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Cost-Effectiveness of Using Clinical Risk Factors with and without DXA for Osteoporosis Screening in Postmenopausal Women

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ABSTRACT

Background: According to several guidelines, the assessment of postmenopausal fracture risk should be based on clinical risk factors (CRFs) and bone density. Because measurement of bone density by dual x-ray absorptiometry (DXA) is quite expensive, there has been increasing interest to estimate fracture risk by CRFs.
Objective: The aim of this study was to determine the cost-effectiveness of osteoporosis screening of CRFs with and without DXA compared with no screening in postmenopausal women in Germany.
Methods: A cost-utility analysis and a budget-impact analysis were performed from the perspective of the statutory health insurance. A Markov model simulated costs and benefits discounted at 3% over lifetime.
Results: Cost-effectiveness of CRFs compared with no screening is €4607, €21,181, and €10,171 per quality-adjusted life-year (QALY) for 60-, 70-, and 80-year-old women, respectively. Cost-effectiveness of DXA plus CRFs compared with CRFs alone is €20,235 for 60-year-old women. In women above the age of 70, DXA plus CRFs dominates CRFs alone. DXA plus CRFs results in annual costs of €175 million, or 0.4% of the statutory health insurance's annual budget.
Conclusion: Funders should be careful in adopting a strategy based on CRFs alone instead of DXA plus CRFs. Only if DXA is not available, assessing CRFs only is an acceptable option in predicting a woman's risk of fracture.
Keywords: cost-utility analysis, modeling, osteoporosis, secondary prevention, women's health.

Introduction

Osteoporosis, a multifactorial disorder resulting in increased bone fragility, occurs in women after menopause and is one of the most important disorders affecting the elderly [1]. Population aging is expected to increase the number of osteoporosis-related fractures such as hip fractures and, hence, the economic burden for society.

Bone mineral density (BMD) is considered an important predictive factor for osteoporotic fractures and is measured by densitometry. Densitometry results are usually reported as a *t*-score, which is the number of standard deviations between the value of an individual and the mean value of a group of young adults of the same sex [2]. According to the criteria of the World Health Organization (WHO) osteoporosis is defined by a *t*-score of ≤–2.5 [3]. If bone density is measured by dual x-ray absorptiometry (DXA), the risk of hip fracture (other fractures) increases by a factor between 3.7 (1.2) at age 50 and 1.7 (1.6) at age 90 for each standard deviation decrease in BMD at the femoral neck [4]. This increase in fracture risk for each standard deviation change is called the gradient of risk (GR/SD) [4].

DXA is expensive, not available everywhere, and to a certain degree unreliable because BMD can vary by up to 20% to 50% around an individual's true BMD [5]. Furthermore, different scanners for bone density used in the same patients vary considerably in the proportion of those who receive a diagnosis of osteoporosis [6]. While, in Germany, the prevalence of osteoporosis in women varies between 7% (age: 55) and 19% (age: 80) [7], the majority of fractures occur in women who do not have osteoporosis [7]. Thus, the use of DXA in primary or secondary prevention is disputed [8].

Recently, several risk factors for fracture have received attention [9]. These include prior fragility fractures, a family history of hip fracture, low body mass index (BMI), smoking, alcohol intake, and the use of oral corticosteroids. Combinations of these risk factors were used to develop decision rules for BMD referrals [10]. Although a case finding based on DXA alone (compared with fractures that will occur in the following 10 years) has a specificity (proportion of true-negatives) of approximately 90%, its sensitivity (proportion of true-positives) is only 34% [11]. Different strategies based on CRFs alone, in turn, have shown to exceed a sensitivity of 80% although their specificity is only about 50% (compared with the reference standard low BMD measured by DXA) [12]. Thus, predicting fracture risk based on CRFs in addition to BMD increases the GR for the prediction of hip and other fractures [4]. As a result, the sensitivity and the positive predictive values (proportion of women with positive test results who will have a fracture in the following 10 years) increase [13,14].

To guide treatment based on a combined use of CRFs and BMD, several organizations recently have recommended using CRFs and BMD to assess an individual's absolute 10-year risk of fracture [9,15] or annual incidence of fracture [16]. According to the German osteology umbrella organization, Dachverband Osteologie (DVO) guideline, DXA should be provided for women when there is a 10-year risk of combined vertebral (clinical and morphometrical) and hip fractures of ≥20%. Drug treatment should be provided for women with a combined risk of ≥30% for vertebral and hip fractures [7]. The *t*-score required to reach this risk threshold varies by age. A 55-year-old woman, for example,

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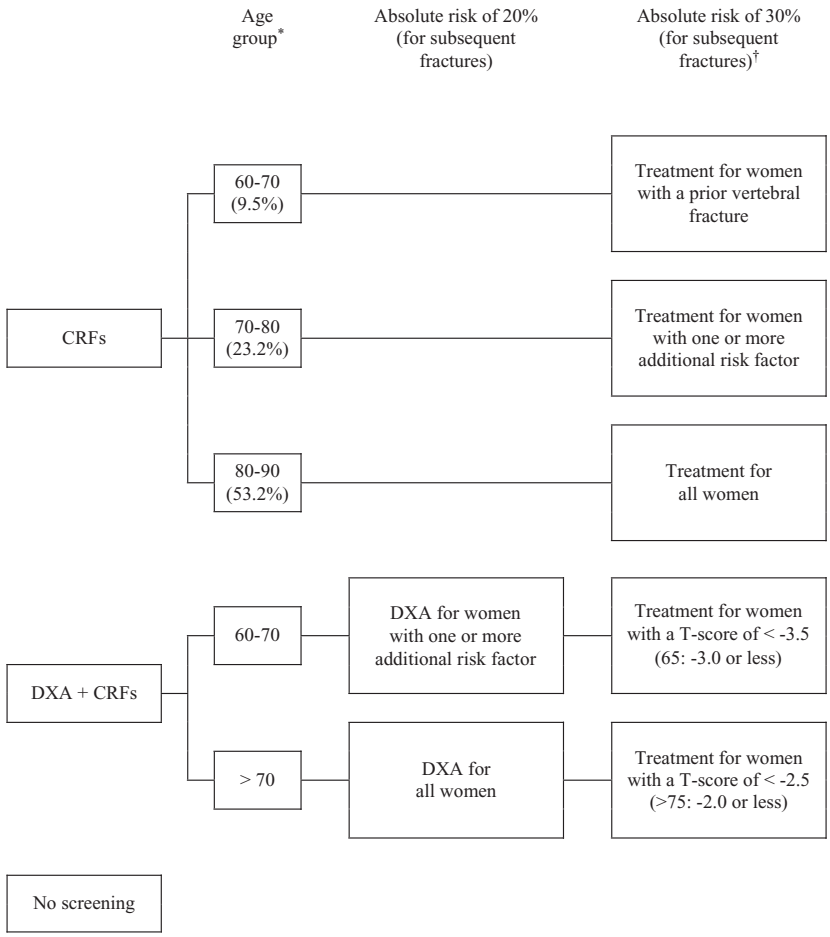

Figure 1 Overview of screen-and-treat strategies (clinical risk factors (CRFs) alone, dual x-ray absorptiometry (DXA) plus CRFs, no screening). *Numbers in parentheses indicates the 10-year risk of vertebral and hip fractures in women of this age group. †The true bone mineral density (BMD) of women in the CRFs group is unknown because women in this group can have normal, osteopenic, or osteoporotic BMD.

receives treatment for a *t*-score of –4, whereas a 67-year-old woman receives it based on a *t*-score of –3. Additional risk factors further increase the *t*-score required to reach the threshold [7].

While this and other recently developed screen-and-treat strategies agree that CRFs should be given more attention, treatment recommendations still tend to center on DXA [7,15,16]. Although the combined use of DXA and CRFs improves the GR/SD [4], for women aged >65 years, its sensitivity is only 60% even if a risk threshold of 30% is chosen [13]. This is an increase of 80% compared with DXA alone in women aged 70 to 79 years, but the price to pay for this improvement is a decrease in specificity by 16% [11,13]. The usage of CRFs alone, however, may be of diagnostic value for predicting fracture risk because age-specific GRs are similar to those of BMD alone [4]. Thus, a strategy where fracture risk is calculated by CRFs alone may improve the cost-effectiveness compared with an expensive DXA-centered strategy. The National Institute for Health and Clinical Excellence, for example, recommends bisphosphonates in postmenopausal women aged 75 years and older even without the need for DXA if the clinician considers DXA to be clinically inappropriate or unfeasible [16].

In the vast majority of cost-effectiveness analyses on postmenopausal osteoporosis treatment, women at increased risk were selected by low BMD [17]. Nevertheless, the use of CRFs as a prescreening tool for DXA (i.e., DXA only for those women with elevated CRFs) has been shown to be cost-effective when compared with mass screening with DXA alone [18]. In addition, there are two modeling studies that analyzed the cost-effectiveness of treatment in postmenopausal women, based on long-term fracture risk rather than on BMD alone [19,20]. In contrast to our analysis, these studies did not consider treatment costs of false positives, selected women at increased risk based on additional risk factors (e.g., BMI or the use of oral glucocorticoids), used a 10-year modeling horizon, and assumed that beyond 10 years, women would have a mortality rate equal to that of an age- and sex-matched population [19,20,21].

The present study investigated the cost-effectiveness of the following strategies: 1) screening based on CRFs alone (without information about BMD) and treatment with alendronate in case of risk of ≥30% (age groups 60–70 and 70–80), or treatment with alendronate for all women (age group: 80–90); 2) screening with DXA plus CRFs (plus alendronate); and 3) no screening (Fig. 1). While different medical treatment options are recommended, we chose alendronate, an antiresorptive biphosphonate, as the sole drug because, in our previous cost-utility analysis, it has shown to be most cost-effective [22].

Methods

The analysis was performed from the perspective of the German statutory health insurance (SHI). For the base case we considered a cohort of 10,000 women aged 60, 70, and 80 years. Because patients with osteoporosis face fracture risk that is continuous over time, we developed a Markov model in Microsoft Excel

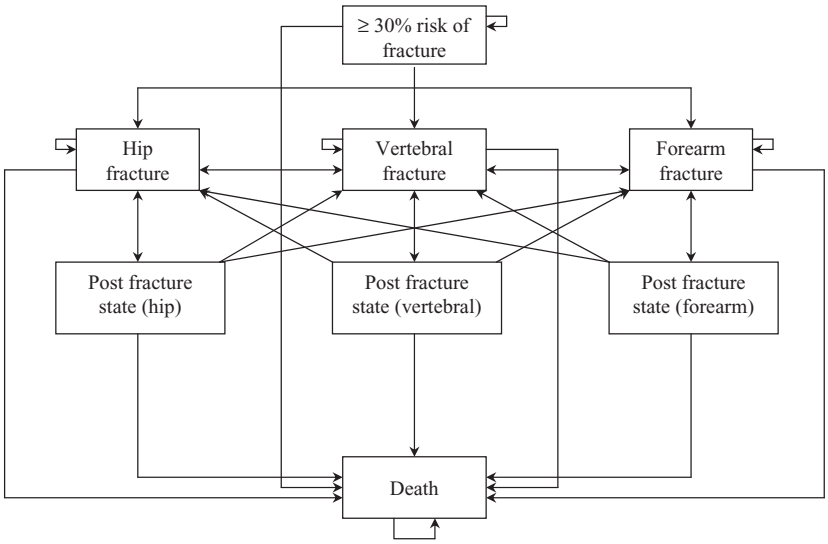

Figure 2 Health states.

2003 (Microsoft Corporation, Redmond, WA). The health benefit was estimated in terms of quality-adjusted life-year (QALYs), and incremental cost-effectiveness ratios (ICERs) were calculated. Preference weights are expressed by values between 1 for perfect health and 0 for the death [23]. A budget impact analysis (BIA) was performed by multiplying incremental costs per woman by the number of women who are insured by the SHI [24]. The BIA included future costs for unrelated health conditions during added years of life. The annual expected resource use for the SHI was estimated based on public databases [24,25]. Lost productivity was not included in the BIA because it is not relevant to the expenditure side of the SHI. As recommended for chronic diseases, a lifetime horizon was chosen [26].

Overview and Model Design

The Markov model uses age-specific fracture rates. The cycle length is 1 year because transition probabilities obtained from the literature refer to periods of at least 1 year. The model starts with a cohort of high-risk women who are identified on the basis of CRFs with and without DXA and who have a combined 10-year risk of ≥30% for vertebral and hip fractures. It stops at the age of 100 because, for Germany, there are no survival data beyond the age of 100 [27]. There are eight health states (Fig. 2): no fracture (≥30% probability of fracture in the 10 years from the start of the model), three-fracture states (hip, vertebral, and forearm), the corresponding postfracture states, and death. All women start in a state with a long-term risk of ≥30%. For each cycle, there is a defined probability of staying in the no-fracture state, experiencing a fracture, or dying. A woman who is in a fracture state can have another fracture at the same or another site. Women, who have a fracture change to the postfracture state, stay in the same fracture state if they have a refracture, change to another fracture state, or die. We conducted a half-cycle correction. Costs and benefits were discounted at an annual rate of 3% [28]. All costs are presented in euros and year 2006 values and were adjusted for inflation based on the German Consumer Price Index [29].

The structure of this Markov cohort model is similar to that of an established reference model [30]. As recommended there, a lifelong time horizon with a cycle length of 1 year was used, effectiveness was assumed to decrease linearly for a given "offset time," and fracture states for hip, vertebral, and forearm were modeled [30]. In contrast to the reference model, in our model, a woman may suffer a vertebral or forearm fracture after a hip fracture. Excess mortality after hip or vertebral fracture was modeled as well as the conservative assumption that costs of vertebral and wrist fractures only incur during the first year after the fracture. Although a state for other osteoporotic fractures was not modeled, for all fracture sites included in the analysis, postfracture states were added to reflect a persistent decrease in health-related quality of life (QoL) (hip, vertebral fractures) and the sustained risk increase for subsequent fractures.

Data

Efficacy/Effectiveness. Data on effectiveness of alendronate were taken from a meta-analysis that was based on large randomized controlled trials [31]. While effectiveness data on high-risk women selected by DXA were restricted to patients with osteoporosis or severe osteoporosis, effectiveness data on high-risk women selected by CRFs were also based on osteopenic women [31], resulting in lower effectiveness in women selected by CRFs.

Alendronate was offered for 4 years, which is in the range of recommended treatment duration in Germany (3–5 years) [7]. Effectiveness was assumed to decrease in linearly over a period of 4 years after the last intake [32]. Basing on the effectiveness data used for our analysis, we assumed that alendronate has no relevant side effects [31].

Medication compliance (or adherence) for individuals with chronic diseases such as osteoporosis is poor. Compliance is defined as the "extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [33]. To adjust drug effectiveness and costs for the rate of noncompliance in the real world, we multiplied effectiveness (at full compliance) and costs of alendronate and checkups by the "medication possession ratio" (the number of doses dispensed in relation to the dispensing period [33]) for daily intake of oral bisphosphonates (more than 12 months) using German prescription data [34]. Persistence, which is defined as "the duration of time from initiation to discontinuation of therapy" [33], was not modeled.

Absolute long-term risk and incidence. The number of women at risk was taken from the DVO guideline, which modeled an absolute 10-year fracture risk for the German population, based on published data on population age, prior vertebral fractures, and bone density [35,36].

In women below the age of 80, incidence rates of the general population [37–39] were increased to be at the level of the average fracture risk in women above the treatment threshold. The average risk in a group of women selected by CRFs depends on the GR and the ratio of the chosen risk threshold to the population risk. If treatment is provided on the basis of CRFs alone, the GR varies from 1.4 to 2.1, depending on age and fracture site [4]. An absolute risk of 30% in the age group of 70 to 80, e.g., means that this threshold equals 1.3 times the population risk, although the average risk, which is higher than the threshold, equals 1.9 times the population risk for hip fracture and 1.7 times for vertebral or forearm fractures, respectively [14] (details of formulae used for calculations of incidence can be found at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12i8_Mueller.asp). In women above the age of 80, incidence rates of the general population were used because all women receive treatment.

For women with a prior fracture, we assumed that the risk increases for all subsequent fractures. The risk of a woman who suffered fractures in two or more different sites was assumed to be determined only by the last fracture. The magnitude of the risk increase depends on the location of the prior fracture [40].

Mortality and health-related QoL. Mortality data were obtained from a public database of the Federal Statistical Office (Wiesbaden, Germany) [41] and were adjusted for women at increased risk [42–44]. Long-term mortality and life expectancy associated with hip fractures were modeled in a previous article [45]. In this model, inpatient mortality was based on a high-quality study analyzing the volume–outcome relationship of hip fracture surgery in German hospitals [46]. Mortality from revision surgeries was also considered in this model. QoL data were based on the EuroQol, a preference-based questionnaire [47].

For the state "Long-term risk ≥30%," we used QoL data of the general population, that is, utility values of <1 for all ages, estimated by a time trade-off questionnaire [48]. The reason is that individuals with osteoporosis may suffer from additional diseases causing disutility. QoL of women aged 60 to 70 years was further reduced because, in this group, a long-term risk of ≥30% can only be reached if a woman had a prior vertebral fracture [7]. QoL for forearm and clinical vertebral fractures was also based on surveys that used the EuroQol [49]. Because a value of 1 was assigned to the no-fracture state, data were multiplied by health-related QoL (HR-QoL) data from the general population [48]. For the postfracture states, we assumed an improvement of QoL, though not to the prior level. These values were not changed except when additional fractures occurred or patients died. In women with a forearm fracture and a prior vertebral fracture, we did not use values of forearm fractures because these were higher than values for the status post vertebral fracture. For women with a forearm or vertebral fracture and a prior hip fracture, the lower preference weight of the prior hip fracture was maintained.

Validity of the diagnosis. According to the DVO the combined 10-year risk of vertebral and hip fracture in the age group 60 to 70 is 10%. The threshold of 30% can only be reached if a woman has had a vertebral fracture because other risk factors do not increase the risk sufficiently [7]. A pretest x-ray is recommended in Germany for women with severe low-back pain or moderate low-back pain for >4 weeks [50]. In Germany, the 1-year prevalence of back pain in women aged 60 to 70 years is estimated to be 23% [51], and the proportion of these women undergoing an x-ray is 35% [52]. Hence, only 8% of all women in the model undergo a routine x-ray, provided that all women with lasting back pain attend a physician. Nevertheless, this group includes only 35% of all vertebral fractures because 65% are not recognized clinically [53]. Furthermore, in women with clinically apparent fractures who undergo the pretest, a high prevalence of unspecific back pain, morphological changes, and misinterpreted x-rays confounds the validity of the diagnosis [54]. As a result, 2.4% of all women screened receive treatment with alendronate (90% of these women are true-positive).

Because the 10-year risk of vertebral and hip fracture for 70- to 80-year-old women is already 23%, the German DVO considers this risk to be ≥30% if a woman has a prior fracture, has a parental history of a femur fracture, is a smoker, is immobile, or has a tendency to fall [7]. This decision rule is consistent with the case-finding strategy of the National Osteoporosis Foundation, which is carried out to identify individuals with osteoporosis compared with low BMD as a reference standard [55,56]. Based on a *t*-score of –2.5, which in this age group corresponds to the threshold of 30%, 85% of all women undergo treatment because they are suspected as being at risk as a result of one or more CRFs (26% of these women are true-positive) [10].

All women aged >80 years receive drug treatment because the therapeutic threshold of 30% is assumed to be reached by age alone (Table 1).

The validity of DXA plus CRFs is extensively described in our prior analysis [22]. Briefly, for women aged 60 to 70 years, 24% of all women screened receive treatment (23% of these women are true-positive). In women the age of more than 70 and 80, the proportion of women who undergo treatment is 33% (42% of these are true-positive) and 44% (73%), respectively.

Costs

Our analysis considers the costs of screening as well as treatment costs of false- and true-positives. General health-care costs in added years of life were also taken into consideration. As a cost of screening, we applied the costs of routine checkups, which include a face-to-face interview, an evaluation of the medical history, and a physical examination. Therefore, we assumed that risk factors such as a prior fracture, a parental history of a femur fracture, smoking, immobility, and tendency to fall are assessed during routine visits and do not require specific equipment. The costs of initial x-rays were not included because patients with severe or persistent back pain in Germany routinely undergo an x-ray [50].

Although costs of treating vertebral and forearm fractures were calculated for the year of the fracture, they were not applied to subsequent years [30], which is a conservative assumption. Costs of treating hip fractures were taken from a recent German analysis modeling long-term cost and effects of hip fracture surgeries, which includes costs of initial hospitalization for hip implants, readmissions, transportation services, outpatient treatment, rehabilitation, long-term care, and costs in added years of life [45]. All long-term costs of hip fractures were considered, including those of refractures. For double counting of refracture costs to be avoided, a hip fracture can only occur once in the Markov model. If a woman with a prior hip fracture suffered a forearm or a vertebral fracture, the costs of this additional fracture would be added to the costs of the hip fracture. Costs were

Table 1 Diagnostic performance of screening for osteoporosis based on clinical risk factors*

Age group (10-year risk of fracture in the general population)

60–70 (9.5%)				70–80 (23.2%)				80–90 (53.2%)
x-Ray vertebral fracture	Test +	Test −		≥one risk factor	Test +	Test −		
Fracture in T0–T10†	220	113	333	Fracture in T0–T10	2,232	88	2,320	Treatment is recommended for all women.
No fracture in T0–T10	24	448	472	No fracture in T0–T10	6,313	1,367	7,680	
	244	561	805		8,545	1,455	10,000	
Sensitivity = 0.660 Specificity = 0.950		PPV = 0.902 NPV = 0.799		Sensitivity = 0.962 Specificity = 0.178 (*t*-score = 2.5 or less)		PPV = 0.261 NPV = 0.940		

*Figures presented are numbers of patients. The calculations of women at increased risk for the different age groups are based on an absolute 10-year fracture risk and a cohort of 10,000 women.
†Period of 10 years.
NPV, negative predictive value; PPV, positive predictive value.

stratified by age group. All input data used for the model are described in Tables 2 and 3. Copayments by patients were subtracted.

Sensitivity Analysis

We carried out a one-way sensitivity analysis for all model variables. In addition, a threshold analysis was performed to determine the level of risk at different cost-effectiveness thresholds. The combined risk for vertebral and hip fractures was calculated based on cost-effectiveness thresholds between €5000 and €35,000. When varying the risk of vertebral and hip fractures simultaneously, an equal relative risk increase or decrease was assumed; that is, the relative risks of hip and vertebral fractures were varied by the same factor.

To assess how a simultaneous change of several variables affected the cost-effectiveness ratio, we performed a Monte Carlo simulation of model variables listed in Tables 2 and 3 (except for the discount rate as well as costs of checkups, alendronate, and hospitalizations caused by vertebral and forearm fractures).

For variables on a scale between 0 and 1, we assumed a beta distribution ($0 \leq \theta \leq 1$, $a > 0$, $b > 0$). For cost data, we assumed a gamma distribution ($a > 0$ and $b > 0$), with the mean a/b and the variance a/b^2 [65]. We conducted 1000 iterations. Given that the interpretation of negative cost-effectiveness ratios is ambiguous, we transformed cost-effectiveness ratios into net monetary benefits (NMBs) using the following equation [66]:

$$\mathrm{NMB} = \lambda * \Delta E - \Delta C, \quad (1)$$

where λ = maximal willingness to pay, ΔE = incremental benefit (QALYs), and ΔC = incremental costs.

The decision rule we used was to adopt the screen-and-treat strategies in question if NMB was greater than 0.

Results

Base-Case Analysis

The ICERs of a screen-and-treat strategy based on CRFs alone versus no screening are below €22,000 in all age groups (Table 4). Compared with women aged 70 to 80 years, the increased absolute fracture risk in women aged >80 years makes immediate treatment of all women more cost-effective. Using DXA plus CRFs compared with CRFs alone (i.e., immediate treatment in women aged 80–90 years), there is an increase in QALYs in all age groups (Fig. 3). In women above the age of 70 years, a strategy based on DXA plus CRFs dominates a strategy based on CRFs alone; that is, it is more effective but less expensive. Although, in women aged 60 to 70 years, CRFs alone are considerably more cost-effective than DXA plus CRF, less than one quarter of women at increased risk are detected. In contrast, DXA plus CRFs detects 58% of women at increased risk.

If a screen-and-treat strategy based on CRFs alone was implemented in Germany, costs would total €560 million, or 0.4% of the SHI's total annual budget [67] (Table 5). The major cost driver is treatment with alendronate for 5.4 million women across all age groups including both high- and low-risk women. Nevertheless, 60% of these women are not at risk (false-positives). When providing DXA plus CRFs in women above the age of 70 years, costs of DXA are offset by lower costs of treatment for false-positives. Only in women aged 60 to 70 years is DXA plus CRFs more expensive than CRFs alone. Thus, over all age groups, a screening strategy based on DXA plus CRFs decreases annual costs by €385 compared with a strategy with CRFs alone (Table 5).

Sensitivity Analysis

One-way analysis. For the comparison of CRFs alone versus no screening and of DXA plus CRFs versus no screening, efficacy of alendronate and the discount rate have the largest impact on the cost-effectiveness ratio. Assuming a lower efficacy of alendronate or a higher discount rate increases the ratio of both comparisons by 40% to 60%. In contrast, assuming a higher efficacy or a lower discount rate improves the cost-effectiveness ratio of both comparisons by approximately 20%. Decreasing QoL for fracture states or increasing the incidence, the risk increase in subsequent fractures, or compliance improves the ICER by approximately 25% and thus makes the use of CRFs or DXA plus CRFs more favorable. Lower rates of these variable or higher QoL increases the ICER to the same degree and makes CRFs or DXA plus CRFs less favorable. Results are robust to the variation of other variables.

When comparing DXA plus CRFs with no screening, a lower GR increases the ratio between 30% and 90%. In contrast, assuming a higher GR improves the cost-effectiveness ratio by approximately 30% to 40%.

When comparing DXA plus CRFs with CRFs alone, base-case results are robust to changes in most variables. Nevertheless, when a lower GR is assumed, the increase in QALYs by adding DXA is attenuated or even negative (age group: 70–80 years)

Table 2 Cost data

Parameter*		Price per unit (€)	Annual frequency	Mean annual cost† per patient (€)	Reference
1. Diagnosis	Routine visit (initial)	25.56	1	25.56	[57]
	Check-ups (physician)		3 (year 1, 2)	76.68	
			1.5 (year 3, 4)	38.34	
2. Medication	Alendronate, 5–10 mg daily	1.20	365	438.00	[58]
3. Vertebral fractures					
Outpatient treatment	Consultation for osteoporosis with pathological fracture (M80)		14.4	286.16	[25]
Physical therapy	Physiotherapy (WS2)	14.50	18	234.90	[59,60]
	Heat (WS2)	7.21	18	116.82	
	Ergotherapy (SB1)	23.80	20	428.40	
Total of outpatient and physical therapy				1,066.28 [853–1,279]	
Inpatient treatment including rehabilitation				3,222.00	[61,62]
4. Forearm fractures					
Outpatient treatment	Consultation for forearm fracture (S52, 69% of all forearm fractures)		16	363.42	[25]
	Consultation for wrist fracture (S62, 31% of all forearm fractures)		14.4	295.15	
Physical therapy	S52 and S62 weighted		15.5	342.26	
	Physiotherapy (EX2/3)	14.50	24	313.00	[59,60]
	Cryotherapy (EX2/3)	6.63	24	143.28	
	Lymphatic drainage (LY1)	13.04	12	140.88	
Total of outpatient and physical therapy				939.42 [752–1,127]	
Inpatient treatment including rehabilitation				3,174.00	[61,62]
5. Hip fractures‡§ (total costs)				50 years: 69,231 [67,289–71,443]	[45]
				55 years: 62,591 [61,435–64,019]	
				60 years: 54,264 [52,674–55,887]	
				65 years: 47,837 [46,703–49,167]	
				70 years: 42,432 [41,287–43,664]	
				75 years: 39,586 [38,551–40,735]	
				80 years: 32,957 [32,087–33,878]	
				85 years: 29,417 [28,435–30,273]	
				90 years +: 26,187 [25,331–26,973]	
6. Costs in added life years‖				60–65 years: 3,150	[63]
				65–85 years: 6,150	
				>85 years: 12,405	

*Diagnosis and treatment codes are shown in parentheses (for physical therapy, we used the German Heilmittelkatalog, for vertebral and forearm fractures ICD-10 numbers are cited).
†95% confidence intervals are shown in parentheses. For outpatient treatment and physical therapy, we varied mean values by 20%. All costs are given in 2006 Euros and were adjusted for inflation based on the German Consumer Price Index [29].
‡Lifetime costs discounted at 3% (this discounting applies only to hip fractures).
§These costs included costs of inpatient care in hospitals, hip replacements, revisions, readmissions, transportation services, outpatient treatment, rehabilitation, and long-term care.
‖For hip fractures, costs in added years of life are included in the total costs of hip fractures.

because the average risk decreases more in women identified by DXA plus CRFs than in women identified by CRFs alone. Assuming a higher GR improves the ICER of DXA plus CRFs by 25% to 50% compared with CRFs alone. Using less conservative assumptions such as a higher risk increase by prior fractures improves the cost-effectiveness ratio of DXA plus CRFs compared with CRFs alone. Further details on this can be found at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12i8_Mueller.asp.

Threshold analysis. Using a threshold cost-effectiveness ratio of €30,000, CRFs become cost-effective in women aged >60 years with a combined average fracture risk of 10.3% (hip: 1.3%). For a ratio of €10,000, this risk increases to 27.2% (3.7) (Fig. 3a). Assuming all women identified for being at increased risk would have a combined average fracture risk of exactly 30% (hip, age 60 years: 3.8%; age 70 years: 6.2%; age 80 years: 9.9%), the ICERs are €9575 (age 60 years), €47,351 (age 70 years), and €18,496 (age 80 years), respectively.

Using a threshold cost-effectiveness ratio of €30,000, DXA plus CRFs compared with no screening becomes cost-effective in women aged >60 years with a combined average fracture risk of 25.3% (hip: 2.6%), in women aged >70 years with an average fracture risk of 30.6% (6.3), and in those aged >80 years with a risk of 11.5% (5.0). Using a threshold ratio of €10,000, the risks increases to 80.1% (14.4), 69.2% (15.5), and 29.4% (13.6), respectively (Fig. 3). Assuming all women identified for being at increased risk would have a combined average fracture risk of exactly 30% (hip, age 60 years: 3.3%, age 70 years: 5.8%, age 80 years: 12.8%), the ICERs are

Table 3 Input variables for the model (95% confidence intervals or estimates thereof are shown in brackets)

Parameter		Range (95% CI or estimates thereof)	References
Incidence (%)*	Vertebral fracture	60 years 0.95 (0.62–1.39), 65 years 1.23 (0.82–1.77), 70 years 1.79 (1.20–2.57), 75 years 2.93 (1.80–4.36)	[38]
	Hip fracture	60 years 0.09, 65 years 0.16, 70 years 0.34, 75 years 0.70, 80 years 1.38, 85 years 2.94, 90 years 3.82, 95 years 3.06	[37]
	Forearm fracture	60 years 0.49 (0.40–0.60), 65 years 0.58 (0.50–0.70), 70 years 0.73 (0.61–0.84), 75 years 0.71 (0.60–0.82), 80 years 0.77 (0.62–0.91), 85 years 1.04 (0.86–1.12), 90 years 0.94 (0.83–1.02)	[39]
10-year risk of fracture (%)		60 years 9.5 (7.6–11.4), 70 years 23.2 (18.6–27.8), 80 years 53.2 (42.6–63.8)	[7]
Relative mortality risk	Osteoporosis	1.19 (1.04–1.36)	[42]
	Vertebral fracture	1.66 (1.51–1.80) for clinical fractures	[43]
		1.16 (1.03–1.30) for morphometrical fractures	[44]
Relative risk of secondary fractures	60–90 years	Initial fracture hip 2.79 (2.06–3.77) Initial fracture forearm 1.69 (1.35–2.12) Initial fracture vertebral 2.52 (1.99–3.19)	[40]
Health-related quality of life	No fracture (general population data)	60 years 0.83 (0.78–0.88), 65 years 0.81 (0.75–0.86), 70 years 0.75 (0.69–0.80), 75 years 0.73 (0.67–0.79), 80 years 0.70 (0.61–0.78), 85 years 0.68 (0.59–0.76)	[48]
	Fracture states	Clinical vertebral, first years 0.63 (0.50–0.75), Subsequent years 0.91 (0.83–0.98) Morphometrical vertebral, first years 0.82 (0.72–0.92), Subsequent years 0.91 (0.84–0.99) Forearm first years 0.98 (0.96–1.00), Subsequent years 1.00 (0.99–1.00)	[49]
Quality-adjusted life expectancy†	Hip fracture	60 years 10.98 (8.97–12.34), 65 years 8.17 (6.4–10.17), 70 years 6.13 (4.79–7.69), 75 years 4.67 (3.65–5.97), 80 years 3.39 (2.41–4.58), 85 years 2.55 (1.78–3.54), 90 years 1.64 (1.32–2.21)	[45]
Relative fracture risk (alendronate)	CRFs	Forearm: 0.64 (0.30–1.35), hip: 0.62 (0.40–0.98), vertebral 0.56 (0.46–0.68)	[31]
	DXA plus CRFs	Forearm: 0.48 (0.31–0.75), hip: 0.46 (0.23–0.91), vertebral: 0.53 (0.42–0.67)	[31]
Proportion of inpatient cases		Vertebral fracture 0.17 (0.11–0.24), forearm fracture 0.44 (0.19–0.51)	[37,64]
Discount rate		3% (0–7)	[28]
Compliance		0.38 (0.30–0.46)	[34]
Validity of diagnosis	X-ray of vertebral fracture	$P(T+/D+) = 0.66$ (0.64–0.68r), $P(T^-/D^-) = 0.95$ (0.93–0.97)	[54]
	Decision rule	$P(T+/D+) = 0.96$ (0.94–0.98), $P(T^-/D^-) = 0.18$ (0.16–0.20)	[10]
Gradient of risk		60–70 years, hip: 1.95 (1.63–2.33), vertebral/forearm: 1.48 (1.39–1.58) 70–80 years, hip: 1.84 (1.65–2.05), vertebral/forearm: 1.55 (1.48–1.62)	[4]
Fracture risk increase in women above the risk threshold compared with general population		60–70 years, hip: 4.15 (3.72–4.67), vertebral/forearm: 3.54 (3.43–3.66) 70–80 years, hip: 1.94 (1.78–2.11), vertebral/forearm: 1.70 (1.64–1.76)	Calculated from [4,14]
Proportion of clinical vertebral fractures		0.35 (0.29–0.41)	[53]
Proportion of x-rays in women with back pain	60–70 years	0.35 (0.30–0.40)	[52]

*The incidence of hip fractures was not varied because the whole German population was sampled.
†Quality-adjusted-life years were discounted at 3%.
CI, confidence interval, CRF, clinical risk factor; DXA, dual x-ray absorptiometry; RG, gradient of risk, P, probability, T, test, D, disease.

€49,308 (age 60 years), €30,735 (age 70 years), and €9750 (age 80 years), respectively.

Monte Carlo simulation. Uncertainty in cost-effectiveness as estimated by the Monte Carlo simulation is presented in the cost-effectiveness acceptability curves in Figure 4. The probability of CRFs alone or DXA plus CRFs being cost-effective depends on the willingness to pay (WTP) for an additional QALY. In women aged 60 to 70 years, both CRFs alone and DXA plus CRFs are more likely to yield a higher net benefit when societal WTP for an additional QALY exceeds €10,000. Below this value, no screening is more likely to be cost-effective in this age group. At WTPs between €5000 and €35,000, CRFs are more cost-effective than DXA plus CRFs. In women above 70 years, the probability of cost-effectiveness of CRFs at each WTP is 0%. In women aged >80 years, DXA plus CRFs is cost saving, with a probability of 7% compared with CRFs alone or no screening. Over all age groups, the higher the WTP, the more DXA plus CRFs becomes the preferred strategy.

Discussion

This analysis presents data on the cost-effectiveness of two screen-and-treat strategies in which the treatment threshold is defined by 10-year risk of fracture, based on CRFs alone or DXA plus CRFs. Compared with screening with DXA plus CRF, a strategy based on CRFs alone is more expensive and less effective in women above the age of 70 years. Note again that using CRFs implies treatment of all women above the age of 80 years. Compared with no screening, the cost-effectiveness of CRFs alone at an intervention threshold of ≥30% is fairly moderate in all age groups and similar to those of other generally accepted medical interventions such as hypertension treatment with thiazide diuretics in patients with systolic blood pressure of 140 mm Hg [68].

Conclusions

Treatment should be based on bone density as long as DXA is available for screening women above the age of 70 years. There-

Table 4 Results of the base-case analysis (costs are presented in €, year 2006)*

Intervention	Costs†	QALYs	Control	Incremental costs	Incremental QALYs	ICER (costs/QALY)
Women aged 60–70 years						
No screening	114,040	20.208				
CRFs alone	114,318	20.268	No screening	278	0.060	4,607
DXA plus CRFs	118,431	20.471	i) No screening	4,391	0.263	16,696
			ii) CRFs alone	4,113	0.203	20,235
Women aged 70–80 years						
No screening	103,144	13.276				
CRFs alone	107,683	13.490	No screening	4,539	0.214	21,181
DXA plus CRFs	105,037	13.562	i) No screening	1,893	0.286	6,611
			ii) CRFs alone			Dominates
Women aged 80–90 years						
No screening	74,137	7.452				
Immediate treatment	76,512	7.686	No treatment	2,375	0.234	10,171
DXA plus CRFs	74,967	7.806	i) No screening	830	0.354	2,346
			ii) Immediate treatment			Dominates

*Incremental costs and QALYs are presented per high-risk woman treated over lifetime and were discounted at 3%.
†Costs in added years of life are included.
CRF, clinical risk factor; DXA, dual x-ray absorptiometry, ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life years.

fore, health policy should aim to increase the availability of DXA. Only in cases where DXA is not available, the usage of CRFs alone is justified. In women aged 60 to 70 years, where CRFs are superior, there is substantial uncertainty in the results. Because cost-effectiveness acceptability curves (CEACs) do not indicate the costs of making a wrong decision, funders should be careful in adopting CRFs alone instead of DXA plus CRFs.

In this analysis, ICERs were calculated based on an intervention threshold of ≥30%. Lowering this threshold would decrease specificity, and, as a result, treatment costs for false positives would largely increase. Thus, we would expect a lower threshold to be less cost-effective. In contrast, raising the threshold above 30% may improve the ICER in women aged ≥70 years because the number of false positives would decrease.

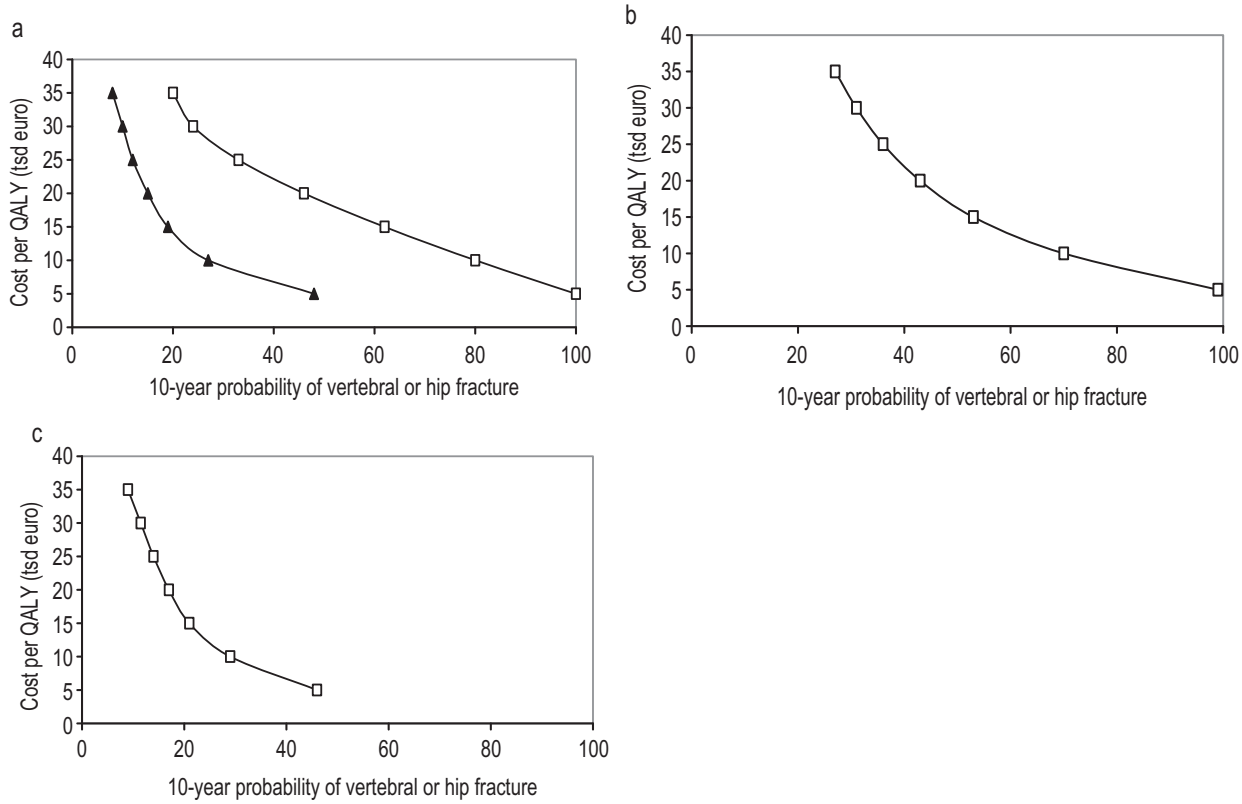

Figure 3 (a) Cost (€) per quality-adjusted life year gained by combined 10-year risk for hip and vertebral fractures in women aged 60–70 (□ = DXA plus CRFs, ▲ = CRFs alone). (b) Cost (€) per quality-adjusted life year gained by combined 10-year risk for hip and vertebral fractures in women aged 70–80 (DXA plus CRFs). (c) Cost (€) per quality-adjusted life year gained by combined 10-year risk for hip and vertebral fractures in women aged 80–90 (DXA plus CRFs). CRF, clinical risk factors; DXA, dual x-ray absorptiometry; QALY, quality-adjusted life years.

Table 5 Results of the budget impact analysis (in million €)

Age group (years)	CRFs/no screening	DXA + CRFs/ no screening	DXA + CRFs/ CRFs alone
60–70	1	46	45
70–80	220	57	−163
80–90	339	72	−267
Total	560	175	−385

CRF, clinical risk factor; DXA, dual X-ray absorptiometry.

Nevertheless, these assumptions could not be tested because of a lack of data.

Our analysis has several strengths. It considers long-term follow-up costs of hip fractures in Germany including costs of hip implants, revision surgery, transportation services, rehabilitation care, and long-term care [45]. Moreover, in contrast to many economic analyses in the field of osteoporosis prevention, which did not consider the costs of case finding [69], our analysis includes all screening costs including costs of women being diagnosed incorrectly (false-positives). Furthermore, in contrast to the model by Zethraeus and colleagues [30], our model is able to consider the occurrence of vertebral and forearm fracture after hip fracture. The no-memory assumption of Markov models was avoided by creating health states that correspond to combined health states [70].

An important limitation is that the number of women at increased risk in the age group of 60 to 70 years is based solely on prior vertebral fractures. Additional risk factors to increase the number of women at high risk could not be used because their distribution in the German population has not been sufficiently evaluated yet [7]. This results in a lower ICER than that of screening in women aged 70 and 80 years although fracture risk increases with age and the ICERs of screening strategies usually decrease with age. The reason is that the cost-effectiveness ratio is very sensitive to specificity that is, based on this strategy, 95% for screening in women aged <70 years, but only 20% in women aged 70 years, and 0% in women aged 80 years. If it were possible to calculate the risk increase by combining several risk factors, the detection of more women at risk would be inevitably attenuated by a significant decrease of specificity in the identification of nonosteoporotic women, as shown in the evaluation of many decision rules for CRFs in osteoporosis screening [10,12].

There are a number of reasons why the results of our study are rather conservative. First, when calculating the costs of fracture treatment, analgesics were not considered. A recent cost analysis showed that osteoporotic patients receive three times more prescriptions for analgesics than nonosteoporotic patients do [71] and that those who have received nonsteroidal antiphlogistics were significantly more often hospitalized for peptic ulcer disease than those who have not received nonsteroidal antiphlogistics. Including these and other drug costs in the calculation of treatment costs for vertebral and forearm fractures would improve cost-effectiveness of CRFs with and without DXA.

Second, our analysis incorporated an increased risk of subsequent fractures for women who have suffered a prior fracture. This risk increase was determined only by the last fracture because there were no data available on the relationship between risk increase and the number of prior fractures. Consideration of

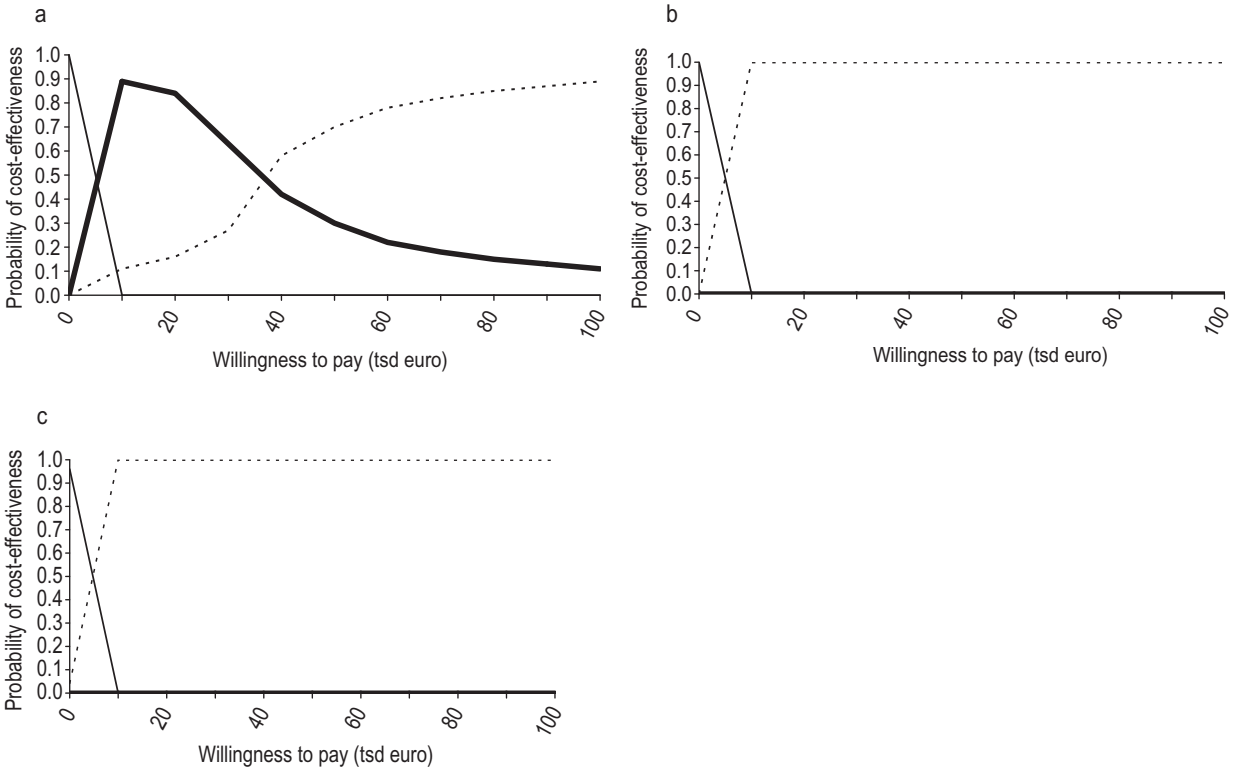

Figure 4 (a) Cost-effectiveness acceptability curves for screening and treatment in women aged 60–70 (b) Cost-effectiveness acceptability curves for screening and treatment in women aged 70–80 (c) Cost-effectiveness acceptability curves for screening and treatment in women aged 80–90 (▬ CRFs, --- DXA plus CRFs, — no screening). CRF, clinical risk factors; DXA, dual x-ray absorptiometry.

two or more prior fractures would probably further increase the risk of a subsequent fracture and improve the cost-effectiveness ratio of CRFs with and without DXA. If these data become available, individual patient-level models could be more accurate in simulating the relationship between the number of prior fractures and subsequent fractures than between cohort-based approaches [72]. Moreover, by considering only the last fracture, in women with a prior hip or vertebral fracture who have a forearm fracture, the risk of subsequent fractures decreases. Continuing the higher risk increase of the prior fracture would improve the ICERs of CRFs and DXA plus CRFs.

Finally, the fracture states in this model are the same as in the reference model [30] except for fractures at "other" sites that were not modeled here. By considering only hip, vertebral, and forearm fractures, our analysis may have underestimated potential cost savings from the prevention of fractures at other skeletal sites. Although studies on alendronate did not show a significant reduction of other fractures [31], a study on risedronate, which also belongs to the class of bisphosphonates, reported a significant reduction of nonvertebral fractures by 39% (defined as fractures of the clavicle, humerus, wrist, pelvis, hip, or leg) [73].

On the other hand, there are also several reasons why a screen-and-treat strategy based on CRFs alone may be less cost-effective than that calculated by the base-case analysis. First, there is contradictory evidence whether individuals selected for treatment based on CRFs alone benefit from treatment or not. To date, efficacy data have to be taken from a population selected by the WHO criterion of BMD including individuals with osteopenia [21]. It remains unclear whether these data reflect the true efficacy of a population with a 30% long-term risk based on CRFs. In some efficacy trials, however, pharmacological interventions with bisphosphonates have been shown effective in patients not selected on the basis of low BMD [74–77].

Third, alendronate was assumed to be efficacious in all age groups although there have not been studies in women above the age of 80 [31].

Finally, for the state "long-term risk of ≥30%," disutility of women aged 70 to 80 was underestimated. The reason is that an unknown number of women in this group suffer from prior fractures causing disutility. If a lower QoL was assumed, the incremental gain in QoL using CRFs with and without DXA compared with no intervention would be reduced, and, therefore, both strategies would become less cost-effective. Nevertheless, the increase of the ICER would be negligible, as shown in the sensitivity analysis.

The structure of this Markov cohort model is similar to that of an established reference model [30] although there are also some discrepancies: in our model, a state for other osteoporotic fractures was not modeled, and a woman may suffer a vertebral or forearm fracture after a hip fracture. As recommended there, a lifelong time horizon with a cycle length of 1 year was adopted, effectiveness was assumed to decrease linearly for a given "offset time," and increased mortality after hip or vertebral fracture was modeled. In addition, for all fracture states, a postfracture state was included to reflect the sustained risk increase for subsequent fractures.

To compare the results of this analysis to those of other models, we used two cost-effectiveness studies for treatment with bisphosphonates in postmenopausal women [19,20], which are also based on long-term fracture risk. In these analyses, intervention thresholds for cost-effectiveness of bisphosphonates in women at different T-scores with or without prior fracture were calculated. Although the 5-year baseline risks of hip fracture were similar (e.g., 7.1% and 12.3% for women with a fracture history aged 70 and 80 years, respectively, compared with 6.7% and 12.1%, respectively, in our analysis) [19], the results of these analyses are quite different from our results. But again, there are important methodological differences compared with our study: costs of hip fracture are much lower given that costs beyond the first year after fracture were not included, treatment costs of false-positives were not considered, the discount rates used for costs (6%) and benefits (1.5%) differed from our study, and compliance was not considered in the base case. In addition, the selection of women at increased risk was based on several other risk factors such as BMI, history of peripheral fractures, use of oral glucocorticoids, and history of rheumatoid arthritis [19,20]. Consideration of several risk factors is likely to have decreased the specificity of the identification of nonosteoporotic women and thus increased the cost-effectiveness ratio.

If we assumed a societal perspective for our analysis, we would expect similar results. Copayments for drugs may be partly outweighed by savings for copayments for fracture treatment. Costs through loss of productivity are of minor importance because the proportion of women aged >60 years being employed in Germany is below 15% [78].

We do not know whether our findings are transferable to other countries. The main reason is that, for costs and epidemiological data, German sources were preferred as inputs to the model, so differences in resource consumption and prices may exist.

There are several important areas for future research. First, predicting fracture risk based on CRFs is still not accurate enough. Whereas risk factors such as a prior vertebral fracture and low BMD can be used for precise measurements of the risk increase [7], other risk factors such as low BMI and immobility only are known to be indicators of low BMD [7]. Thus, their interrelationship has yet to be formalized with more precision.

Second, effectiveness of alendronate has to be shown in clinical trials with patients selected on the basis of CRFs instead of low BMD [31].

Finally, this analysis compared different screen-and-treat strategies, based on an arbitrary risk threshold of 30% for hip or vertebral fractures. It would be of general interest to determine ICERs for different intervention thresholds of screen-and-treat strategies, using different ratios of hip to vertebral fracture risk or hip to nonhip–fracture risk. In our analysis, the ICERs of a combined risk of exact 30% were calculated for a specific ratio of hip to vertebral fracture risk. Nevertheless, different risk factors have different impacts on fracture sites and, thus, different impacts on QoL, costs, and mortality [20]. For example, if the absolute fracture risk threshold is reached by risk factors that are assumed to have a larger impact on the risk of hip fractures than on vertebral fractures (e.g., use of corticosteroids), treatment is more cost-effective because hip fractures have a higher impact on costs and mortality than fractures at other sites do [20].

In summary, CRFs are of considerable value for decision-making regarding the treatment of postmenopausal osteoporosis. Nevertheless, until the interrelationships between CRFs have been evaluated more extensively and until treatment with bisphosphonates in women selected by risk factors has shown to be as effective as in women selected by BMD, their usage should be combined with DXA. As recommended also by National Institute for Health and Clinical Excellence, providing treatment without DXA should be limited to older women only if the responsible clinician considers it to be clinically appropriate or unfeasible [20]. As long as DXA is available, the implementation of any approach based on CRFs alone will result in an uncontrolled increase in health expenditures.

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