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Article *in* Osteoporosis International · March 2011

DOI: 10.1007/s00198-011-1592-3 · Source: PubMed

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Osteoporos Int (2012) 23:391–397
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SHORT COMMUNICATION

High fracture probability with FRAX® usually indicates densitometric osteoporosis: implications for clinical practice

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Received: 10 January 2011 / Accepted: 7 February 2011 / Published online: 2 March 2011

Abstract
Summary Most patients designated as high risk of fracture using fracture risk assessment tool (FRAX®) with femoral neck bone mineral density (BMD) (i.e., 10-year major osteoporotic fracture probability exceeding 20% or hip fracture exceeding 3%) have one or more T-scores in the osteoporotic range; conversely, almost no high risk patients have normal T-scores at all bone mineral density measurement sites.
Introduction We determined the agreement between a FRAX® designation of high risk of fracture [defined as 10-year major osteoporotic fracture probability (≥20%) or hip fracture probability (≥3%)] and the WHO categorizations of bone mineral density according to T-score.
Methods Ten-year FRAX® probabilities calculated with femoral neck BMD were derived using both Canadian and US white tools for a large clinical cohort of 36,730 women and 2,873 men age 50 years and older from Manitoba, Canada. Individuals were classified according to FRAX fracture probability and BMD T-scores alone.
Results Most individuals designated by FRAX as high risk of major osteoporotic fracture had a T-score in the osteoporotic range at one or more BMD measurement sites (85% with Canadian tool and 83% with US white tool). The majority of individuals deemed at high risk of hip fracture had one or more T-scores in the osteoporotic range (66% with Canadian tool and 64% with US white tool). Conversely, there were extremely few individuals (<1%) who were at high risk of major osteoporotic or hip fracture with normal T-scores at all BMD measurement sites.
Conclusions A FRAX designation of high risk of fracture is usually associated with a densitometric diagnosis of osteoporosis.

Keywords Bone mineral density · Clinical risk factors · Fracture prediction · FRAX® · Osteoporosis

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Introduction

Historically, fracture risk assessment in individuals without a clinical diagnosis of osteoporosis based upon established fragility fractures was determined by bone mineral density (BMD) measurements. The World Health Organization (WHO) established operational definitions for interpreting T-scores of the lumbar spine, hip, and distal forearm which were initially intended for epidemiologic purposes but were subsequently adopted into routine clinical practice for classification and management of individual patients [1–3]. These criteria were initially restricted to postmenopausal Caucasian (white) women, but have subsequently been broadened to apply to older men (over age 50) and all ethnic groups. The WHO has designated the femoral neck site measured with dual-energy X-ray absorptiometry (DXA) as the reference standard for diagnosis of osteoporosis based upon T-score −2.5 or lower using a standardized reference population [Third National Health and Nutrition Examination Survey (NHANES III)] [2].

Although reduced bone mass is an important and easily quantifiable measurement, studies have shown that most fractures occur in individuals with a BMD T-score above the operational threshold for osteoporosis [4]. Recently, the use of clinical risk factors (CRFs) has been shown to enhance the performance of BMD in the prediction of hip and major osteoporotic fractures [5]. In addition to a prior fragility fracture, CRFs include age, sex, body mass index (BMI), use of glucocorticoids, secondary osteoporosis, rheumatoid arthritis, parental history of hip fracture, current smoking, and alcohol intake of three or more units/day [5]. The WHO fracture risk assessment tool (FRAX®) allows for estimation of individual 10-year major osteoporotic and hip fracture probabilities [6]. Analyses have confirmed that there is improvement in fracture prediction using BMD and CRFs together compared with using either BMD alone or CRFs alone [4, 5]. This has led to broad endorsement of FRAX and its integration into several clinical practice guidelines [7–15]. For example, a 10-year major osteoporotic fracture probability of greater than or equal to 20% is considered high risk and is an indication for intervention according to the National Osteoporosis Foundation (NOF) of the United States and Osteoporosis Canada [7, 8, 16]. The NOF also recommends that a 10-year hip fracture probability of 3% or greater be considered for intervention, in addition to those with any BMD measurements in the osteoporotic range and those with prior spine or hip fractures.

On the other hand, the eligibility criteria for most clinical trials of osteoporosis therapy have been based upon the presence of a prior fracture and/or reduced BMD and not on predicted risk of future fracture. No clinical trials to date have used FRAX probability as eligibility criteria. Some post hoc reanalyses of clinical trials data have shown greater antifracture efficacy in individuals at higher risk [17, 18] whereas others have shown benefit across the range of fracture probabilities (with greater absolute risk reductions in those at higher risk) [19]. Still, there is ongoing debate over the magnitude of the antifracture effect from osteoporosis treatments in individuals without BMD in the osteoporotic range. It is possible for a patient to be at high predicted risk of fracture according to FRAX and have BMD in the normal range, or for a patient to have osteoporotic BMD results but deemed under FRAX to be at such low risk of fracture that treatment may not be warranted. Therefore, we undertook the present study to quantify the magnitude of these possibilities by examining the degree of concordance between high risk classification based upon FRAX probability estimates and conventional densitometric criteria.

Methods

Subjects and setting

In the province of Manitoba, Canada, health services are provided to virtually all residents through a single public health care system. Bone density testing with DXA has been managed as an integrated program since 1997; criteria and testing rates for this program have been published [20]. The program maintains a database of all DXA results which can be linked with other population-based computerized health databases through an anonymous personal identifier. The DXA database has been previously described with completeness and accuracy in excess of 99% [21].

For this retrospective cohort study, we identified all individuals age 50 years and older with valid DXA measurements from the lumbar spine and femoral neck. Although the FRAX tool does not currently use lumbar spine BMD in the risk calculation, this site still affects treatment decision-making under the US [7, 8] and Canadian guidelines [14]. Subjects were required to have medical coverage from Manitoba Health during the observation period starting in April 1997 and ending March 2008. For those with more than one eligible set of measurements, only the first record was included. The study was approved by the research ethics board for the University of Manitoba and access to the data was granted by the Health Information Privacy Committee of Manitoba.

Bone density measurements

Proximal femur (femoral neck, total hip, and trochanter) and lumbar spine DXA scans were performed and analyzed in accordance with manufacturer's recommendations. Femoral neck hip T-scores (number of SDs above or below young adult

mean BMD) and Z-scores (number of SDs above or below age-matched mean BMD) were calculated from the revised NHANES III white female reference values (Prodigy version 8.8) [3, 22]. No comparable international reference standard exists for the lumbar spine, and T-scores and Z-scores were calculated using the manufacturer US white female reference values. Vertebral levels affected by artifact were excluded by experienced physicians using conventional criteria [23]. When there were bilateral hip replacements, then the patient was excluded. Prior to 2000, DXA measurements were performed with a pencil-beam instrument (Lunar DPX, GE Lunar, Madison WI) and after this date a fan-beam instrument was used (Lunar Prodigy, GE Lunar, Madison WI). Instruments were cross-calibrated using anthropomorphic phantoms and 59 volunteers and no clinically significant differences were identified. Densitometers showed stable long-term performance [coefficient of variation (CV) <0.5%] and satisfactory in vivo precision (CV 1.7% for L1–4 and 1.1% for the total hip) [24]. Weight and height were recorded at the time of the DXA examination (prior to 2000, this was by self-report and starting in 2000, height was assessed with a wall-mounted stadiometer and weight was assessed without shoes using a standard floor scale). BMI (in kg/m^2) was calculated as weight (in kilograms) divided by height squared (in meters).

Fracture probability calculations

Prior fracture and other conditions required for calculating fracture probability with FRAX were assessed through a combination of hospital discharge abstracts (diagnoses and procedures coded using the ICD-9-CM prior to 2004 and ICD-10-CA thereafter) and physician billing claims (coded using ICD-9-CM) [25]. For purposes of the FRAX calculation, prior fragility fracture was taken to be a major osteoporotic fracture (hip, clinical vertebral, forearm, and humerus fracture) before BMD testing that was not associated with severe trauma as previously described [26]. A diagnosis of rheumatoid arthritis testing was taken from physician office visits or hospitalizations with a compatible ICD-9-CM/ICD-10-CA code in a 3-year period prior to BMD testing. Proxies were used for smoking (COPD diagnosis) and high alcohol intake (alcohol or substance abuse diagnosis) over the same time frame. Prolonged corticosteroid use (over 90 days dispensed in the year prior to DXA testing at a mean prednisone-equivalent dose of 7.5 mg per day or greater) was obtained from the provincial pharmacy system [27]. We adjusted for the effect of missing parental hip fracture information on FRAX probability estimates prior to 2005 using age- and sex-specific adjustment factors derived from 2005 to 2008 parental hip fracture responses as previously described [28].

Ten-year probability of a major osteoporotic fracture or hip fracture was calculated for each subject by the WHO Collaborating Centre based on the Canadian FRAX tool (version 3.1) using the previously defined variables and femoral neck BMD without knowledge of the fracture outcomes. FRAX estimates with this tool agree closely with observed fracture rates in the Canadian population [28]. To assess the robustness of these findings, analyses were performed using both the US white and Canadian FRAX tools. Major osteoporotic fracture probability ≥20% and hip fracture probability ≥3% were categorized as high risk in accordance with the NOF criteria [7, 8].

Analysis

All statistical analyses were performed with Statistica (Version 8.0, StatSoft Inc, Tulsa, OK).

Results

Patient characteristics

The final cohort included almost 40,000 patients (36,730 women and 2,873 men). Baseline characteristics of the population are summarized in Table 1. The mean age was 65.9±9.8 years and 93% were women. The femoral neck T-score was in the osteoporotic range for 14% of the cohort and the lowest T-score was osteoporotic in 30% of the cohort. In general, the US white FRAX tool gave slightly higher mean probabilities for major osteoporotic fractures than the Canadian tool (12.2%±7.3% versus 10.9%±7.3%).

Table 1 Baseline characteristics of study cohort at the time of BMD measurement

	N=39,603
Age (years)	65.9±9.8
Sex (women)	36,730 (92.7)
Femoral neck T-score (SD)	−1.5±1.0
Femoral neck T-score ≤−2.5	5,527 (14.0)
Lowest T-score (SD)[a]	−1.9±1.1
Lowest T-score ≤−2.5	11,890 (30.0)
Major osteoporotic fracture probability (Canada)	10.9%±7.3%
Major osteoporotic fracture probability (US white)	12.2%±7.3%
Hip fracture probability (Canada)	2.8%±4.4%
Hip fracture probability (US white)	3.1%±4.7%

Data expressed as mean±SD or *N* (%)

[a] Lowest T-score measurement from among those available for the lumbar spine and hip

A similar difference was seen for mean hip fracture probability (3.1%±4.7% versus 2.8%±4.4%). There was a high degree of correlation between the US white and Canadian FRAX probabilities (rank correlation coefficients >0.99, linear regression slope coefficient 0.99 for major osteoporotic fractures, and 1.06 for hip fractures). Major osteoporotic fracture probability exceeded the NOF cutoff for high risk in 11% of the cohort using the Canadian FRAX tool and 13% using the US white tool. Many more patients were designated as high risk using the 10-year probability of hip fracture (28% Canadian FRAX tool, 31% US white tool).

Concordance for lowest T-score

We found that the vast majority of individuals predicted to be at high risk of major osteoporotic fractures according to FRAX had BMD in the osteoporotic range at one or more measurement sites: 85% with the Canadian tool and 83% with the US white tool (Table 2). Results were similar when stratified by age and sex (range, 75% to 86%). Conversely, there were extremely few individuals (<1%) at a predicted high risk of major osteoporotic fracture with BMD results that were classified as normal at all measurement sites.

When hip fracture probability according to FRAX was used to define high risk rather than any major osteoporotic fracture probability, the majority of individuals also had their lowest T-scores in the osteoporotic range: 66% with the Canadian tool and 64% with the US white tool. Once again, <1% of those predicted to be at high risk of hip fracture had BMD results that were classified as normal at all measurement sites.

Of the 11,890 individuals with one or more osteoporotic T-scores, the majority (63% with the Canadian tool and 67% with the US white tool) had a major osteoporotic or hip FRAX probability value that exceeded NOF intervention cutoffs.

Concordance for femoral neck T-score

Analyses were repeated using the femoral neck T-score (Table 3). Among those with major osteoporotic fracture probability ≥20%, femoral neck T-scores were in the osteoporotic range for 71% of the population with the Canadian tool and 66% with the US white tool. In contrast, among those with ≥3% 10-year risk of hip fracture, less than half had a femoral neck T-score in the osteoporotic range: 44% with the Canadian tool and 42% with the US white tool. Of the 5,527 individuals with an osteoporotic femoral neck T-score, the vast majority (90% with the Canadian tool and 92% with the US white tool) had a major osteoporotic or hip FRAX probability value that exceeded NOF intervention cutoffs.

Table 2 Number (percentage) of individuals with predicted high risk of major osteoporotic fracture and hip fracture as a function of lowest T-score

				Major osteoporotic probability ≥20%		Hip probability ≥3%	
Sex	Age	Lowest T-score	*N*	Canadian	US white	Canadian	US white
Both	50+	Normal	8,248	10 (0.2)	12 (0.2)	82 (0.7)	102 (0.8)
	50+	Low bone mass	19,465	637 (15.1)	859 (17.3)	3,741 (33.2)	4,308 (35.0)
	50+	Osteoporosis	11,890	3,573 (84.7)	4,102 (82.5)	7,436 (66.0)	7,902 (64.2)
		Subtotal	39,603	4,220 (100)	4,973 (100)	11,259 (100)	12,312 (100)
Women	50–64	Normal	5,128	2 (0.8)	4 (0.8)	0 (0.0)	0 (0.0)
	50–64	Low bone mass	9,750	31 (12.8)	108 (22.3)	69 (9.2)	130 (12.8)
	50–64	Osteoporosis	3,437	210 (86.4)	373 (76.9)	682 (90.8)	888 (87.2)
		Subtotal	18,315	243 (100)	485 (100)	751 (100)	1,018 (100)
Women	65+	Normal	2,198	7 (0.2)	7 (0.2)	44 (0.5)	52 (0.5)
	65+	Low bone mass	8,319	590 (15.2)	722 (16.6)	3,159 (33.1)	3,586 (35.1)
	65+	Osteoporosis	7,898	3,297 (84.7)	3,622 (83.2)	6,348 (66.5)	6,591 (64.4)
		Subtotal	18,415	3,894 (100)	4,351 (100)	9,551 (100)	10,229 (100)
Men	50–64	Normal	388	1 (6.3)	1 (3.1)	1 (0.9)	1 (0.7)
	50–64	Low bone mass	554	2 (12.5)	7 (21.9)	45 (39.8)	60 (43.5)
	50–64	Osteoporosis	177	13 (81.3)	24 (75.0)	67 (59.3)	77 (55.8)
		Subtotal	1,119	16 (100)	32 (100)	113 (100)	138 (100)
Men	65+	Normal	534	0 (0.0)	0 (0.0)	37 (4.4)	49 (5.3)
	65+	Low bone mass	842	14 (20.9)	22 (21.0)	468 (55.5)	532 (57.4)
	65+	Osteoporosis	378	53 (79.1)	83 (79.0)	339 (40.2)	346 (37.3)
		Subtotal	1,754	67 (100)	105 (100)	844 (100)	927 (100)

Table 3 Number (percentage) of individuals with predicted high risk of major osteoporotic fracture and hip fracture as a function of femoral neck T-score

				Major osteoporotic probability ≥20%		Hip probability ≥3%	
Sex	Age	Femur neck T-score	*N*	Canadian	US white	Canadian	US white
Both	50+	Normal	11,876	16 (0.4)	26 (0.5)	133 (1.2)	164 (1.3)
	50+	Low bone mass	22,200	1,226 (29.1)	1,662 (33.4)	6,180 (54.9)	7,043 (57.2)
	50+	Osteoporosis	5,527	2,978 (70.6)	3,285 (66.1)	4,946 (43.9)	5,105 (41.5)
		Subtotal	39,603	4,220 (100)	4,973 (100)	11,259 (100)	12,312 (100)
Women	50–64	Normal	7,354	2 (0.8)	9 (1.9)	0 (0.0)	0 (0.0)
	50–64	Low bone mass	9,846	56 (23.0)	193 (39.8)	168 (22.4)	310 (30.5)
	50–64	Osteoporosis	1,115	185 (76.1)	283 (58.4)	583 (77.6)	708 (69.5)
		Subtotal	18,315	243 (100)	485 (100)	751 (100)	1,018 (100)
Women	65+	Normal	3,369	13 (0.3)	16 (0.4)	83 (0.9)	97 (0.9)
	65+	Low bone mass	10,903	1,146 (29.4)	1,425 (32.8)	5,365 (56.2)	5,999 (58.6)
	65+	Osteoporosis	4,143	2,735 (70.2)	2,910 (66.9)	4,103 (43.0)	4,133 (40.4)
		Subtotal	18,415	3,894 (100)	4,351 (100)	9,551 (100)	10,229 (100)
Men	50–64	Normal	520	1 (6.3)	1 (3.1)	1 (0.9)	1 (0.7)
	50–64	Low bone mass	539	3 (18.8)	12 (37.5)	61 (54.0)	82 (59.4)
	50–64	Osteoporosis	60	12 (75.0)	19 (59.4)	51 (45.1)	55 (39.9)
		Subtotal	1,119	16 (100)	32 (100)	113 (100)	138 (100)
Men	65+	Normal	633	0 (0.0)	0 (0.0)	49 (5.8)	66 (7.1)
	65+	Low bone mass	912	21 (31.3)	32 (30.5)	586 (69.4)	652 (70.3)
	65+	Osteoporosis	209	46 (68.7)	73 (69.5)	209 (24.8)	209 (22.5)
		Subtotal	1,754	67 (100)	105 (100)	844 (100)	927 (100)

Discussion

In a large clinical cohort, we found that more than 80% of patients with a FRAX designation of "high risk" of any major osteoporotic fracture over 10 years had at least one T-score measurement of −2.5 or lower, and more than 99% had a T-score below the normal range cutoff of −1.0. Among those defined as high risk based on a 3% or greater probability of hip fracture over 10 years, two thirds had at least one T-score measurement of −2.5 or lower and 99% had a T-score below the normal range. These findings were very similar across strata defined by age and sex. Conversely, the majority of individuals satisfying a densitometric diagnosis of osteoporosis had a major osteoporotic or hip FRAX probability value that exceeded the intervention cutoffs suggested by the NOF [7, 8].

Given the current debate regarding the relative importance of 10-year predicted probability of fracture versus BMD T-scores for setting treatment thresholds [29, 30], our findings demonstrate general concordance with respect to these two approaches. Whether based on assessment of validated clinical risk factors, screening older patients with BMD to determine T-scores, or some combination of the two, a designation of high risk of future fracture that warrants intervention, however arrived at, should broadly mean the same thing to patients, physicians, and policy makers. Our findings of general concordance should therefore be reassuring. Indeed, less than 1% of patients at high risk of a major osteoporotic fracture over the next decade have normal BMD at all measurement sites. Although we cannot directly address the issue in our study, our findings imply that concerns about confusion related to discordant findings between FRAX estimates of risk and BMD test results are probably unwarranted—at least in the case of patients predicted to be at the highest risk of fracture and who appear to derive the greatest benefit from osteoporosis pharmacotherapy [17–19]. The NOF has suggested that FRAX probabilities only be used for treatment intervention in individuals with BMD in the low bone mass range (formerly termed "osteopenia") when other indications for treatment do not apply. These recommendations have now been implemented on DXA machine software sold in the USA as the "FRAX filter", but this approach has been the subject of debate [29, 30]. Of relevance in our study was the small number of individuals in whom FRAX probability exceeded the NOF intervention cutoffs and who had BMD in the normal range—the very group which the FRAX filter is intended to suppress.

Many more individuals were designated at high risk from hip fracture probability than from major osteoporotic fracture probability. It has previously been reported that over 90% of women and over 50–70% of

men age 85 years and older having a hip fracture probability 3% or greater [31]. This has led to the suggestion that the primary designation of risk should be based upon the global assessment of major osteoporotic fracture probability [10, 14].

Despite its strengths, our study has several limitations. First, there may be some issues related to spectrum bias as all patients had been referred for BMD testing by their physicians. For instance, 30% of patients had at least one T-score −2.5 or lower, a figure slightly higher than the general population [31]. This bias is mitigated to some degree since the same spectrum bias should apply to both clinical risk factors as well as the decision to refer for a BMD test. Second, we did not directly collect all elements of FRAX, but necessarily had to rely on diagnostic codes, proxy measures, and in the case of family history, adjustment for missing information. In addition, patients who were on treatment at the time of BMD testing were not excluded. Although FRAX cannot be used to determine risk reduction associated with therapy, it may still provide helpful information in terms of an individual's fracture risk in the absence of treatment by reflecting the theoretical risk for a hypothetical patient who is treatment naive. Lastly, some may be concerned about the wider applicability of our findings as they are based on data from referred patients with universal health care coverage from one region of Canada.

In conclusion, there is a reassuringly high concordance for the designation of high risk of fracture whether determined by FRAX probability or BMD categorization. A FRAX designation of high fracture risk under the NOF or Canadian guidelines should have the same implications for treatment selection as when treatment is initiated for an osteoporotic T-score.

Acknowledgments The authors are indebted to Manitoba Health for the provision of data (HIPC File No. 2007/2008-49). The results and conclusions are those of the authors, and no official endorsement by Manitoba Health is intended or should be inferred. This article has been reviewed and approved by the members of the Manitoba Bone Density Program Committee.

Conflicts of interest William D. Leslie: Speaker fees and unrestricted research grants from Merck Frosst Canada Ltd; unrestricted research grants from Sanofi-Aventis, Procter & Gamble Pharmaceuticals, Novartis, Amgen Pharmaceuticals, Genzyme; advisory boards for Genzyme, Novartis, and Amgen Pharmaceuticals.
Lisa M. Lix: Unrestricted research grants from Amgen Pharmaceuticals.
John A Kanis: Nothing to declare for FRAX and the context of this paper, but numerous ad hoc consultancies for:
Industry: Abiogen, Italy; Amgen, USA, Switzerland, and Belgium; Bayer, Germany; Besins-Iscovesco, France; Biosintetica, Brazil; Boehringer Ingelheim, UK; Celtrix, USA; D3A, France; Gador, Argentina; General Electric, USA; GSK, UK and USA; Hologic, Belgium and USA; Kissei, Japan; Leiras, Finland; Leo Pharma, Denmark; Lilly, USA, Canada, Japan, Australia, and UK; Merck Research Labs, USA; Merlin Ventures, UK; MRL, China; Novartis, Switzerland, and USA; Novo Nordisk, Denmark; Nycomed, Norway; Ono, UK and Japan; Organon, Holland; Parke-Davis, USA; Pfizer, USA; Pharmexa, Denmark; Procter and Gamble, UK and USA; ProStrakan, UK; Roche, Germany, Australia, Switzerland, and USA; Rotta Research, Italy; Sanofi-Aventis, USA; Schering, Germany and Finland; Servier, France and UK; Shire, UK; Solvay, France and Germany; Strathmann, Germany; Tethys, USA; Teijin, Japan; Teva, Israel; UBS, Belgium; Unigene, USA; Warburg-Pincus, UK; Warner-Lambert, USA; Wyeth, USA.
Governmental and NGOs: National Institute for Health and Clinical Excellence (NICE), UK; International Osteoporosis Foundation; INSERM, France; Ministry of Public Health, China; Ministry of Health, Australia; National Osteoporosis Society (UK); WHO.
Others: None.

Sources of support: SRM is a health scholar supported by the Alberta Heritage Foundation for Medical Research. LML is supported by a Canadian Institutes of Health Research (CIHR) New Investigator Award and a Centennial Research Chair at the University of Saskatchewan.

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