rehab_nursing	Beta, Real-numbered parameters, alpha = ((0.459459459^2)*(1-0.459459459)/((0.459459459*0.20)^2)), beta = (0.459459459*(1-0.459459459)/((0.459459459*0.20)^2))-((0.459459459^2)*(1-0.459459459)/((0.459459459*0.20)^2)); Expected value: 0,459459459
distr_p_remain_vert_seq	Beta, Real-numbered parameters, alpha = ((0.3^2)*(1-0.3)/(0.03^2)), beta = (0.3*(1-0.3)/(0.03^2))-((0.3^2)*(1-0.3)/(0.03^2)); Expected value: 0,3
distr_p_taxi_physio	Beta, Real-numbered parameters, alpha = ((0.33^2)*(1-0.33)/((0.33*0.20)^2)), beta = (0.33*(1-0.33)/((0.33*0.20)^2))-((0.33^2)*(1-0.33)/((0.33*0.20)^2)); Expected value: 0,33
distr_taxi_from_hosp	Beta, Real-numbered parameters, alpha = ((0.2^2)*(1-0.2)/((0.2*0.20)^2)), beta = (0.2*(1-0.2)/((0.2*0.20)^2))-((0.2^2)*(1-0.2)/((0.2*0.20)^2)); Expected value: 0,2
distr_p_taxi_wrist	Beta, Real-numbered parameters, alpha = ((0.67^2)*(1-0.67)/((0.67*0.20)^2)), beta = (0.67*(1-0.67)/((0.67*0.20)^2))-((0.67^2)*(1-0.67)/((0.67*0.20)^2)); Expected value: 0,67
Distr_ER_replacement_wrist	Normal, Mean = 2564, Std Dev = 2554*0.1; Expected value: 2564

Distr_cost_GP	Normal, Mean = 274, Std Dev = 274*0.1; Expected value: 274
distr_p_vert_seq	Beta, Real-numbered parameters, alpha = ((0.333333333^2)*(1-0.333333333)/((0.333333333*0.20)^2)), beta = (0.333333333*(1-0.333333333)/((0.333333333*0.20)^2))-((0.333333333^2)*(1-0.333333333)/((0.333333333*0.20)^2)); Expected value: 0,333333333
distr_p_ambulance_from_hosp	Beta, Real-numbered parameters, alpha = ((0.8^2)*(1-0.8)/((0.8*0.20)^2)), beta = (0.8*(1-0.8)/((0.8*0.20)^2))-((0.8^2)*(1-0.8)/((0.8*0.20)^2)); Expected value: 0,8
distr_p_poly_control	Normal, Mean = 1.25, Std Dev = 0.25; Expected value: 1,25
distr_nvGP1yr	Gamma, alpha = (1^2)/((1*0.5)^2), lambda = 1/((1*0.5)^2); Expected value: 1
distr_n_BMD_following	Gamma, alpha = (0.5^2)/((0.5*0.50)^2), lambda = 0.5/((0.5*0.50)^2); Expected value: 0,5
distr_n_physio_hip	Gamma, alpha = (24^2)/((24*0.50)^2), lambda = 24/((24*0.50)^2); Expected value: 24
distr_n_physio_vertebral	Gamma, alpha = (12^2)/((12*0.50)^2), lambda = 12/((12*0.50)^2); Expected value: 12
distr_n_physio_wrist	Gamma, alpha = (5^2)/((5*0.50)^2), lambda = 5/((5*0.50)^2); Expected value: 5
distr_cost_home_help	Normal, Mean = 22100, Std Dev = 22100*0.1; Expected value: 22100
distr_cost_nursing_home	Normal, Mean = 666138, Std Dev = 666138*0.1; Expected value: 666138
distr_cost_control_poly	Normal, Mean = 700, Std Dev = 700*0.1; Expected value: 700
distr_cost_physio	Normal, Mean = 252, Std Dev = 252*0.1; Expected value: 252
distr_cost_X_ray	Normal, Mean = 675, Std Dev = 675*0.1; Expected value: 675
distr_per_diem_other_rehab	Normal, Mean = 1726, Std Dev = 1726*0.1; Expected value: 1726
distr_unit_cost_ambulance	Normal, Mean = 10000, Std Dev = 10000*0.10; Expected value: 10000
distr_unit_price_painkillers	Normal, Mean = 0.9, Std Dev = 0.9*0.1; Expected value: 0,9

distr_unit_price_taxi	Normal, Mean = 500, Std Dev = 500*0.1; Expected value: 500
distr_vfrm	Log-Normal, u (mean of logs) = Ln(1.95), sigma (std dev of logs) = (Ln(1.97)-Ln(1.94)/1.96*2)*200; Expected value: 2,083759869
Distr_spread_factor_incidence	Normal, Mean = 1, Std Dev = 0.029522176; Expected value: 1
Distr_compl_yr_0	Beta, Real-numbered parameters, alpha = ((0.96^2)*(1-0.96)/(0.1^2)), beta = (0.96*(1-0.96)/(0.1^2))-((0.96^2)*(1-0.96)/(0.1^2)); Expected value: 0,96
distr_factor_RR_Tvs_O	Log-Normal, u (mean of logs) = 0, sigma (std dev of logs) = 0.0005; Expected value: 1,000000125
distr_compl_yr_1	Beta, Real-numbered parameters, alpha = ((0.62^2)*(1-0.62)/(0.1^2)), beta = (0.62*(1-0.62)/(0.1^2))-((0.62^2)*(1-0.62)/(0.1^2)); Expected value: 0,62
disrt_compl_yr_2	Beta, Real-numbered parameters, alpha = ((0.42^2)*(1-0.42)/(0.1^2)), beta = (0.42*(1-0.42)/(0.1^2))-((0.42^2)*(1-0.42)/(0.1^2)); Expected value: 0,42
distr_compl_yr_3	Beta, Real-numbered parameters, alpha = ((0.3^2)*(1-0.3)/(0.1^2)), beta = (0.3*(1-0.3)/(0.1^2))-((0.3^2)*(1-0.3)/(0.1^2)); Expected value: 0,3
distr_comple_yr_4	Beta, Real-numbered parameters, alpha = ((0.22^2)*(1-0.22)/(0.1^2)), beta = (0.22*(1-0.22)/(0.1^2))-((0.22^2)*(1-0.22)/(0.1^2)); Expected value: 0,22
distr_vfrm2	Log-Normal, u (mean of logs) = ln(1.94), sigma (std dev of logs) = sqrt(ln(1.95/1.94)*2); Expected value: 1,95
distr_p_hip_sequelae	Beta, Integer parameters only, n = 420, r = antall_p_hip_seq; Expected value: 0,730952381
distr_p_sev_sequelae	Beta, Integer parameters only, n = 307, r = antall_p_sev_seq; Expected value: 0,234527687
q_HipEvent	Gamma, alpha = ((1-0.7)^2)/(.065^2), lambda = (1-0.7)/(.065^2); Expected value: 0,3
q_VertebralEvent	Gamma, alpha = ((1-0.59)^2)/(.185^2), lambda = (1-0.59)/(.185^2); Expected value: 0,41
q_WristEvent	Gamma, alpha = ((1-0.956)^2)/(.065^2), lambda = (1-0.956)/(.065^2); Expected value: 0,044
q_MildHipSeq	Gamma, alpha = ((1-0.882)^2)/(.28^2), lambda = (1-0.882)/(.28^2); Expected value: 0,118
q_ModHipSeq	Gamma, alpha = ((1-0.80)^2)/(.14^2), lambda = (1-0.80)/(.14^2); Expected value: 0,2
q_SevHipSeq	Gamma, alpha = ((1-0.660051)^2)/(.28^2), lambda = (1-0.660051)/(.28^2); Expected value: 0,339949

q_VertSeq	Gamma, alpha = ((1-0.934)^2)/(.025^2), lambda = (1-0.934)/(.025^2); Expected value: 0,066
vert_distr_compl_m2	Beta, Real-numbered parameters, alpha = 2584, beta = 437; Expected value: 0,855345912
hip_distr_compl_m2	Beta, Real-numbered parameters, alpha = 1675, beta = 352; Expected value: 0,826344351
wrist_distr_compl_m2	Beta, Real-numbered parameters, alpha = 1675, beta = 352; Expected value: 0,826344351
vert_distr_compl_1_5	Beta, Real-numbered parameters, alpha = 3542, beta = 1033; Expected value: 0,77420765
hip_distr_comp_1_5	Beta, Real-numbered parameters, alpha = 3543, beta = 1033; Expected value: 0,774256993
wrist_distr_compl_1_5	Beta, Real-numbered parameters, alpha = 3543, beta = 1033; Expected value: 0,774256993
vert_distr_compl_2u	Beta, Real-numbered parameters, alpha = 3848, beta = 1067; Expected value: 0,782909461
hip_distr_compl_2u	Beta, Real-numbered parameters, alpha = 3543, beta = 1033; Expected value: 0,774256993
wrist_distr_compl_2u	Beta, Real-numbered parameters, alpha = 3543, beta = 1033; Expected value: 0,774256993
vert_distr_compl_2_5	Beta, Real-numbered parameters, alpha = 4757, beta = 1152; Expected value: 0,805043155
hip_distr_compl_2_5	Beta, Real-numbered parameters, alpha = 5330, beta = 1274; Expected value: 0,807086614
wrist_distr_compl_2_5	Beta, Real-numbered parameters, alpha = 5330, beta = 1274; Expected value: 0,807086614
distr_RR_former_fx	Log-Normal, u (mean of logs) = ln(1.62), sigma (std dev of logs) = (Ln(2.01)-Ln(1.30))/(2*1.96); Expected value: 1,630040859
distr_RR_former_high_risk	Beta, Real-numbered parameters, alpha = ((0.5^2)*(1-0.5)/(0.1^2)), beta = (0.5*(1-0.5)/(0.1^2))-((0.5^2)*(1-0.5)/(0.1^2)); Expected value: 0,5

APPENDIX 11: GRADE AND UNCERTAINTY IN PSA

We used the GRADE system to evaluate the quality of the evidence behind the efficacy estimates. In the GRADE system the quality of the evidence is labelled of being of high, moderate, low or very low quality. The confidence we can put in the estimates reflects how likely it is that new research have the potential to change the estimate. As this is a type of uncertainty, we decided to incorporate this uncertainty in the model by assigning a wider spread to the probability distributions for the efficacy parameters for the estimates that were considered more uncertain. The connection between the GRADE system and the uncertainty in the model is presented in table 28.

Table 28: Connection between GRADE and efficacy parameter uncertainty in MOON

Quality of evidence in GRADE terms	**Confidence interval reported in study (95% CI) assumed to represent the following confidence interval in distributions**
High	0.95
Moderate	0.90
Low	0.80
Very low	0.70

APPENDIX 12 T-SCORES AND Z-SCORES

Table 29: Relationship between T-scores and Z-scores in Norwegian women (118)

T-score	Z-score 55	Z-score 65	Z-score 75
-1.5	-0.7	-0.3	0.1
-2.0	-1.2	-0.8	-0.4
-2.5	-1.7	-1.3	-0.9