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ORIGINAL ARTICLE

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

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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

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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-score≤−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-score≤−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× 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× CHF 70,272) published by the Swiss Federal Statistical Office (SFSO) [68]. A sensitivity analysis at lower WTP thresholds of 1 and 1.5× 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

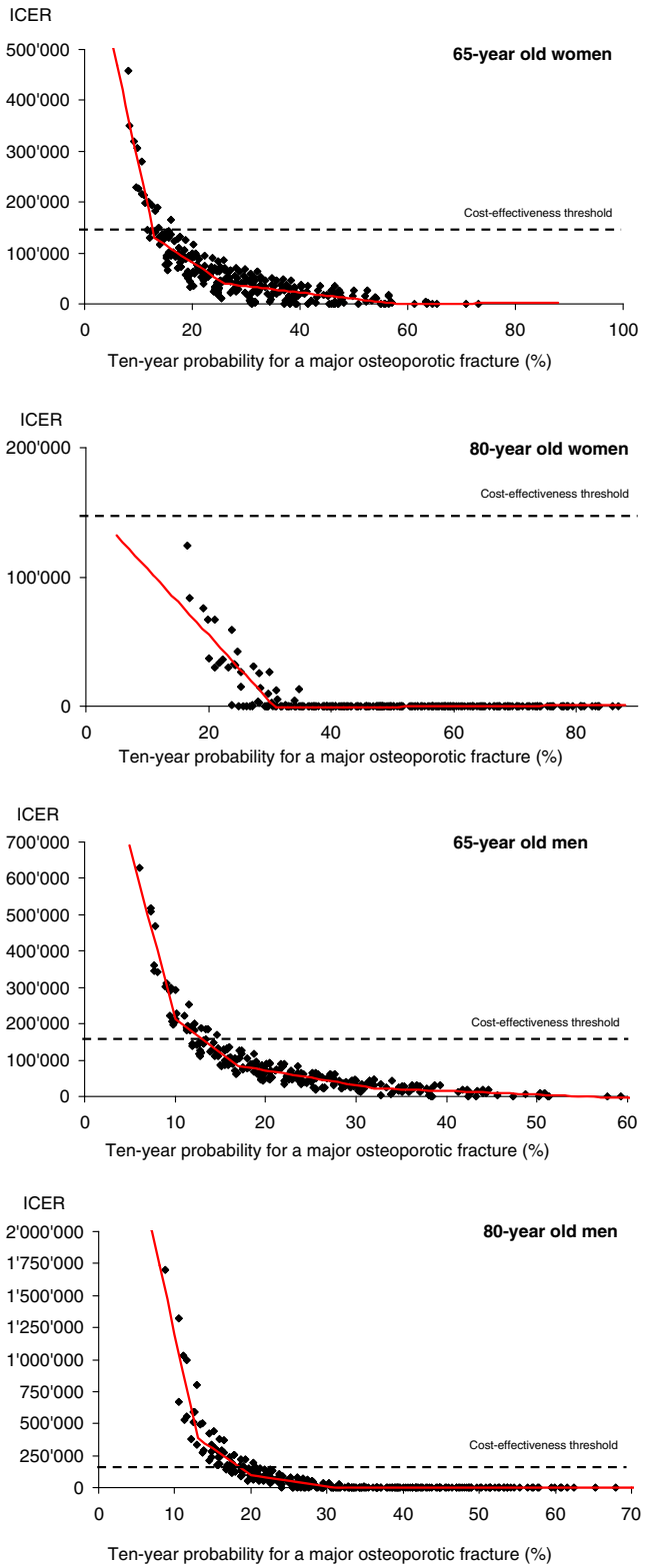

Fig. 1 Association between the 10-year probability of a major osteoporotic fracture and cost-effectiveness. BMI was set to 25 kg/m^2. The cost-effectiveness threshold was set at a willingness to pay of 2× GDP/capita

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×, and 1.0× 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.

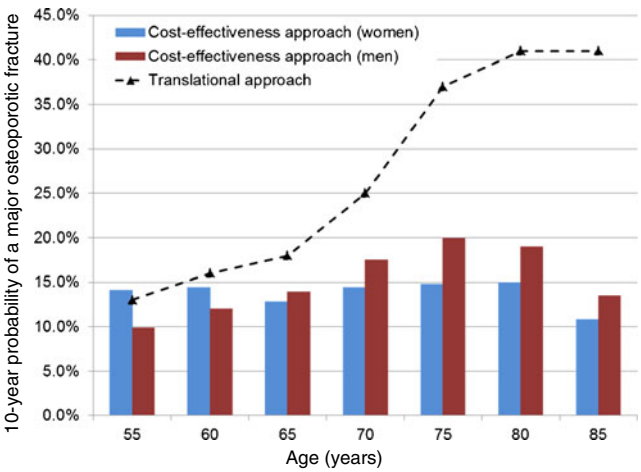

Fig. 2 Intervention thresholds for drug therapy reducing fracture risk at the female and male population level: translational approach (age-dependent risk equivalence with positive history of fragility fracture) vs. cost-effectiveness approach (cost-effective intervention threshold by sex)

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.

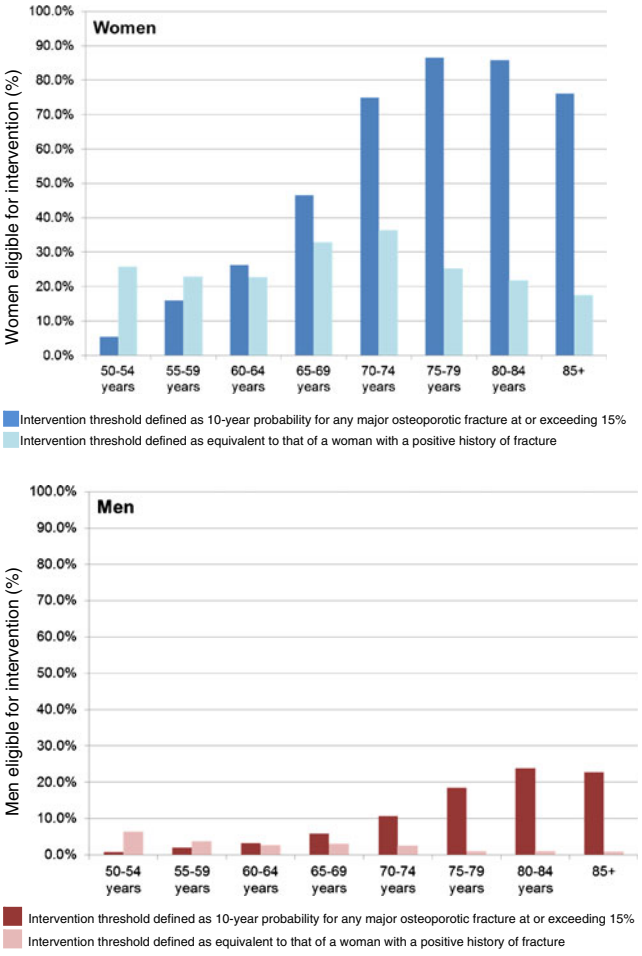

Fig. 3 Distribution of the target population (percent of women and men in each age category) with age-dependent and age-independent intervention thresholds

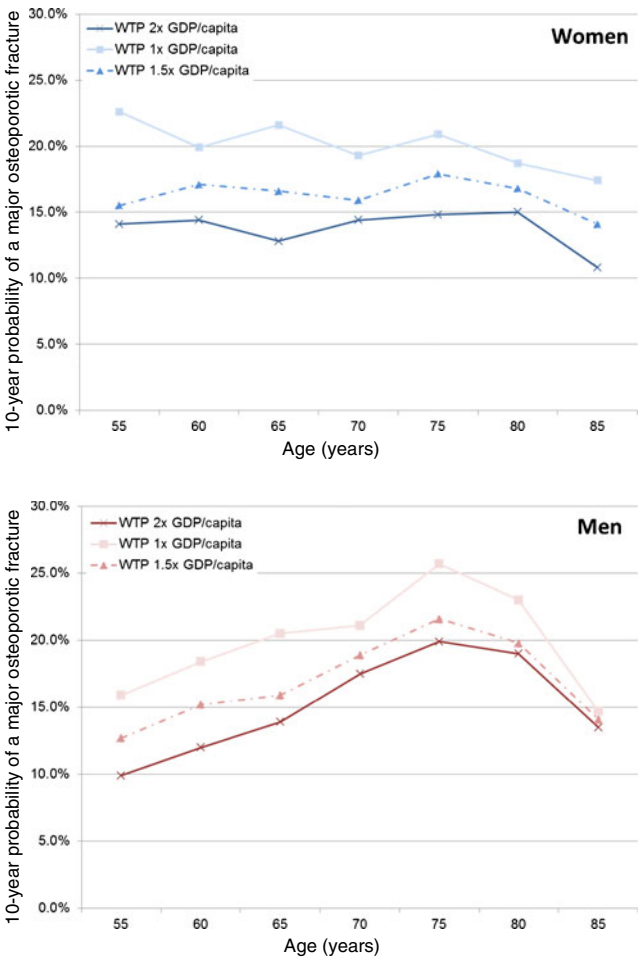

Fig. 4 Sensitivity analysis. Cost-effective intervention thresholds at WTP of 2.0×, 1.5×, and 1.0× GDP per capita in women and men

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 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.

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Conflicts of interest None

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