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ORIGINAL ARTICLE

FRAX® assessment of osteoporotic fracture probability in Switzerland

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Abstract
Summary A Swiss-specific FRAX® model was developed. Patient profiles at increased probability of fracture beyond currently accepted reimbursement thresholds for bone mineral density (BMD) measurement by dual X-ray absorptiometry (DXA), and osteoporosis treatment were identified.
Introduction This study aimed to determine which constellations of clinical risk factors, alone, or combined with BMD measurement by DXA, contribute to improved identification of Swiss patients with increased probability of fracture.
Methods The 10-year probability of hip and any major osteoporotic fracture was computed for both sexes, based on Swiss epidemiological data, integrating fracture risk and death hazard, in relation to validated clinical risk factors, with and without BMD values.
Results Fracture probability increased with age, lower body mass index (BMI), decreasing BMD T-score, and all clinical risk factors used alone or combined. Several constellations of risk factor profiles were identified, indicating identical or higher absolute fracture probability than risk factors currently accepted for DXA reimbursement in Switzerland. With identical sex, age and BMI, subjects with parental history of hip fracture had as high a probability of any major osteoporotic fracture as patients on oral glucocorticoids or with a prevalent fragility fracture. The presence of additional risk factors further increased fracture probability.
Conclusions The customised FRAX® model indicates that a shift from the current DXA-based intervention paradigm, toward a fracture risk continuum based on the 10-year probability of any major osteoporotic fracture may improve identification of patients at increased fracture risk.

Keywords Clinical risk factors · FRAX® · Hip fracture · Osteoporotic fracture · 10-year fracture probability

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Introduction

Osteoporotic fractures are one of the leading causes of morbidity in men and women living in industrialised countries. Switzerland belongs to the countries at highest risk for osteoporotic fractures [1, 2]. Life expectancy at birth is amongst the highest worldwide [3], and Switzerland ranks second worldwide with regard to the proportion of elderly in its population [4]. Furthermore, the number of persons older than 65 years is expected to double between the years 2005 and 2050 [5]. Based on health economic modelling, ageing of the population is expected to lead to a massive increase in health expenditure due to osteoporotic fractures in coming decades if current diagnostic and treatment behaviour remains unchanged [6]. Thus, the reality of osteoporosis in Switzerland today may be considered as a paradigm for the future of other industrialised countries.

The current gold standard for the diagnosis of osteoporosis is the measurement of bone mineral density (BMD) by dual X-ray absorptiometry (DXA). The WHO proposed an

operational definition of osteoporosis as a BMD that lies 2.5 SD or more below the average mean value of young healthy women (T-score≤−2.5 SD), accepting by inference the same definition for men [7, 8], more recently made explicit [9]. This definition has been readily accepted by most regulatory agencies and used as a cut-off for limiting treatment access. In Switzerland, bisphosphonates are the mainstay of drug therapy for osteoporosis and are generally reimbursed if the patient has documented osteoporosis defined as a BMD T-score ≤−2.5 SD measured by DXA and/or a fracture. Reimbursement of DXA examination is mainly restricted to patients with clinically overt osteoporosis or a fracture caused by a low-energy trauma. It is also possible for those with hypogonadism, gastrointestinal diseases leading to malabsorption, primary hyperparathyroidism and chronic users of glucocorticoids. Therefore, currently reimbursed DXA indications exclude patients presenting with other well-known major risk factors for osteoporosis, such as a parental history of hip fracture, tobacco and/or alcohol abuse and rheumatoid arthritis.

Prospective epidemiological studies have shown that, although fracture risk increases with decreasing BMD, many fractures occur in subjects with a BMD T-score value above the operational threshold [10–12]. The recent Swiss OsteoCare survey measured BMD by DXA at the lumbar spine, the total hip and/or the femoral neck in 1,152 patients presenting with a fragility fracture at an emergency ward. This study found that 46% of patients had osteoporosis, 35% had osteopenia (−2.5<T-score≤−1 SD) and 19% had normal BMD (T-score>−1.0 SD) [12]. Thus, 54% of all patients with a fragility fracture have bone mass above the diagnostic threshold for osteoporosis.

Recently, the use of clinical risk factors has been shown to enhance the performance of BMD in the prediction of hip and osteoporotic fractures in men and women [13]. In order to identify the major clinical risk factors for osteoporotic fracture, the data from nine prospective primary cohorts and 11 prospective validation cohorts, including more than 275,000 persons corresponding to 1.4 million person-years with more than 22,711 reported fractures, were analysed [13]. The validation analysis included the results from the Swiss SEMOF-cohort [14]. In addition to any prior fragility fracture that occurred after age 50, age, sex, body mass index and additional risk factors were considered. These included prior use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis, a parental history of hip fracture, current cigarette smoking, and alcohol intake of three or more units/day. These factors were identified as clinical predictors of osteoporotic fracture probability, independently of BMD [13]. Taking into account local epidemiological data, the impact of these risk factors on the 10-year absolute probability of fracture can allow for country-specific prediction of individual fracture probability, based on the individual risk factor profile. This case-finding algorithm, known as FRAX®, has been developed in collaboration with the WHO and has been customised to the epidemiology of several countries including the UK [1], the USA [15] and Japan [16].

In an earlier publication, all of the elements required to populate a Swiss-specific FRAX® model were validated [17]. The aim of the present study was to determine which constellations of clinical risk factors, alone or in combination, and with or without a BMD measurement by DXA, would contribute to improved identification of patients with increased probability of fracture in the Swiss environment.

Methods

The effect of BMD, gender and age on the 10-year absolute probability of hip and any major osteoporotic fracture (hip, vertebral, distal radius and proximal humerus) by 5-year age groups has been previously reported [17]. Baseline data included the incidence of hospitalisation for fractures and osteoporotic fractures in the year 2000 as published by the Swiss Federal Office of Statistics [2] and results from the prospective Swiss OsteoCare survey [12] standardised for hip fractures. These values were extrapolated for the determination of the total number of major clinical osteoporotic fractures (hospitalised and non-hospitalised). Additional baseline data included death risk and incidence tables for Switzerland in 1999 published by the WHO [18] and femoral neck BMD T-scores derived from the National Health and Nutrition Examination Survey (NHANES) III data for Caucasian women aged 20–29 years [19].

The clinical risk factors identified in the nine prospective validated cohorts [13] were applied to the Swiss epidemiological data using the methodology previously described for the development of the FRAX® fracture probability assessment model in the UK [20]. Briefly, BMI, as mathematically derived from height and weight, BMD T-scores at the femoral neck, and age between 50 and 90 years were used as continuous variables. The following clinical risk factors, consistently reported in all primary cohorts, were used as dichotomous variables: current cigarette smoking, alcohol intake of three or more units daily, rheumatoid arthritis, other causes of secondary osteoporosis, current and prior use of glucocorticoids, previous fragility fracture, including morphometric vertebral fractures discovered by chance on an X-Ray, and parental history of hip fracture. ‘Use of glucocorticoids’ depicts either current or previous treatment with oral glucocorticoids with an exposure period of ≥3 months at a dose of ≥5 mg daily of prednisolone or equivalent doses of other glucocorticoids. The effects of all these factors on the 10-year probability of fracture were modelled for hip and major clinical osteoporotic fractures, with and without BMD

for both sexes. For each model, fracture and death were computed as continuous hazard functions using a Poisson regression as previously reported [20].

Importantly, rheumatoid arthritis was considered separately from other causes of secondary osteoporosis. The presence of rheumatoid arthritis was shown to increase fracture probability independently of BMD and glucocorticoid intake [21]. Other forms of secondary osteoporosis, such as hypogonadism or premature menopause (<45 years) [22–24], inflammatory bowel diseases [25–28], immobilisation due to spinal cord injury [29] and thyroid disorders [30], are generally associated with increased fracture probability; however, whether these are independent of BMD remains controversial. Therefore, for FRAX® modelling purposes, other causes of secondary osteoporosis were attributed the same level of risk as rheumatoid arthritis in the absence of a BMD value and no additional risk if a BMD value was available. In the presence of rheumatoid arthritis and another cause of secondary osteoporosis, the risks allocated are those for rheumatoid arthritis only. BMD refers to the femoral neck BMD as measured by DXA in men or women. For the purpose of this manuscript, BMI was set at 25 kg/m^2 and age at 65 years unless otherwise indicated.

Results

Effect of BMI and BMD on fracture probability

At any age, the absolute 10-year fracture probability was higher in men and women with lower BMI values (Fig. 1). In addition, the contribution of a low BMI on fracture probability was higher in elderly compared to younger patients. At any BMI value, 90-year old patients had a lower absolute 10-year fracture probability than 80-year old patients, the effect being more pronounced in men than in women. This reflects the fact that in the FRAX® model, death hazard from all causes and fracture probability are competing events. As shown in Fig. 2, absolute 10-year fracture probabilities increased exponentially with decreasing T-score values. The effect of BMD on fracture probability again decreased in very old men and women, indicating that, with advanced age, there is a higher probability of dying from any other competing cause rather than sustaining an osteoporotic fracture.

Fracture probability in the presence of single risk factors

Fracture probability was always found to be higher in women than in men. This was consistent across any given age, BMI value, T-score value, and for any single risk factor. In the absence of any validated risk factor selected for FRAX® modelling, the 10-year probability of a major

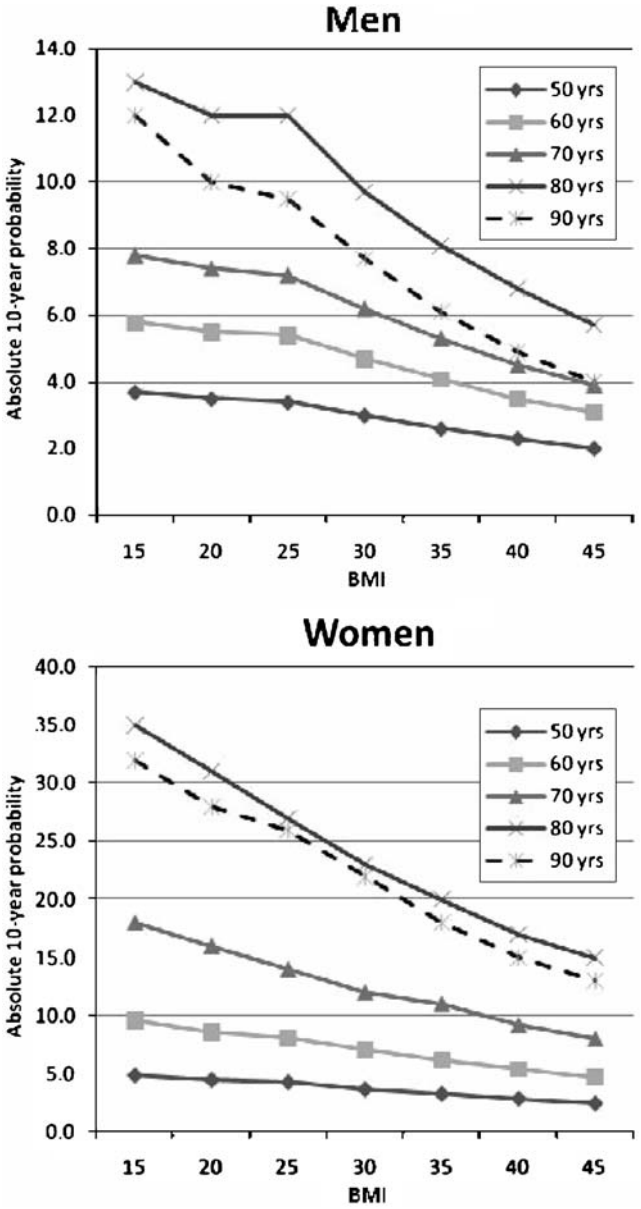

Fig. 1 Absolute 10-year major fracture probability at various levels of BMI (kg/m^2) and at different ages for Swiss men and women, without clinical risk factors

osteoporotic fracture at age 65 years and at a BMI of 25 kg/m^2 (base case) was 5.6% in men and 9.5% in women. The data presented in Table 1 indicate that the presence of risk factors increased this base case probability. Large increases in fracture probability were observed in the case of a previous fragility fracture or of parental history of hip fracture. Both of these factors doubled the probability, reaching 11.0% and 18.0% in men and women, respectively. At age 65, a BMD T-score of −2.5 SD measured at the femoral neck increased 10-year fracture probability to 11.0% and 14.0% in men and women, respectively. This fracture probability further increased up to 18.0% in men

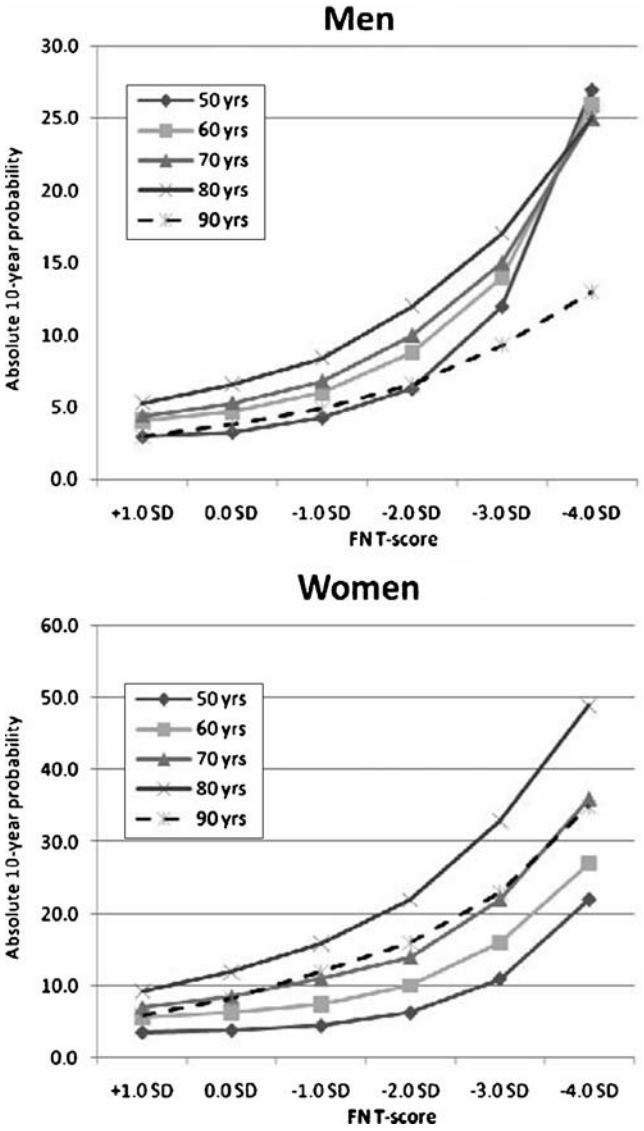

Fig. 2 Absolute 10-year major fracture probability by age and femoral neck BMD in Swiss men and women. BMI was set at 25 kg/m^2

and 24.0% in women, depending on which associated single clinical risk factor was present.

As shown in Table 2, the 10-year absolute probability of any major osteoporotic and hip fracture in the presence of a single risk factor increased with advancing age in both sexes. Between a 50-year-old man without risk factors and an 80-year-old man with a parental history of hip fracture, the individual probability of any major osteoporotic fracture increased 6.5-fold (from 3.4% to 22.0%). In women, this probability increased 10.2-fold. For equivalent scenarios, the probability of suffering a hip fracture increased 75-fold in men and 100-fold in women from base line levels.

Fracture probability was found to increase with decreasing BMD T-score values in both sexes, as shown in Table 3 and Fig. 2. In the absence of any risk factor, the 10-year probability of a major osteoporotic fracture for a 65-year-old woman presenting with the commonly accepted treatment threshold T-score of −2.5 SD was 14.0%. This fracture probability was equal to or lower than that of a woman with a T-score of −2.0 SD and either rheumatoid arthritis, present or past glucocorticoid treatment, previous fragility fracture during adulthood or parental history of hip fracture. The fracture probability was also lower than that of a woman with a T-score of −1.0 SD and a parental history of hip fracture. In addition, in men without clinical risk factors and a T-score of −2.5 SD, the absolute 10-year fracture probability for any major osteoporotic fracture was 11.0%. With a parental history of hip fracture, the same level of absolute fracture probability was achieved at a T-score of −1.0 SD. However, based on the current thresholds for reimbursement, treatment with a bisphosphonate would be reimbursed in the former case, but not in the latter, despite the probability of a fracture being equal in both cases.

Fracture probability with multiple risk factors

The absolute 10-year major osteoporotic or hip fracture probability was found to increase exponentially with the number of associated risk factors. In the absence of an available BMD T-score value and in the base case (BMI of 25 kg/m^2 and age of 65 years), the probability of any major osteoporotic fracture was increased 8.2-fold in men presenting with all risk factors (46.0%) compared to men with no risk factors (5.6%) and 7.5-fold (71.0% and 9.5%, respectively) in women as shown in Table 4. In the case of patients having all risk factors, a BMD T-score of −2.5 SD compared to no BMD value available contributed only modestly to fracture probability in women (72.0% vs. 71.0%) but considerably more in men (58.0% vs. 46.0%). These results indicate that, depending on sex and age, the relevance of a T-score value with regard to fracture probability varied.

At the age of 65 and for any major osteoporotic fracture resulting from long-term treatment with oral glucocorticoids, the lowest 10-year fracture probability corresponding to that currently reimbursed in Switzerland was 8.7% in men and 15.0% in women. As shown in Table 5, several pairs of other risk factors gave an equivalent or higher fracture probability level. Similarly, with the treatment threshold set at ≤−2.5 SD as required for reimbursement of drug therapy of osteoporosis, the corresponding 10-year fracture probabilities were 11.0% in men and 14.0% in women. At a T-score of −1.0 SD, several pairs of associated clinical risk factors resulted in fracture probabilities higher than that achieved for this threshold. These were exceeded even more frequently when more than two risk factors were present in the same patient.

Table 1 Ten-year probability (in per cent) of a major osteoporotic or hip fracture in men and women according to the presence of a single risk factor

	Without BMD				T-score=−2.5 SD			
	Men		Women		Men		Women	
	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip	Osteoporotic[a]	Hip
No clinical risk factors	5.6	0.9	9.5	1.5	11.0	4.0	14.0	3.4
Current cigarette smoking	5.9	1.3	10.0	2.2	12.0	6.4	15.0	5.7
Alcohol intake>2 units daily	6.9	1.3	12.0	2.2	14.0	6.1	17.0	5.1
Rheumatoid arthritis	7.7	1.6	13.0	2.6	14.0	5.7	18.0	4.8
Oral glucocorticoids	*8.7*	*1.8*	*15.0*	*3.1*	*17.0*	*7.0*	*22.0*	*6.2*
Previous fragility fracture	*11.0*	*2.2*	*18.0*	*3.6*	*18.0*	*6.6*	*22.0*	*5.6*
Parental history of hip fracture	11.0	1.2	18.0	1.9	18.0	4.2	24.0	3.6

Rows in italics indicate clinical risk factors included in FRAX® and currently accepted for DXA reimbursement in Switzerland. BMI set at 25 kg/m^2, age set at 65 years

[a] Hip, clinical spine, humeral, or forearm fracture

Discussion

The present study shows that levels of 10-year fracture probability equivalent to those currently accepted for reimbursement of BMD measurement by DXA in Switzerland are achieved with several clinical risk factor profiles and combinations. These include risk factors not (yet) accepted for reimbursement, such as a parental history of fracture, tobacco and/or alcohol abuse and rheumatoid arthritis. This suggests that, with identical 10-year fracture probabilities, adequate diagnostic workup is not equally accessible to all patients presenting with identical fracture risk. Consequently, with current access to osteoporosis diagnosis, too few patients at increased probability of fracture are adequately identified and subsequently treated. This is consistent with earlier reports indicating that a significant proportion of osteoporotic fractures occur in patients with a T-score above −2.5 SD [11, 12].

Low bone mass, as measured by DXA, is an important single predictor of fracture risk [31–34], and BMD measured at the femoral neck has been shown to outperform clinical risk factors alone at all ages for hip fracture prediction [13]. However, as shown by the present findings, BMD alone does not capture all determinants of fracture probability, and the consideration of additional risk factors

Table 2 Ten-year probability (in per cent) of a major osteoporotic or hip fracture in men and women according to age and the presence of a single risk factor

	Osteoporotic fracture[a]				Hip fracture			
	50	60	70	80	50	60	70	80
Men								
No clinical risk factors	3.4	5.4	7.2	12.0	0.2	0.5	1.6	4.8
Current cigarette smoking	3.6	5.6	7.5	12.0	0.3	0.7	2.2	6.1
Alcohol intake>2 units daily	4.1	6.5	9.0	15.0	0.3	0.8	2.4	7.2
Rheumatoid arthritis	4.6	7.3	10.0	17.0	0.3	0.9	2.8	8.2
Oral glucocorticoids	*5.5*	*8.5*	*11.0*	*16.0*	*0.4*	*1.0*	*3.0*	*7.9*
Previous fragility fracture	*7.3*	*11.0*	*13.0*	*19.0*	*0.7*	*1.5*	*3.4*	*7.3*
Parental history of hip fracture	6.8	10.0	11.0	22.0	0.2	0.7	3.4	15.0
Women								
No clinical risk factors	4.3	8.1	14.0	27.0	0.3	0.8	2.8	10.0
Current cigarette smoking	4.5	8.6	15.0	30.0	0.4	1.2	4.2	14.0
Alcohol intake>2 units daily	5.1	9.7	17.0	33.0	0.4	1.2	4.3	15.0
Rheumatoid arthritis	5.8	11.0	19.0	37.0	0.5	1.4	5.0	17.0
Oral glucocorticoids	*7.0*	*13.0*	*22.0*	*40.0*	*0.6*	*1.7*	*5.8*	*19.0*
Previous fragility fracture	*9.1*	*16.0*	*25.0*	*42.0*	*1.1*	*2.3*	*5.9*	*15.0*
Parental history of hip fracture	8.4	15.0	22.0	44.0	0.4	1.1	6.0	30.0

Rows in italics indicate clinical risk factors included in FRAX® and currently accepted for DXA reimbursement in Switzerland. BMI set at 25 kg/m^2

[a] Hip, clinical spine, humeral or forearm fracture

Table 3 Ten-year probability (in per cent) of a major osteoporotic fracture in men and women according to Femoral neck BMD and presence of a single risk factor

Osteoporotic fracture[a]	T-score= −4.0 SD	T-score= −3.0 SD	T-score= −2.5 SD	T-score= −2.0 SD	T-score= −1.5 SD	T-score= −1.0 SD	T-score= 0.0 SD	T-score= +1.0 SD	Without BMD
Men									
No clinical risk factors	24.0	14.0	11.0	8.6	7.0	5.8	4.5	3.8	5.6
Current cigarette smoking	31.0	17.0	12.0	9.4	7.4	5.9	4.4	3.6	5.9
Alcohol intake>2 units daily	32.0	18.0	14.0	11.0	8.7	7.1	5.4	4.5	6.9
Rheumatoid arthritis	32.0	18.0	14.0	11.0	9.1	7.5	5.8	4.9	7.7
Oral glucocorticoids	*36.0*	*22.0*	*17.0*	*13.0*	*11.0*	*9.0*	*7.0*	*6.0*	*8.7*
Previous fragility fracture	*37.0*	*22.0*	*18.0*	*14.0*	*12.0*	*9.7*	*7.6*	*6.5*	*11.0*
Parental history of hip fracture	33.0	22.0	18.0	15.0	13.0	11.0	9.0	7.9	11.0
Women									
No clinical risk factors	30.0	17.0	14.0	11.0	9.0	7.9	6.6	5.6	9.5
Current cigarette smoking	37.0	20.0	15.0	12.0	9.3	8.0	6.4	5.4	10.0
Alcohol intake>2 units daily	38.0	22.0	17.0	13.0	11.0	9.5	7.8	6.6	12.0
Rheumatoid arthritis	38.0	22.0	18.0	14.0	12.0	10.0	8.4	7.2	13.0
Oral glucocorticoids	*45.0*	*27.0*	*22.0*	*17.0*	*14.0*	*13.0*	*10.0*	*8.9*	*15.0*
Previous fragility fracture	*45.0*	*27.0*	*22.0*	*18.0*	*15.0*	*13.0*	*11.0*	*9.3*	*18.0*
Parental history of hip fracture	43.0	29.0	24.0	20.0	17.0	16.0	13.0	11.0	18.0

Rows in italics indicate clinical risk factors included in FRAX® and currently accepted for DXA reimbursement in Switzerland. BMI set at 25 kg/m^2, age set at 65 years

Boxes indicate the current fracture probability threshold for treatment reimbursement in Switzerland

[a] Hip, clinical spine, humeral or forearm fracture

Table 4 Ten-year probability (in per cent) of a major osteoporotic or hip fracture in men and women with multiple risk factors as a function of Femoral neck BMD

	Without BMD		BMD T-score=−2.5 SD		BMD T-score=−1.0 SD	
	Osteoporotic fracture[a]	Hip fracture	Osteoporotic fracture[a]	Hip fracture	Osteoporotic fracture[a]	Hip fracture
Men						
No clinical risk factors	5.6	0.9	11.0	4.0	5.8	0.9
Current cigarette smoking	5.9	1.3	12.0	6.4	5.9	1.5
+Alcohol intake>2 units daily	7.3	1.9	16.0	9.6	7.4	2.3
+Rheumatoid arthritis	10.0	3.4	21.0	13.0	9.7	3.3
+Oral glucocorticoids	16.0	6.5	32.0	21.0	15.0	5.7
+Previous fragility fracture	31.0	15.0	46.0	33.0	24.0	9.3
+Parental history of hip fracture	46.0	20.0	58.0	34.0	37.0	9.8
Women						
No clinical risk factors	9.5	1.5	14.0	3.4	7.9	0.7
Current cigarette smoking	10.0	2.2	15.0	5.7	8.0	1.2
+Alcohol intake>2 units daily	13.0	3.3	19.0	8.6	9.7	1.8
+Rheumatoid arthritis	18.0	5.8	25.0	12.0	13.0	2.5
+Oral glucocorticoids	29.0	12.0	39.0	21.0	20.0	4.7
+Previous fragility fracture	51.0	27.0	56.0	33.0	31.0	7.7
+Parental history of hip fracture	71.0	34.0	72.0	34.0	51.0	8.1

BMI set at 25 kg/m^2, age set at 65 years

The sign "+" indicates that the individual risk factors are successively added (incremental risk)

[a] Hip, clinical spine, humeral or forearm fracture

Table 5 Ten-year probability (in per cent) of a major osteoporotic fracture in men and women according to femoral neck BMD and risk factors combined by pairs

	Without BMD							With BMD T-Score = -2.5 SD							With BMD T-Score = -1.0 SD						
	No clinical risk factors	Current cigarette smoking	Alcohol intake > 2 units daily	Rheumatoid arthritis	*Oral glucocorticoids*	*Previous fragility fracture*	Parental history of hip fracture	No clinical risk factors	Current cigarette smoking	Alcohol intake > 2 units daily	Rheumatoid arthritis	Oral glucocorticoids	Previous fragility fracture	Parental history of hip fracture	No clinical risk factors	Current cigarette smoking	Alcohol intake > 2 units daily	Rheumatoid arthritis	Oral glucocorticoids	Previous fragility fracture	
Men																					
No clinical risk factors	5.6							**11.0**							5.8						
Current cigarette smoking		5.9							**12.0**							5.9					
Alcohol intake > 2 units daily		7.3	6.9						**16.0**	**14.0**						7.4	7.1				
Rheumatoid arthritis		8.2	9.6	7.7					**16.0**	**18.0**	**14.0**					7.7	9.2	7.5			
Oral glucocorticoids		*9.1*	***11.0***	***12.0***	*8.7*				***19.0***	***21.0***	***22.0***	***17.0***				*9.1*	***11.0***	***12.0***	*9.0*		
Previous fragility fracture		***12.0***	***13.0***	***15.0***	***17.0***	***11.0***			***20.0***	***22.0***	***23.0***	***27.0***	***18.0***			***11.0***	***12.0***	***12.0***	***15.0***	*9.7*	
Parental history of hip fracture		**11.0**	**13.0**	**14.0**	***16.0***	***20.0***	**11.0**		**19.0**	**22.0**	**23.0**	**27.0**	**29.0**	**18.0**		**11.0**	**13.0**	**14.0**	**17.0**	**18.0**	**11.0**
Women																					
No clinical risk factors	9.5							**14.0**							7.9						
Current cigarette smoking		10.0							**15.0**							8.0					
Alcohol intake > 2 units daily		13.0	12.0						**19.0**	**17.0**						9.7	9.5				
Rheumatoid arthritis		**14.0**	**16.0**	13.0					**20.0**	**22.0**	**18.0**					10.0	12.0	10.0			
Oral glucocorticoids		***17.0***	***19.0***	***21.0***	***15.0***				***24.0***	***27.0***	***28.0***	***22.0***				*13.0*	***15.0***	***16.0***	*13.0*		
Previous fragility fracture		***20.0***	***22.0***	***25.0***	***29.0***	***18.0***			***24.0***	***27.0***	***28.0***	***34.0***	***22.0***			*13.0*	***16.0***	***17.0***	***21.0***	*13.0*	
Parental history of hip fracture		**19.0**	**21.0**	**24.0**	***28.0***	***32.0***	**18.0**		**25.0**	**28.0**	**30.0**	**36.0**	**37.0**	**24.0**		**15.0**	**18.0**	**20.0**	**24.0**	**25.0**	**16.0**

Italic fonts indicate clinical risk factors included in FRAX® and currently accepted for DXA reimbursement in Switzerland

Boxes indicate the current fracture probability threshold for treatment reimbursement in Switzerland. Higher probabilities indicated in bold fonts

BMI set at 25 kg/m^2, age set at 65 years

improves its predictive value. Screening with DXA alone is generally not considered sensitive enough, and thus, the identification of patients with osteoporosis generally relies on case-finding strategies [1]. Therefore, FRAX® represents a unique opportunity for identifying those subjects who should benefit from further diagnostic measures, including the assessment of risk factors not captured by FRAX® such as risk factors for falls, gastrointestinal malabsorption syndromes, increased biochemical markers of bone turnover and/or vitamin D insufficiency. The need for additional diagnosis by X-ray examination or a laboratory assessment of calcium phosphate metabolism can also be indicated following FRAX® assessment. Depending on the findings and the T-score value measured at the femoral neck and its deviation from the mean T-score value in a population of the same age and sex, the absolute 10-year fracture probability may assist in determining which patients would benefit from treatment. Previous analysis of population-based screening with DXA followed by alendronate treatment, in the presence of osteoporosis or of fracture and osteopenia, has been shown to be cost-effective in postmenopausal women after the age of 70 years for the Swiss healthcare system [35]. A FRAX®-based pre-identification of patients eligible for DXA is likely to improve cost-effectiveness by increasing the specificity and sensitivity of case finding.

An interesting finding of the present analysis was that in 65-year old patients with all risk factors included in the FRAX® algorithm, a T-score of −2.5 SD did not increase fracture probability in women, though it did in men. This could be related to the fact that BMD T-score is computed from the NHANES reference range for women. Thus, in 65-year-old women, a T-score of −2.5 SD corresponds more or less to the average of the female population of that age with multiple clinical risk factors. In men, however, this T-score (derived from the female reference range) is lower than average for men of this age, and a T-score of -2.5 SD thus adds a significant component to fracture probability.

Setting a treatment cut-off based on a T-score alone does select patients at increased probability of fracture. However, it also categorises patients at equal or higher fracture probability as non-eligible for treatment if additional clinical risk factors are not integrated in fracture risk assessment. The determination of the individual 10-year fracture probability with FRAX® would at least ensure that patients at equal risk would have equal chances of getting appropriate treatment. Interestingly, in the field of osteoporosis, treatment access is usually restricted in accordance with the inclusion criteria of the fracture endpoint trials. In the vast majority of these studies, patients were included on the basis of low bone mass measured by DXA and/or prevalent vertebral fractures [36–

40]. However, in the subgroup post hoc analyses performed in all these studies, there was no evidence in favour of differences in efficacy related to the presence or absence of these clinical risk factors [36–40]. Moreover, several trials indicate enhanced effectiveness of pharmacologic intervention in patients with higher fracture probabilities as determined by the FRAX® tool [41, 42].

The clinical risk factor approach in FRAX® should be considered to be conservative. Calculated fracture probabilities are limited to major clinical osteoporotic fractures, i.e. those of the hip, spine, distal forearm and proximal humerus. In the year 2000 in Switzerland, these fractures represented 63% and 76% of all hospitalised fractures [2] and 63% and 71% of total (hospitalised and non-hospitalised) clinical fractures in the OsteoCare survey [12] in men and women, respectively. This study only considered clinical fractures, although the more prevalent morphometric vertebral fractures and deformities also did increase the risk of future fracture at any site [43]. In addition these fractures are associated with substantial increases in back pain and functional limitation due to back pain [44]. Furthermore, vertebral fractures, including asymptomatic fractures, may be responsible of a loss in height. In these patients, BMI derived from body weight (kilogram) and height (square meter) will be mathematically higher, leading to a theoretical underestimation of fracture probability. Therefore, true fracture incidence and derived fracture probabilities are generally likely to be underestimated. In contrast, the validated risk factors independent of BMD used in FRAX® modelling are those that allow consistent linking with BMD T-scores, age, and BMI in nine international cohorts [13]. This suggests that still other risk factors may also independently contribute to fracture risk but are not accommodated in the FRAX® algorithm. As an example, the history of falls, propensity to falling, biochemical markers of bone turnover and vitamin D status are important determinants of fracture probability not included in FRAX®. Moreover, the magnitude of the effect on fracture probability of some of the validated risk factors used in FRAX®, for which the model assumes average exposure, may depend on dosage, quantity and/or duration of exposure. In particular, the individual circumstances of the use of glucocorticoids, tobacco smoking and alcohol consumption will affect the individual fracture probability. Currently, the FRAX® tool does not integrate a dose-dependent influence. Finally, BMD measured at other sites than the femoral neck is a proven risk factor for fractures, which is not included in FRAX®. FRAX® results also do not integrate BMD increases achieved with previous or ongoing drug therapies against osteoporosis. The present study cannot address these issues. Therefore, one of the key determinants for adequate interpretation of the individual 10-year probability of fracture delivered by FRAX® will remain clinical judgement.

The findings of the present study are consistent with the need for a paradigm shift in osteoporosis management. The current, solely BMD threshold-dependent prevention/treatment concept needs to evolve to a fracture probability continuum for which new intervention thresholds, based on the 10-year probability of any major osteoporotic or hip fractures, need to be defined. FRAX® based future cost-effectiveness analyses will certainly contribute to identifying medically and economically optimised osteoporosis case-finding strategies.

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