

Cost-effective intervention thresholds against osteoporotic fractures based on FRAX® in Switzerland

K. Lippuner · H. Johansson · F. Borgström ·
J. A. Kanis · R. Rizzoli

Received: 18 October 2011 / Accepted: 1 December 2011 / Published online: 6 January 2012

© International Osteoporosis Foundation and National Osteoporosis Foundation 2011

Abstract

Summary FRAX-based cost-effective intervention thresholds in the Swiss setting were determined. Assuming a willingness to pay at 2× Gross Domestic Product per capita, an intervention aimed at reducing fracture risk in women and men with a 10-year probability for a major osteoporotic fracture at or above 15% is cost-effective.

Introduction The fracture risk assessment algorithm FRAX® has been recently calibrated for Switzerland. The aim of the present analysis was to determine FRAX-based fracture probabilities at which intervention becomes cost-effective.

Methods A previously developed and validated state transition Markov cohort model was populated with Swiss epidemiological and cost input parameters. Cost-effective FRAX-based intervention thresholds (cost-effectiveness approach) and the

cost-effectiveness of intervention with alendronate (original molecule) in subjects with a FRAX-based fracture risk equivalent to that of a woman with a prior fragility fracture and no other risk factor (translational approach) were calculated based on the Swiss FRAX model and assuming a willingness to pay of 2 times Gross Domestic Product per capita for one Quality-adjusted Life-Year.

Results In Swiss women and men aged 50 years and older, drug intervention aimed at decreasing fracture risk was cost-effective with a 10-year probability for a major osteoporotic fracture at or above 13.8% (range 10.8% to 15.0%) and 15.1% (range 9.9% to 19.9%), respectively. Age-dependent variations around these mean values were modest. Using the translational approach, treatment was cost-effective or cost-saving after the age 60 years in women and 55 in men who had previously sustained a fragility fracture. Using the latter approach leads to considerable underuse of the current potential for cost-effective interventions against fractures.

Conclusions Using a FRAX-based intervention threshold of 15% for both women and men should permit cost-effective access to therapy to patients at high fracture probability based on clinical risk factors and thereby contribute to further reduce the growing burden of osteoporotic fractures in Switzerland.

Keywords Alendronate · Cost-effectiveness · FRAX® · Intervention thresholds · Osteoporosis · Switzerland · 10-year fracture probability

K. Lippuner

Osteoporosis Policlinic, Inselspital,
Bern University Hospital and University of Bern,
Bern, Switzerland

H. Johansson · J. A. Kanis

WHO Collaborating Centre for Metabolic Bone Diseases,
University of Sheffield Medical School,
Sheffield, UK

F. Borgström

LIME/MMC, Karolinska Institutet,
Stockholm, Sweden

R. Rizzoli

Division of Bone Diseases, Department of Medical Specialties,
University Hospital and Medical Faculty of Geneva,
Geneva, Switzerland

K. Lippuner (✉)

University Hospital and University of Bern,
CH-3010 Bern, Switzerland
e-mail: kurt.lippuner@insel.ch

Introduction

Osteoporosis and its complications impose a high economic burden on industrialized countries [1, 2]. At the age of 50 years, the remaining lifetime probability of sustaining a

major osteoporotic fracture (clinical fracture of the hip, spine, distal radius, and proximal humerus) in Switzerland is 51.3% and 20.2% in women and men, respectively [3]. Thus, Switzerland is amongst the countries at highest risk for osteoporotic fractures [3]. In addition, Switzerland ranks second worldwide with regard to the proportion of elderly in its population [4], and the number of persons older than 65 years is expected to double between the years 2005 and 2050 [5]. As a result, health economic projections have shown that in the absence of targeted interventions, the economic burden of osteoporotic fractures to the Swiss healthcare system will considerably increase in coming decades [6].

Bone mineral density (BMD) measured by dual X-ray absorptiometry (DXA) is the current reference standard for the diagnosis of osteoporosis. A femoral neck BMD at or below 2.5 standard deviations (SD) the average mean value of young healthy women ($T\text{-score} \leq -2.5$ SD) was proposed by the World Health Organization (WHO) as an operational definition of osteoporosis [7–9]. The WHO also defined T-scores between -1.0 and -2.49 SD as osteopenia [7–9]. As fracture risk continuously increases with decreasing BMD, these definitions were initially established to define normal ranges and for epidemiologic purposes, and not intended as thresholds for prescribing drugs [7]. However, since BMD is one of the strongest predictors of fracture risk [10–12], many regulatory agencies worldwide, including the Swiss health authorities [13], have adopted these criteria for reimbursement and ipso facto as intervention thresholds. In Switzerland, bisphosphonates, and more recently the monoclonal antibody denosumab, are generally reimbursed if the patient has a BMD $T\text{-score} \leq -2.5$ SD at the lumbar spine or the hip. The available SERMs (raloxifene and bazedoxifene) are reimbursed at a T-score value of -1 SD or below. In addition, all bone active substances are generally reimbursed if the patient has sustained a fragility fracture.

T-score-based intervention in osteoporosis has the merit of simplicity for payers, controllers, physicians, and patients. However, prospective epidemiological studies have shown that many fractures occur in individuals with a BMD T-score value above the operational threshold [14, 15]. In the Swiss Osteo-Care survey, more than half of all patients presenting at an emergency ward with a fragility fracture had BMD measured by DXA at the lumbar spine or the hip above -2.5 SD, of which two thirds had osteopenia [16]. Similarly, in a Swiss fracture service liaison service, 60% of the patients with a fragility fracture had BMD values above -2.5 SD [17].

Currently, there is no universally accepted policy for screening to identify patients at high risk of fracture so that individual patient identification depends on a case-finding strategy generally relying upon the detection of individuals with clinical risk factors for fracture in whom BMD tests are subsequently undertaken [1]. Recently, the FRAX[®] assessment algorithm (<http://www.shef.ac.uk/FRAX>), which is

based on an individual risk factor profile, has been calibrated for Swiss-specific fracture risk and life expectancy [3, 18, 19]. It identified several constellations of risk factors in which patients were at identical or higher level of fracture risk than that based on the T-score alone [18]. In other words, individuals at high fracture risk could be identified who, on the basis of BMD testing, would be ineligible for treatment under current guidance. Conversely, individuals at low fracture risk could be identified who, on the basis of BMD testing, would be eligible for treatment under current guidance. With the development of probability-based fracture assessment, the question arises at what threshold of fracture probability intervention should be recommended.

Due to the large epidemiological and economical variability across countries, cost-effective intervention thresholds based on FRAX[®] will by nature be country-specific. As an example, in the UK, a probability for a major osteoporotic fracture of 7% was considered a cost-effective intervention threshold [20] and in the US, a 3% probability for hip fracture and 20% probability for any major osteoporotic fracture were recommended as cost-effective [21–23].

The objective of the present analysis was to characterize intervention thresholds in a Swiss setting, with branded alendronate in women and men aged 50 years or more that could be justified from a cost-effectiveness assessment.

Methods

Two FRAX[®]-based approaches were used to explore intervention thresholds. The first was to determine the fracture probability at which intervention became cost-effective. The second approach was to examine the cost-effectiveness of intervention thresholds developed in the UK by the National Osteoporosis Guideline Group (NOGG) [24] applied to a Swiss setting. NOGG recommends a case-finding approach incorporating FRAX, with or without BMD. Intervention thresholds are age-specific and based on the probability of fracture in women presenting with history of a prior fragility fracture, irrespective of BMD. The rationale for this derives from the fact that many guidelines [24–27], including in Switzerland [28], recommend that women with a prior fragility fracture should be considered for treatment. Thus, individuals with a fracture probability equal to or exceeding that of women with a prior fragility fracture should also be considered for treatment. This approach, derived from prior guidelines in the UK [27], is in effect a translation of old guidelines to probability-based fracture risk assessment—and has been termed a “translational approach” [29].

Ten-year probabilities of major osteoporotic fractures were calculated using the Swiss-specific FRAX[®] tool [3, 18]. The distributions of clinical risk factors and BMD in women were assumed to be identical to those in the original FRAX[®]

cohorts [30, 31], which were cross-validated with the Swiss Evaluation of Measurement methods of Osteoporosis Fracture risk (SEMOF) cohort [32].

The cost-effectiveness of branded alendronate was compared to no intervention in a Swiss setting by simulating costs and outcomes in cohorts of women and men aged 50 years and older at different probabilities for a major osteoporotic fracture. The perspective was that of the Swiss healthcare system. Only direct medical costs were included. Health effects were measured as quality-adjusted life-years gained (QALYs, i.e., taking into account quality of life as well as life-years) and major results are presented as the incremental cost-effectiveness ratio (ICER).

Utilities

As no utility data are available for Switzerland, we used age-specific utility data from a representative sample of the population of the United Kingdom assessed by the EuroQoL EQ-5D questionnaire, encompassing the health dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [33]. The effect of fractures on quality of life during the first year post event was based on Swedish estimates for disutility following hip, vertebral, forearm, [34], and other fractures [35]. For subsequent years, the quality of life after a hip, vertebral, and radius fracture were estimated at 91%, 93%, and 100% of that of an age-matched healthy individual, respectively [36].

Simulation model

The simulation model was an adaptation of a well-validated transition state Markov cohort model suggested as a reference model for the evaluation of osteoporotic treatments [37–39]. Details of the model structure have been previously described [20, 36, 40–42].

Population fracture risks and mortality

Age-differentiated annual fracture risks in the Swiss population for hip, vertebral, and forearm fractures were derived from a previous study [2]. Country-specific population fracture risks for other fracture sites (pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures) were not available. Fracture risks at these sites were imputed from more complete Swedish data [43, 44] by assuming that the age-specific ratio between the incidence of hip fracture and other fractures in Switzerland would be similar to that in Sweden.

Age-specific population mortality for men and women was derived from WHO statistics for year 2008 [45]. A FRAX[®]-dependent relative risk of death based on a patient's risk factor profile was applied to the mortality rates

to reflect the mortality in the simulated patients' groups. Age-differentiated relative risk of death (first and following years) after hip and clinical vertebral fractures were derived from earlier studies [46–48]. Excess mortality after fractures at these sites is in part related to co-morbidity [48, 49], and it was assumed that 30% of the excess mortality was causally related to the fracture event itself [42, 50, 51]. Forearm fractures were assumed not to entail increased mortality. Relative risk of death during the first year after "other fracture" was assumed to be 1.22 [52].

Effect of treatment

The effects of alendronate on fracture risk were taken from the systematic review used for NICE guidance with the following relative risks (95% confidence interval): hip fracture 0.62 (0.40–0.96), vertebral fracture 0.56 (0.46–0.67), distal forearm, and proximal humerus fracture 0.85 (0.67–1.09) [53]. An intervention for 5 years was modelled as used in other studies [36, 42, 54, 55]. Treatment period was 5 years assuming 50% dropouts during the first half-year cycle and no dropouts thereafter [56, 57]. After stopping treatment, risk reduction was assumed to reverse in a linear manner over 5 years as generally assumed in health economic analyses with bisphosphonates [36, 54, 56] and consistent with results from clinical studies with alendronate [58, 59]. Gastrointestinal side effects were assumed to lead to 23.5 additional GP consultations per 1,000 patient-months in the initial treatment period and 3.5 thereafter, and to require the use of a proton pump inhibitor. Symptoms were assumed to persist for 1 month with a utility loss equivalent to a multiplier of 0.91 as used in the appraisals of NICE [60].

Cost assumptions

A public price Swiss Francs (CHF) 504.00 per full treatment year with branded alendronate was used for health economic modelling. Proton-pump inhibitors were costed at CHF 4.25 per tablet for branded omeprazole and CHF 2.65/tablet for generic omeprazole (public prices excluding VAT).

The cost of a physician visit was CHF 40.00 for 15 min consultation with incremental CHF 51.00 for rapid clinical examination or CHF 85.00 for an extensive clinical examination and CHF 7.40 if drugs were dispensed instead of prescribed. The cost of a BMD measurement including fracture risk assessment, an extensive clinical examination, fracture risk assessment, treatment initiation, and instructions to patients was set at CHF 300.00, as used earlier [56]. Year 2000 costs were adjusted for inflation according to OECD statistics (index 100 in year 2000, 108.8 in year 2008) [61]. Thus, the cost of BMD was inflated to CHF 326.00 corresponding to CHF 75.00 for BMD measurement

by DXA at a single site and CHF 251.00 for added medical services, including medical risk assessment.

Daily inpatient cost in acute care and rehabilitation facilities were CHF 1,009.00 and CHF 440.00 in year 2000, respectively [2, 56]. They were adjusted for inflation as described above. The length of acute hospital stay was assumed to be 17.4 days for a hip fracture, 18.0 days for a clinical spine fracture, and 6.4 days for a fracture of the distal radius [2]. The participation rate in a rehabilitation program after hip fracture was set at 68% of women and 36% of men for a mean duration of stay in the rehabilitation program of 59 and 54 days, respectively [62]. The cost of per day in a nursing home was CHF 187.00/day [56], corresponding to CHF 203.00 after adjustment for inflation.

The probability of being hospitalized after a clinical spine fracture was 33% and 53% after a distal radius fracture [3, 63]. The ambulatory costs of fracture were set at CHF 6,442.00, CHF 2,250.00, and CHF 5,628.00 for hip, spine, and distal forearm fractures, respectively [56, 64]. As used earlier, a discount rate for costs and effects of 3% per year was applied [56].

Determination of the intervention thresholds

There is no generally accepted or recommended cost-effectiveness threshold for medical interventions in Switzerland. WHO has suggested a value of three times the gross domestic product (GDP) per capita as the disability-adjusted life-years (DALY) value to be used as cost-effectiveness threshold in countries with developing economies [65], whereby a DALY can be reasonably assumed comparable to a QALY [66]. Borgström et al. [67] have suggested a willingness to pay (WTP) of $2 \times$ GDP/capita for industrialized countries. In this report, the threshold value for a quality-adjusted year of life was defined as a willingness-to-pay corresponding to two times Swiss GDP/capita in year 2008 (i.e., $2 \times$ CHF 70,272) published by the Swiss Federal Statistical Office (SFSO) [68]. A sensitivity analysis at lower WTP thresholds of 1 and $1.5 \times$ GDP/capita was also performed.

Intervention thresholds at each age were determined from the relationship between fracture probabilities and the cost-effectiveness of all possible combinations of CRFs at T-scores between 0 and -3.5 SD in 0.5 SD steps (512 combinations) with a BMI set to 25 kg/m^2 for each sex and each age (55, 60, 65, 70, 75, 80, and 85 years). Thus, the point generated estimates reflect an unweighted array of possible combinations and not a population simulation.

For the cost-effectiveness approach, piecewise linear regression with 10-year probability (%) for osteoporotic fracture (calculated with BMD) as the independent and ICER as dependent variables was applied. A standard-deviation around the regression line was calculated and used to

determine 95% tolerance intervals. The term tolerance interval is used since the regression points are not drawn from a population sample but an array of different clinical scenarios. For the translational approach, the FRAX probability of a major osteoporotic fracture for a Swiss woman with a previous fragility fracture was calculated for each age, with BMI set at 25 kg/m^2 , no other clinical risk factors, and no BMD. Thereafter, for both sexes at each age and at the specific FRAX values, the corresponding tolerance interval of the ICER was derived from its standard deviation around the regression line.

Results

Cost-effectiveness approach

There was a close relationship between the 10-year probability of a major osteoporotic fracture, derived from the combinations of clinical risk factors and BMD, and the ICER at all ages. Results for women and men at the age of 65 and 80 years are shown in Fig. 1. At the chosen willingness to pay threshold (CHF 140,000/QALY), which corresponds to twice GDP per capita, a majority of the risk factor combinations were cost-effective in women and men at either age. An ICER with a null value may even represent a cost-saving situation.

As shown in Table 1, the intervention threshold (i.e., the fracture probability at which treatment became cost-effective) was relatively stable across all ages and similar in both sexes. The arithmetic mean probability of a major osteoporotic fracture across all age groups at which it became cost-effective to intervene with alendronate was 13.8% (95% tolerance interval 12.3 to 15.9%) and 15.1% (95%TI 12.6 to 20.7%) in women and men, respectively. Therefore, on average, an intervention aimed at reducing fracture risk with alendronate can be considered as generally cost-effective in Switzerland when the 10-year probability of a major osteoporotic fracture exceeds 14% in women and 15% in men aged 50 years or more.

Translational approach

The cost-effectiveness of treating women and men for preventing fractures at a FRAX[®] probability threshold corresponding to a major osteoporotic fracture probability equivalent to that of women with a positive history of fragility fracture with branded alendronate is shown in Table 2. For this universally accepted risk factor and hence probability level for a major osteoporotic fracture, intervention against fracture was cost-effective from the age of 60 years in women and 55 years in men.

As shown in Fig. 2, the intervention thresholds obtained by following a cost-effectiveness approach are consistently lower than those resulting from the translational approach in

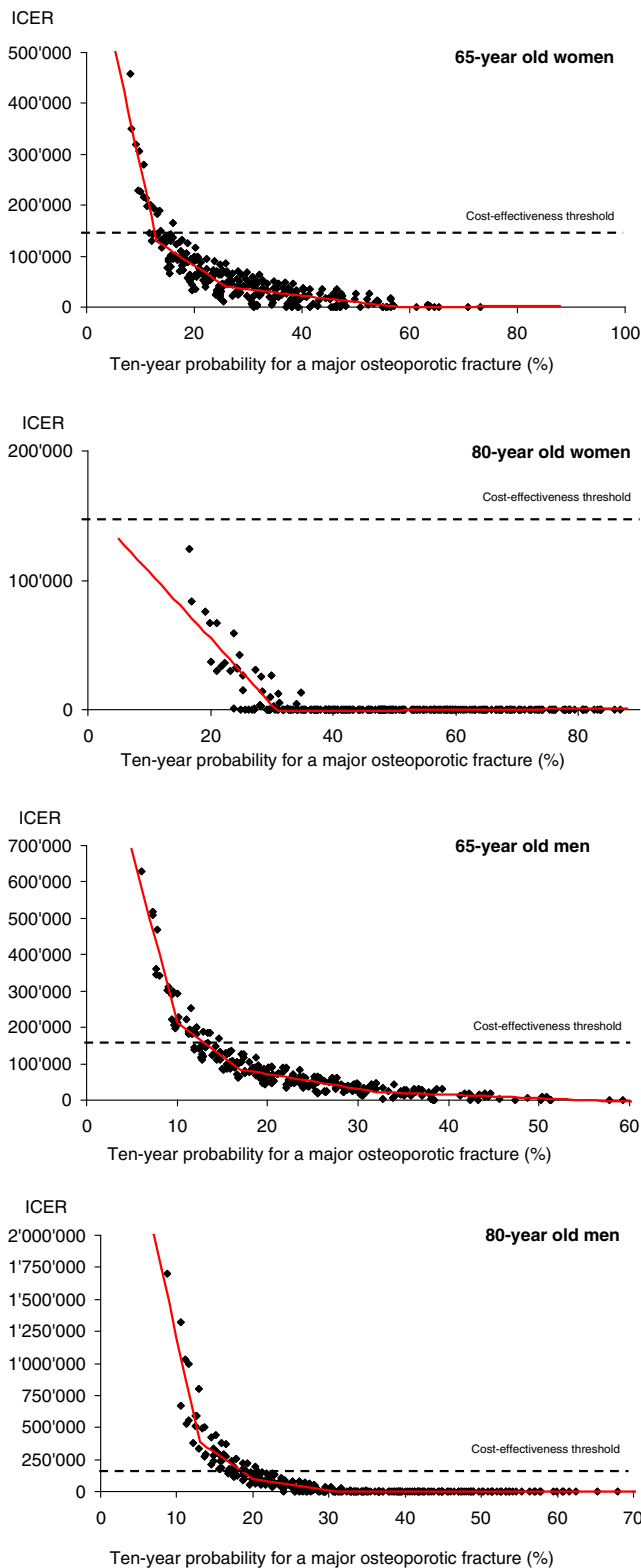


Fig. 1 Association between the 10-year probability of a major osteoporotic fracture and cost-effectiveness. BMI was set to 25 kg/m². The cost-effectiveness threshold was set at a willingness to pay of 2× GDP/capita

Table 1 Ten-year probabilities (percent) of a major osteoporotic fracture (with 95% tolerance interval; TI) at which it was cost-effective to intervene with alendronate with a cost-effectiveness threshold set at a willingness to pay of 2× GDP/capita

Age (years)	Women		Men	
	Probability	95% TI	Probability	95% TI
55	14.1	12.1–17.3	9.9	9.2–12.8
60	14.4	11.6–17.2	12.0	9.9–14.9
65	12.8	11.9–17.5	13.9	11.7–16.2
70	14.4	13.3–15.5	17.5	14.9–20.9
75	14.8	13.2–16.3	19.9	15.6–31.2
80	15.0	14.4–15.6	19.0	16.0–28.7
85	10.8	9.6–12.0	13.5	11.0–19.9
Arithmetic mean	13.8	12.3–15.9	15.1	12.6–20.7

both women and men. This shows that interventions aimed at reducing fracture risk in osteoporotic patients can be implemented in a cost-effective manner in patients at high risk of fracture characterized by a FRAX threshold lower than that of patients with prevalent fractures.

As shown in Figure 3, the strategic choice of a cost-effective vs. a translational threshold also has consequences with regard to the distribution of the population eligible for intervention, as an age-independent threshold (cost-effectiveness approach) results in mainly elderly being eligible for treatment while an age-dependent threshold based on fracture risk equivalence (translational approach) skews the distribution towards younger persons. However, as the FRAX[®]-based intervention threshold should be considered incremental to already accepted intervention thresholds (i.e., in addition to patients with a positive history of fracture and/or a T-score ≤−2.5 SD), the increase in the target population at high probability of fracture being given access to treatment based on FRAX[®] will be relatively small. Overall, assuming an intervention threshold equivalent to or higher than the 10-year fracture probability of a person with a prevalent fragility fracture during adulthood (age-dependent intervention threshold, translational approach), 25.8% of all Swiss women (3.4% of men) aged 50 years or older would be eligible for a targeted intervention based on equivalent fracture risk. Alternatively, assuming an intervention threshold defined as a 10-year probability for any major osteoporotic fracture of 15% or more at any age (age-independent intervention threshold, cost-effectiveness approach), 43.8% of all women (6.9% of men) aged 50 years and older living in Switzerland would be eligible for a cost-effective FRAX[®]-based intervention aimed at reducing fracture risk. These patient populations will expectedly overlap in part with patient populations currently eligible for treatment, i.e., patients with a positive history of fracture and/or a

Table 2 Incremental cost-effectiveness ratio (with 95% confidence interval; CI) of intervention at a 10-year probability of major osteoporotic fracture equivalent to that in persons with a positive history of fragility fracture

Age (years)	Risk of major osteoporotic fracture with a positive history of fragility fracture	ICER (95% CI)	
		Women	Men
55	13.0%	168,683 (117,246–220,119)	101,304 (65,053–137,556)
60	16.0%	119,113 (83,211–155,014)	96,431 (65,143–127,718)
65	18.0%	95,035 (53,725–136,345)	80,023 (38,783–121,263)
70	25.0%	44,492 (20,268–68,715)	0 (0–120,839)
75	37.0%	2,779 (0–20,538)	0 (0–116,155)
80	41.0%	0 (0–10,939)	0 (0–120,746)
85	41.0%	0 (0–12,541)	29 (0–138,182)

Scenarios where the ICER was less than a WTP of CHF 140,000/QALY (twice GDP per capita) gained are highlighted in bold

T-score ≤ -2.5 SD and give access to targeted fracture risk reduction interventions to those at increased clinical fracture risk based on their FRAX[®]-score.

Sensitivity analysis

The cost-effective intervention thresholds derived from the cost-effectiveness approach in relation to WTP cut-offs of 2.0, 1.5 \times , and 1.0 \times GDP per capita are shown in Fig. 4. As expected, the mean cost-effective intervention threshold increases with decreasing WTP, from 13.8 to 16.3 and 20.1% in women and from 15.1 to 16.9 and 19.9% in men, respectively. Interestingly, age-dependent variations around these mean values were modest: 14.1%, 12.8%, 14.8%, 10.8% and 9.9%, 13.9%, 19.9%, 13.5% in 55-, 65-, 75-, and 85-year-old women and men in the base case scenario, respectively.

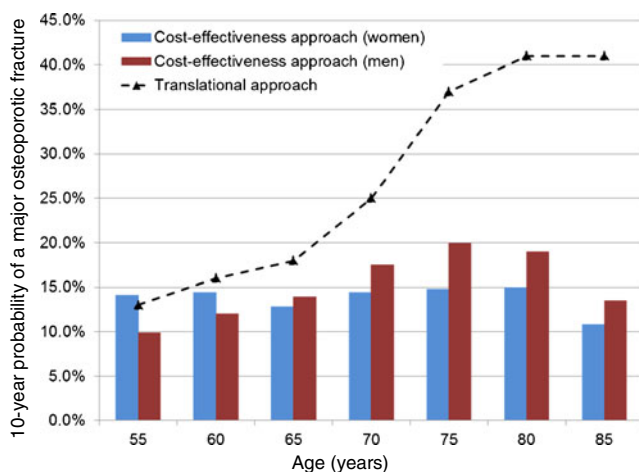


Fig. 2 Intervention thresholds for drug therapy reducing fracture risk at the female and male population level: translational approach (age-dependent risk equivalence with positive history of fragility fracture) vs. cost-effectiveness approach (cost-effective intervention threshold by sex)

Discussion

The currently accepted criteria for treatment of osteoporosis in Switzerland are a BMD T-score ≤ -2.5 SD or a prevalent fragility fracture. The present study shows that intervention can be delivered cost-effectively in women and men in whom the 10-year probability for a major osteoporotic fracture is approximately 15% or more. Age-dependent variations around these mean values were modest. We additionally show that treatment is cost-effective in patients with a fracture probability equivalent to that of a woman with a prior fragility fracture and no other clinical risk factors in women and men from the age of 60 and 55 years, respectively. These findings indicate that treatment should be considered in women and men who exceed these probability thresholds, irrespective of the presence of a prior fracture or a specific T-score criterion.

Several surveys indicate that half or more of all patients presenting with a fragility fracture have BMD T-scores at the lumbar spine or the hip higher than -2.5 SD, i.e., are not osteoporotic [69–71] and similar findings are reported in studies based in Switzerland [16, 17]. In Switzerland, drug therapy against osteoporosis with a bisphosphonate or denosumab is generally reimbursed if the patient has a T-score at or below -2.5 SD and/or a prevalent fragility fracture. Thus, the reimbursement policy disenfranchises a segment of the population at risk. For example, a woman aged 65 years with a prior fragility fracture and no other clinical risk factors has a 10-year probability of a major fracture of 18% (FRAX v3.4 available at <http://www.shef.ac.uk/FRAX>) and qualifies for reimbursed treatment under current restrictions. In contrast, a woman of the same age, with a parental history of hip fracture, and on an average dose of glucocorticoids, is currently ineligible even though her fracture probability is higher than the woman with the fragility fracture (27% vs. 18%). Although treatment is cost-effective of both patients, it is more cost-effective in the latter case.

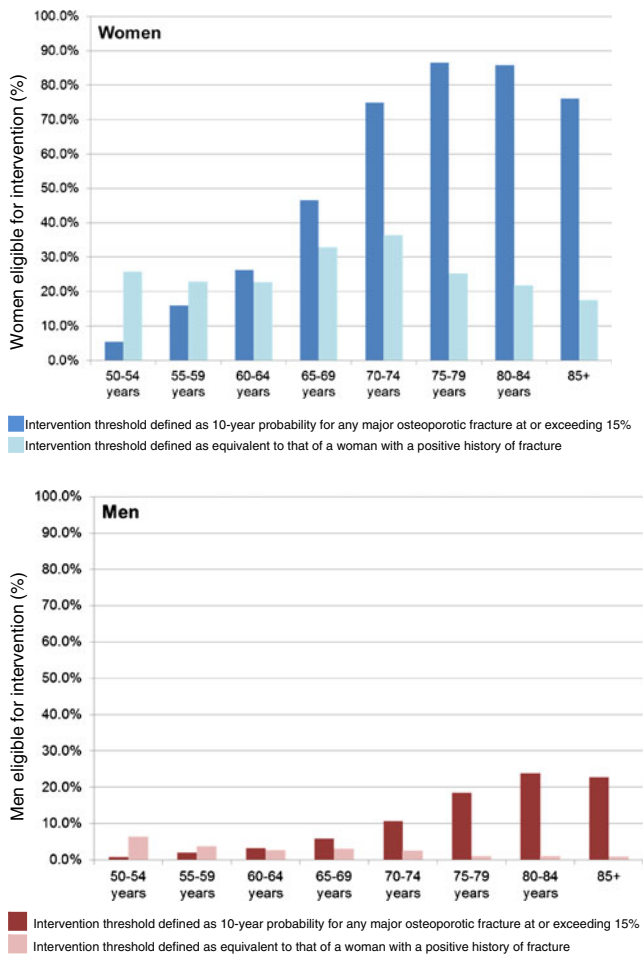


Fig. 3 Distribution of the target population (percent of women and men in each age category) with age-dependent and age-independent intervention thresholds

In order to overcome this inequity, the Swiss 2010 edition of recommendations for the diagnosis and treatment of osteoporosis issued by the Swiss Association against Osteoporosis (SVGO/ASCO) also recommend drug therapy aimed at reducing fracture risk for such patients [28]. A FRAX[®]-based age-dependent intervention cut-off was recommended based on a translational approach, i.e., where the fracture probability exceeded that of a woman with a prior fragility fracture. Whereas this recommendation is cost-effective, as shown in the present study, it does not fully exploit the potential for cost-effective interventions derived from ICER-dependent thresholds. Using this approach, patients with a FRAX[®] probability for any major osteoporotic fracture of 15% or more could be treated cost-effectively.

Approximately 44% of women aged 50 years or more in Switzerland have a 10-year fracture probability that exceeds 15%. The proportion of women with a fracture probability exceeding that of a woman with a prior fracture is 26%. In practice, the increment in the number of women eligible for

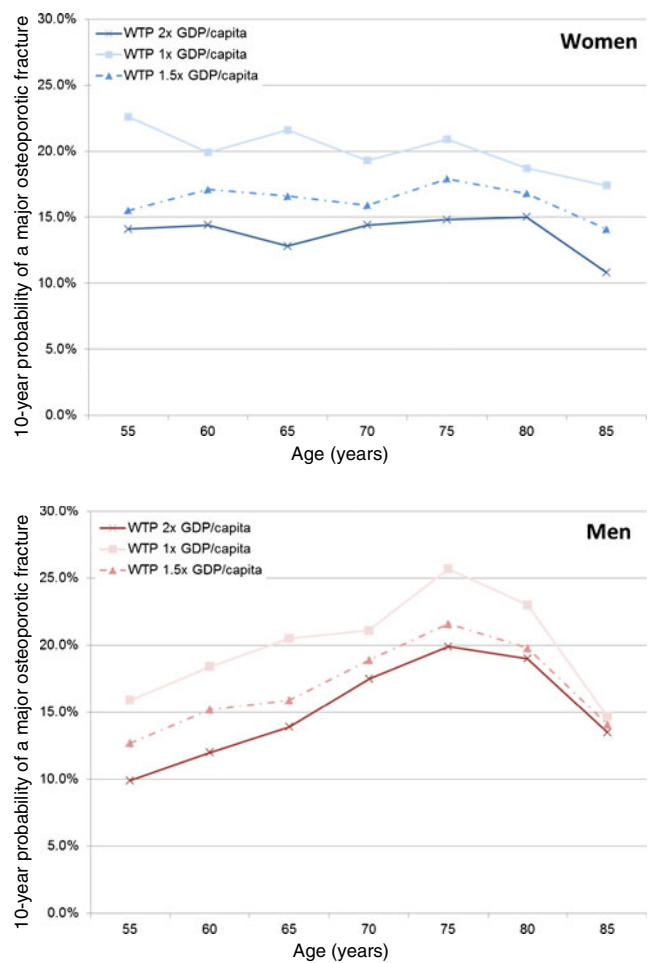


Fig. 4 Sensitivity analysis. Cost-effective intervention thresholds at WTP of 2.0 \times , 1.5 \times , and 1.0 \times GDP per capita in women and men

treatment will be substantially less than 18% (44% minus 26%) because many will already have qualified for treatment on the basis of BMD or prior fracture criteria. In any case, using FRAX-based intervention thresholds instead of or in addition to currently accepted criteria will lead to an increase in health care resource allocation which could be compensated by shifting budgets from less or not cost-effective healthcare interventions towards documented cost-effective interventions such as the treatment of osteoporosis with alendronate based on the FRAX thresholds proposed in the present analysis.

Branded alendronate (alendronate OM) was chosen for the present analysis as it was the most frequently prescribed oral bisphosphonate in Switzerland in year 2008. We assumed treatment with alendronate OM at an annual cost of CHF 504.00. In 2011, the annual cost is CHF 485.10, so that our results are marginally conservative at today's prices. However, other treatments for osteoporosis are available, such as generic alendronate (mean annual drug price of

CHF 361.00, –26% vs. alendronate OM), zoledronate for yearly IV infusion (mean annual drug price of CHF 686.65, excluding cost of administration, +29% vs. alendronate OM) and denosumab for subcutaneous injection (mean annual drug price of CHF 717.00, excluding cost of administration, +32% vs. alendronate OM). Thus, the cost-effectiveness of each therapeutic intervention varies, even when assuming equal efficacy. It could be argued from an economic perspective that each agent would have a different intervention threshold determined by its individual cost-effectiveness. Therefore, there are some patients who cannot take alendronate and who are at a too-low risk to start an alternative treatment purely based on cost-effectiveness. As argued elsewhere [72], this sets an ethical dilemma for the primary care physician in that patients who cannot take alendronate would not be afforded any treatment until their condition had deteriorated sufficiently to provide an alternative treatment. In order to avoid the problem, the National Osteoporosis Guideline Group in the UK used the same intervention thresholds for these alternative agents as used for (generic) alendronate despite their higher price [24]. This position was taken because cost-effective scenarios for these interventions were found at a WTP of GBP 20,000–30,000/QALY which is currently accepted by NICE in the UK [72].

Lower price is an argument for extending treatment to patients at lower risk which may give head room for innovation; i.e., free resources for new treatments (within or outside osteoporosis). Assuming, for example, that all treatments have equal efficacy if used in the correct population, and that the cost of an alternative to generic alendronate was CHF 700.00 per year, then 42% of patients could be offered such new treatments without prejudicing the average cost-effectiveness of an intervention program [20].

Whereas direct comparative head-to-head fracture endpoint trials between alendronate and alternatives are lacking, evidence to date suggests that, at least in terms of fracture risk reduction, zoledronic acid and denosumab are more efficacious than alendronate OM [53]. On the other hand, clinical equivalence between generic and branded bisphosphonates has been recently challenged [73–75]. Clinical chart reviews [74] and the experience of switching from branded to generic formulations [75] suggest that a number of generic formulations are associated with poorer adherence, more frequent side effects, and thus poorer effectiveness than branded agents. This observation of poorer persistence with generic bisphosphonates has implications for cost-effectiveness and is likely to favor the incremental cost-effectiveness of alternative agents [52]. In the present analysis, the adherence assumptions with branded alendronate were consistent with those used in previous work [56, 57]. While the importance of adherence on clinical and economical outcomes is increasingly recognized [76], using other assumptions would have increased or decreased the cost-effective intervention threshold but not

altered the principal conclusion of the present analysis, which is that this threshold is not age-dependent.

The interpretation of our results is dependent on the WTP assumed. There are no universally accepted cost-effectiveness thresholds, but the WHO Commission on Macroeconomics and Health [65] suggests that interventions with a cost-effectiveness ratio lower than three times the GDP per capita for each averted disability-adjusted life year (DALY) should be considered to be cost-effective. Assuming that the values for a DALY and a QALY are reasonably comparable [66], a cost-effective threshold for Switzerland would be CHF 211,000. It is not specified in the report of the WHO Commission what costs are included, but if all costs are included, such as cost of added life-years, then the threshold value should be set at a lower level when a health-care perspective is taken. For this reason, we used a WTP threshold of twice GDP in accordance with previous recommendations [66, 77]. We also explored the effects of more conservative scenarios. With a WTP equal to GDP, cost-effective scenarios were found at a 10-year fracture probability of 20% rather than 15% as used in the base case.

Patients included in fracture endpoint trials with alendronate were not recruited based on FRAX[®] or clinical risk factors but on T-score values and/or prevalence of vertebral fractures. The present health economic evaluation assumes that similar fracture risk reduction effects will be obtained if alendronate was used in patients recruited on the basis of their FRAX[®] score. In the meantime, the adequacy of this assumption has been validated for one bisphosphonate (clodronate [78]), two selective estrogen receptor modulators (basedoxifene [79] and raloxifene [80]), and denosumab [81]. In these analyses, high FRAX[®] probabilities were associated with treatment efficacy even when BMD was not used, supporting the use of this assumption for other bone active substances proven to reduce fracture risk such as alendronate. In addition, selection of high-risk patients on the basis of FRAX (without BMD) preferentially selects patients with low BMD [82].

A limitation of our study is that the sensitivity analysis was restricted to three WTP thresholds. However, while a detailed univariate sensitivity analysis would have increased or decreased the proposed intervention thresholds, it would not have altered the conclusion, which is that age has little to no influence on these thresholds. The epidemiological and cost data used in the present model relied mainly on previously published data from year 2000 [83] which is a limitation of our study. However, cost input parameters were adjusted for inflation up to year 2008. Furthermore, while hospitalizations for hip fractures have declined and the average length of hospital stay after fracture has decreased in Switzerland between 2000 and 2008, the total cost of hospitalizations for major osteoporotic fractures have increased by 27.7% in women and 36.4% in men as a combined effect of a rapidly ageing population, increasing daily costs of hospitalizations, and increasing absolute number of hospitalizations for such

fractures [83, 84]. Therefore, we believe that the epidemiological and cost assumptions underlying modelling results remain conservative. Finally, it should be kept in mind that intervention thresholds based on health economic modelling results should not be used alone for clinical decision making. The thresholds identified in the present analysis should be used in conjunction with all clinically relevant patient characteristics beyond the individual FRAX score.

Conclusion

In Switzerland, drug intervention aimed at decreasing fracture risk is cost-effective in all women and men aged 50 years and older with a 10-year probability for a major osteoporotic fracture calculated with the Swiss specific FRAX[®] algorithm at or above 15%. Using this intervention threshold, the FRAX[®] score should contribute to open access to therapy to patients at high fracture probability based on clinical risk factors and to thereby further reduce the growing burden of osteoporotic fractures in Switzerland.

Acknowledgements We are grateful to Martin Kleman, Innovus, Stockholm, Sweden for his contribution to health economic modelling and running the simulations and to Dr. Philippe Kress, Kressmed, Glattbrugg, Switzerland for his contribution to data analysis and his critical review of the manuscript.

Conflicts of interest None

Disclaimers None

Funding This work was supported by an unrestricted research grant from MSD Switzerland AG. The sponsor had no influence on design, analysis, or interpretation of the data.

References

- Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R (2008) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 19:399–428
- Lippuner K, Golder M, Greiner R (2005) Epidemiology and direct medical costs of osteoporotic fractures in men and women in Switzerland. *Osteoporos Int* 16(Suppl 2):S8–S17
- Lippuner K, Johansson H, Kanis JA, Rizzoli R (2009) Remaining lifetime and absolute 10-year probabilities of osteoporotic fracture in Swiss men and women. *Osteoporos Int* 20:1131–1140
- Robine JM, Paccard F (2005) Nonagenarians and centenarians in Switzerland, 1860–2001: a demographic analysis. *J Epidemiol Community Health* 59:31–37
- Bundesamt für Statistik. Szenarien zur Bevölkerungsentwicklung der Schweiz 2005–2050. <http://www.bfs.admin.ch/bfs/portal/de/index/news/publikationen.Document.83713.pdf>. Last visited May 14, 2008.
- Schwenkglens M, Lippuner K, Hauselmann HJ, Szucs TD (2005) A model of osteoporosis impact in Switzerland 2000–2020. *Osteoporos Int* 16:659–671
- (1993) Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 94(6):646–650
- Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltsev N (1994) The diagnosis of osteoporosis. *J Bone Miner Res* 9: 1137–1141
- Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltsev N (2008) A reference standard for the description of osteoporosis. *Bone* 42:467–475
- Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. *Lancet* 359:1929–1936
- Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 312:1254–1259
- Cummings SR, Black D (1995) Bone mass measurements and risk of fracture in Caucasian women: a review of findings from prospective studies. *Am J Med* 98:24S–28S
- (2011) Bundesamt für Gesundheit (BAG). List of reimbursed medicines in Switzerland (Spezialitätenliste). <http://www.sl.bag.admin.ch>
- Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A (2000) Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. *Bone* 27:585–590
- Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA, Berger ML, Santora AC, Sherwood LM (2001) Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA* 286:2815–2822
- Suhm N, Lamy O, Lippuner K (2008) Management of fragility fractures in Switzerland: results of a nationwide survey. *Swiss Med Wkly* 138(45–46):674–683
- Chevalley T, Hoffmeyer P, Bonjour JP, Rizzoli R (2002) An osteoporosis clinical pathway for the medical management of patients with low-trauma fracture. *Osteoporos Int* 13:450–455
- Lippuner K, Johansson H, Kanis JA, Rizzoli R (2010) FRAX assessment of osteoporotic fracture probability in Switzerland. *Osteoporos Int* 21:381–389
- Kanis JA, Johansson H, Oden A, McCloskey EV (2009) Assessment of fracture risk. *Eur J Radiol* 71:392–397
- Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A (2008) Case finding for the management of osteoporosis with FRAX assessment and intervention thresholds for the UK. *Osteoporos Int* 19:1395–1408
- Dawson-Hughes B, Tosteson AN, Melton LJ 3rd, Baim S, Favus MJ, Khosla S, Lindsay RL (2008) Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. *Osteoporos Int* 19:449–458
- Tosteson AN, Melton LJ 3rd, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, Lindsay RL (2008) Cost-effective osteoporosis treatment thresholds: the United States perspective. *Osteoporos Int* 19:437–447
- Dawson-Hughes B (2008) A revised clinician's guide to the prevention and treatment of osteoporosis. *J Clin Endocrinol Metab* 93:2463–2465
- Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D, McCloskey EV, Reid DM, Selby P, Wilkins M (2009) Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas* 62:105–108
- (2010) National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. <http://www.nof.org/professionals/clinical-guidelines>.
- Papaioannou A, Morin S, Cheung AM et al (2010) 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *Cmaj* 182:1864–1873

27. (1999) Royal College of Physicians. Osteoporosis: clinical guidelines for the prevention and treatment. London, Royal College of Physicians
28. (2010) Diagnostik, Prävention und Behandlung der Osteoporose: Empfehlungen der Schweizerischen Gesellschaft gegen Osteoporose (SVGO). <http://www.svgo.ch/>. Last visited August 8, 2011:
29. Kanis JA, Oden A, Johansson H, Borgstrom F, Strom O, McCloskey E (2009) FRAX and its applications to clinical practice. *Bone* 44:734–743
30. Kanis J (2007) World Health Organization Scientific Group. Assessment of osteoporosis at the primary health care level. Technical report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK.
31. Kanis JA, Oden A, Johnell O et al (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 18:1033–1046
32. Krieg MA, Cornuz J, Ruffieux C et al (2006) Prediction of hip fracture risk by quantitative ultrasound in more than 7000 Swiss women ≥ 70 years of age: comparison of three technologically different bone ultrasound devices in the SEMOF study. *J Bone Miner Res* 21:1457–1463
33. Kind P, Dolan P, Gudex C, Williams A (1998) Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ* 316:736–741
34. Borgstrom F, Zethraeus N, Johnell O et al (2006) Costs and quality of life associated with osteoporosis-related fractures in Sweden. *Osteoporos Int* 17:637–650
35. Kanis JA, Johnell O, Oden A, Borgstrom F, Zethraeus N, De Laet C, Jonsson B (2004) The risk and burden of vertebral fractures in Sweden. *Osteoporos Int* 15:20–26
36. Kanis JA, Adams J, Borgstrom F, Cooper C, Jonsson B, Preedy D, Selby P, Compston J (2008) The cost-effectiveness of alendronate in the management of osteoporosis. *Bone* 42:4–15
37. Kanis JA, Borgstrom F, Zethraeus N, Johnell O, Oden A, Jonsson B (2005) Intervention thresholds for osteoporosis in the UK. *Bone* 36:22–32
38. Kanis JA, Johnell O, Oden A, Borgstrom F, Johansson H, De Laet C, Jonsson B (2005) Intervention thresholds for osteoporosis in men and women: a study based on data from Sweden. *Osteoporos Int* 16:6–14
39. Zethraeus N, Borgstrom F, Strom O, Kanis JA, Jonsson B (2007) Cost-effectiveness of the treatment and prevention of osteoporosis—a review of the literature and a reference model. *Osteoporos Int* 18:9–23
40. Borgstrom F, Strom O, Coelho J, Johansson H, Oden A, McCloskey E, Kanis JA (2010) The cost-effectiveness of risedronate in the UK for the management of osteoporosis using the FRAX. *Osteoporos Int* 21:495–505
41. Borgstrom F, Strom O, Coelho J, Johansson H, Oden A, McCloskey E, Kanis JA (2010) The cost-effectiveness of strontium ranelate in the UK for the management of osteoporosis. *Osteoporos Int* 21:339–349
42. Borgstrom F, Carlsson A, Sintonen H, Boonen S, Haentjens P, Burge R, Johnell O, Jonsson B, Kanis JA (2006) The cost-effectiveness of risedronate in the treatment of osteoporosis: an international perspective. *Osteoporos Int* 17:996–1007
43. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporos Int* 12:417–427
44. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, De Laet C, Jonsson B (2000) Long-term risk of osteoporotic fracture in Malmo. *Osteoporos Int* 11:669–674
45. (2008) Life tables for WHO member states. Switzerland. http://www.who.int/healthinfo/statistics/mortality_life_tables/en/ Accessed May 12, 2011.
46. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Pettersson C, De Laet C, Jonsson B (2004) Mortality after osteoporotic fractures. *Osteoporos Int* 15:38–42
47. Oden A, Dawson A, Dere W, Johnell O, Jonsson B, Kanis JA (1998) Lifetime risk of hip fractures is underestimated. *Osteoporos Int* 8:599–603
48. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B (2004) Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int* 15:108–112
49. Poor G, Atkinson EJ, O’Fallon WM, Melton LJ 3rd (1995) Determinants of reduced survival following hip fractures in men. *Clin Orthop Relat Res* (319):260–265
50. Parker MJ, Anand JK (1991) What is the true mortality of hip fractures? *Public Health* 105:443–446
51. (2008) NICE. Osteoporosis—secondary prevention including strontium ranelate: appraisal consultation document. <http://guidance.nice.org.uk/TA161> under www.nice.org.uk. Accessed May 12, 2011.
52. Jonsson B, Strom O, Eisman JA, Papaioannou A, Siris ES, Tosteson A, Kanis JA (2011) Cost-effectiveness of denosumab for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 22:967–982
53. (2008) National Institute for Health and Clinical Excellence (NICE). Systematic reviews of clinical effectiveness prepared for the guideline ‘Osteoporosis: assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk’ <http://www.nice.org.uk/nicemedia/live/11621/42362/42362.pdf>. Last visited April 18, 2011.
54. Kanis JA, Borgstrom F, Johnell O, Jonsson B (2004) Cost-effectiveness of risedronate for the treatment of osteoporosis and prevention of fractures in postmenopausal women. *Osteoporos Int* 15:862–871
55. Kanis JA, Borgstrom F, Johnell O, Oden A, Sykes D, Jonsson B (2005) Cost-effectiveness of raloxifene in the UK: an economic evaluation based on the MORE study. *Osteoporos Int* 16:15–25
56. Schwenkgenks M, Lippuner K (2007) Simulation-based cost-utility analysis of population screening-based alendronate use in Switzerland. *Osteoporos Int* 18:1481–1491
57. Cramer JA, Gold DT, Silverman SL, Lewiecki EM (2007) A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int* 18:1023–1031
58. Black DM, Schwartz AV, Ensrud KE et al (2006) Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 296:2927–2938
59. Bagger YZ, Tanko LB, Alexandersen P, Ravn P, Christiansen C (2003) Alendronate has a residual effect on bone mass in postmenopausal Danish women up to 7 years after treatment withdrawal. *Bone* 33:301–307
60. Lloyd Jones M, Wilkinson A (2006) Adverse effects and persistence with therapy in patients taking oral alendronate, etidronate or risedronate: a systematic review. NHS R & D HTA SCHARR. <http://www.nice.org.uk/nicemedia/live/11680/36718/36718.pdf>. Accessed May 12, 2011.
61. (2011) OECD Consumer Price Indices. Available from www.oecd.org/std/prices-indices. <http://stats.oecd.org/Index.aspx?querytype=view&queryname=221>. Accessed May 12, 2011.
62. Trombetti A, Herrmann F, Hoffmeyer P, Schurch MA, Bonjour JP, Rizzoli R (2002) Survival and potential years of life lost after hip fracture in men and age-matched women. *Osteoporos Int* 13:731–737
63. Suhm N, Lamy O, Lippuner K (2008) Management of fragility fractures in Switzerland: results of a nationwide survey. *Swiss Med Wkly* 138:674–683

64. Szucs TD, Hauselmann H (2000) Die Wirtschaftlichkeit von Alendronat in der Behandlung der postmenopausalen Osteoporose. *Ökon Qual Manag* 5:99–106
65. (2001) *Macroeconomics and Health: Investing in Health for Economic Development*. Report of the Commission on Macroeconomics and Health. Available under <http://whqlibdoc.who.int/publications/2001/924154550x.pdf>. Last accessed October 4th, 2011. Geneva, World Health Organization
66. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B (2004) Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? *Value Health* 7:518–528
67. Borgstrom F, Johnell O, Kanis JA, Jonsson B, Rehnberg C (2006) At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. *Osteoporos Int* 17:1459–1471
68. Swiss Federal Statistical Office (SFSO). Gross Domestic Product per capita. http://www.bfs.admin.ch/bfs/portal/de/index/themen/04/02/01/key/bip_einw.html. Last visited April 18th, 2011.
69. Siris ES, Chen YT, Abbott TA, Barrett-Connor E, Miller PD, Wehren LE, Berger ML (2004) Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med* 164:1108–1112
70. Pasco JA, Seeman E, Henry MJ, Merriman EN, Nicholson GC, Kotowicz MA (2006) The population burden of fractures originates in women with osteopenia, not osteoporosis. *Osteoporos Int* 17:1404–1409
71. Sanders KM, Nicholson GC, Watts JJ, Pasco JA, Henry MJ, Kotowicz MA, Seeman E (2006) Half the burden of fragility fractures in the community occur in women without osteoporosis. When is fracture prevention cost-effective? *Bone* 38:694–700
72. Kanis JA, McCloskey E, Jonsson B, Cooper A, Strom O, Borgstrom F (2010) An evaluation of the NICE guidance for the prevention of osteoporotic fragility fractures in postmenopausal women. *Archives of Osteoporosis* 5:19–48
73. Kanis JA, Reginster JY, Kaufman JM, Ringe JD, Adachi JD, Hiligsmann M, Rizzoli R, Cooper C (2011) A reappraisal of generic bisphosphonates in osteoporosis. *Osteoporos Int* (in press)
74. Ringe JD, Moller G (2009) Differences in persistence, safety and efficacy of generic and original branded once weekly bisphosphonates in patients with postmenopausal osteoporosis: 1-year results of a retrospective patient chart review analysis. *Rheumatol Int* 30:213–221
75. Sheehy O, Kindundu CM, Barbeau M, LeLorier J (2009) Differences in persistence among different weekly oral bisphosphonate medications. *Osteoporos Int* 20:1369–1376
76. Kanis JA, Cooper C, Hiligsmann M, Rabenda V, Reginster JY, Rizzoli R (2011) Partial adherence: a new perspective on health economic assessment in osteoporosis. *Osteoporos Int* 22:2565–2573
77. Kanis JA, Jonsson B (2002) Economic evaluation of interventions for osteoporosis. *Osteoporos Int* 13:765–767
78. McCloskey EV, Johansson H, Oden A, Vasireddy S, Kayan K, Pande K, Jalava T, Kanis JA (2009) Ten-year fracture probability identifies women who will benefit from clodronate therapy—additional results from a double-blind, placebo-controlled randomised study. *Osteoporos Int* 20:811–817
79. Kanis JA, Johansson H, Oden A, McCloskey EV (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX. *Bone* 44:1049–1054
80. Kanis JA, Johansson H, Oden A, McCloskey EV (2010) A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX. *Bone* 47:729–735
81. McCloskey E, Lewiecki EM, Kanis JA et al (2011) Denosumab reduces the risk of clinical osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX®. *Osteoporos Int* 22(supplement 1):S103
82. Kanis JA, McCloskey E, Johansson H, Oden A, Leslie WD (2011) FRAX® with and without BMD. *Calcif Tissue Int* (in press)
83. Lippuner K, Popp AW, Schwab P, Gitlin M, Schaufler T, Senn C, Perrelet R (2010) Fracture hospitalizations between years 2000 and 2007 in Switzerland: a trend analysis. *Osteoporos Int* (in press)
84. Chevalley T, Guille E, Herrmann FR, Hoffmeyer P, Rapin CH, Rizzoli R (2007) Incidence of hip fracture over a 10-year period (1991–2000): reversal of a secular trend. *Bone* 40:1284–1289