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Can Change in FRAX Score Be Used to "Treat to Target"? A Population-Based Cohort Study

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ABSTRACT

It is unknown how responsive the Fracture Risk Assessment (FRAX) tool is to osteoporosis treatment (OTX) or whether it can serve as a target for "goal-directed" treatment. We studied 11,049 untreated women aged ≥50 years undergoing baseline and follow-up DXA examinations in Manitoba, Canada. We identified clinical risk factors, intervening OTX based on medication possession ratios (MPR), and incident fractures. FRAX scores for major osteoporotic and hip fractures were computed for each scan using the most current (updated) FRAX inputs. Over 4 years, median FRAX scores showed an increase of 1.1% for major fractures and 0.3% for hip fractures, including women highly adherent to OTX (0.6% and 0.1% increases). Few (2.2%) highly adherent women had a decrease in major fracture probability exceeding 4%, whereas 9.0% had a decrease in hip fracture probability exceeding 1%. Compared with untreated women, OTX was associated with a higher dose-dependent likelihood of attenuating the expected increase in major fracture risk: adjusted odds ratios (aOR) 2.3 (95% confidence interval [CI] 1.8–2.9) for MPR <0.50; 7.3 (95% CI 5.6–9.6) for MPR 0.50–0.79; and 12.0 (95% CI 9.5–15.2) for MPR ≥0.80. In the 4 years after the second DXA scan, 620 (6%) women had major fractures (152 hip fractures). FRAX scores were strongly predictive of incident major fractures (adjusted hazard ratios [aHR] per SD increase in FRAX 1.8, 95% CI 1.7–1.9) and hip fractures (aHR per SD 4.5, 95% CI 3.7–5.7); however, change in FRAX score was not independently associated with major fracture ($p = 0.8$) or hip fracture ($p = 0.3$). In conclusion, FRAX scores slowly increased over time, and this increase was attenuated but not prevented by treatment. Few women had meaningful reductions in FRAX scores, and change in FRAX score did not independently predict incident fracture, suggesting that FRAX with BMD is not responsive enough to be used as a target for goal-directed treatment. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; GENERAL POPULATION STUDIES; THERAPEUTICS; FRACTURE RISK ASSESSMENT; MENOPAUSE

Introduction

Osteoporosis is a common, chronic, and costly condition; its only clinical consequence is fracture. Based on bone mineral density (BMD) and clinical risk factors, patients deemed at high risk of fracture are selected for treatment.[1–3] Tools such as the World Health Organization Fracture Risk Assessment (FRAX) score are well validated for predicting an individual's 10-year fracture risk and help to identify those most likely to benefit from osteoporosis treatment.[1] Currently available treatments for osteoporosis are very effective, with several agents safely yielding 40% to 60% reductions in the risk of fracture.[2,3] In general, absence of fracture and lack of BMD loss are considered treatment success (ie, "goal achieved"), whereas fracture and loss of BMD are considered treatment failures.[4–6] That said, it has been difficult to demonstrate that change in BMD (whether or not related to treatment) is consistently associated with changes in fracture risk,[7,8] and so BMD alone cannot be considered an adequate surrogate measure for clinically relevant endpoints: quality of life (fracture), function, or survival.

This situation is different from many other chronic conditions—such as hypertension, dyslipidemia, or diabetes—where validated surrogate measures exist.[9,10] That is, systolic blood pressure, LDL cholesterol, or A1c are quantifiable parameters that respond to treatment and for which there are specific goals to guide therapy.[9,10] The goals are evidence based, and it is well documented that changes in these surrogate measures are tightly linked with clinical endpoints.[9–11] Because of this, goals such as systolic blood pressure <140 mm Hg, LDL cholesterol <2.0 mmol/L, or A1c <7% help direct treatment.[11] The use of well-defined treatment targets to assist physicians in disease management is a strategy often called "treat to target" or "T2T." Establishing treatment targets is intended to simplify clinical decision making, improve clinical outcomes, and permit comparative performance measurement, but this all presupposes the existence of a suitably responsive biomarker. Because

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BMD by itself is inadequate in this regard, it has been proposed that change in FRAX score might well serve the purpose for osteoporosis.[4,5] FRAX can already be used to predict fracture risk, but to attain the status of a treatment goal, it would need to be responsive to changes in risk factors and osteoporosis treatments. Ideally, change in FRAX score would also independently predict the risk of incident fractures. We believe these are testable hypotheses.

Therefore, we undertook the present study using a large clinical dual-energy X-ray absorptiometry (DXA) registry linked with other population-based databases to establish a study cohort of previously untreated older women with serial DXA scans. Our objective was to confirm (or refute) the clinical utility of using change in FRAX scores over time as a surrogate measure that could be used to inform goal-directed therapy and thus guide decisions around initiation and duration of osteoporosis treatment. To do this, we described the natural history of serial FRAX scores and then established how responsive FRAX scores are to initiation and adherence to osteoporosis treatment.

Materials and Methods

Setting and subjects

The Province of Manitoba, Canada, provides health services to 1.25 million residents through a single public health-care system. For this population-based cohort study, we identified all women aged 50 years and older who had medical coverage from Manitoba Health from 1998 through 2011 and who had undergone two DXA assessments at least 1 year apart. We then excluded all women who received prescription medications for osteoporosis in the year before the first (baseline) DXA assessment. 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.

Population Health Research Data Repository

This is a comprehensive collection of continuously updated and population-based health services data sets for all residents provided by the provincial government to the Manitoba Centre for Health Policy after anonymization to preserve confidentiality.[8,12,13] Data include sociodemographic characteristics, vital statistics, physician claims (including primary diagnosis and services), hospitalizations (including most responsible diagnosis, procedures, and up to 24 additional diagnoses), and prescription drugs. Physician claims are coded using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM); hospital discharge diagnoses are coded using the ICD-9-CM before 2004 and the International Classification of Diseases, 10th revision, Canadian version (ICD-10-CA) thereafter. Data sets are linked with a de-identified personal health information number that allows construction of longitudinal medical histories and permits linkage to other databases and clinical registries. These data are well validated and have been used extensively in previous research.[8,12,13]

Bone mineral density measurements

Bone density testing with DXA is an insured service available to all Manitoba residents without charge and has been managed as an integrated program since 1997 (the Manitoba Bone Density Program, a population-based clinical registry); criteria and testing rates for this program have been published.[14,15] The program maintains a database of all DXA results, which can be linked with the Population Health Research Data Repository through an anonymous personal identifier. The DXA database has been previously described with completeness and accuracy in excess of 99%.[14,15] DXA scans were performed in accordance with manufacturer recommendations and showed stable long-term performance (coefficient of variation [CV] <0.5%) and satisfactory in vivo precision (short-term CV 1.1% for total hip, 1.9% for femoral neck, and 1.1% for lumbar spine).[14,15]

FRAX scores

Ten-year probability of a major osteoporotic fracture or hip fracture was calculated for each subject using the most currently available input variables (Canadian FRAX tool, FRAX Desktop Multi-Patient Entry, version 3.7). The creation of the Canadian FRAX model has been previously described in detail[14] and has been independently shown to accurately predict observed fracture rates in the Canadian population.[16,17] Hereafter, whenever we refer to "FRAX score," we define it as the most recent FRAX score calculated with femoral neck BMD. FRAX scores with updated inputs were (re-)estimated at the time of each DXA scan for each woman. Prior fracture was included if a major fracture had been recorded since 1987. A diagnosis of rheumatoid arthritis was identified from hospitalizations and/or physician visits within 3 years before the BMD measurement. Chronic obstructive pulmonary disease (COPD) within 3 years was used as a proxy for smoking, and a diagnosis of alcohol or substance abuse within 3 years was used as a proxy for high alcohol intake. Based on data from the Canadian Multicentre Osteoporosis Study, we found that the prevalence of diagnosed COPD in our study was only slightly less than the current smoking prevalence for women aged ≥50 years; diagnosed alcohol/substance abuse and high alcohol intake were similar in both populations.[16,17] We assessed body mass index (BMI, kg/m^2) at the time of BMD measurement calculated by dividing weight (kg) by height squared (m). Glucocorticoid use was identified in the province-wide retail pharmacy database and noted as positive when cumulative use in the year prior to DXA exceeded 3 months. Parental hip fracture information was not available for all data years, and therefore was not used in the FRAX calculation.

Osteoporosis treatments

Using linkages to the province-wide retail pharmacy network, we identified the date, dose, and quantity dispensed of all available prescription osteoporosis treatments (bisphosphonates, calcitonin, systemic estrogen products, raloxifene, and teriparatide).[18] Drug exposures were classified according to medication possession ratios (MPR) that were indexed to pharmacy dispensing refills and covered the entire time interval between the baseline and second DXA scan. The MPRs were categorized as less than 50% (poor adherence) versus MPR 50% to 79% versus MPR of 80% or more (high adherence).[18] No dispensing was considered as never exposed (MPR = 0) and served as the reference group for analyses.

Major osteoporotic and hip fractures

Manitoba Health records were assessed for the presence of nontraumatic hip, clinical vertebral, forearm, and humerus fracture diagnostic codes (collectively designated "major osteoporotic" fractures) using previously validated algorithms.[12–18]

Analysis

First, we undertook a comprehensive set of descriptive analyses by defining change in median FRAX score for major fractures over time and according to quartiles of change. We examined median change in FRAX score stratified according to DXA testing interval (<3 years between tests versus 3 to 5 years versus >5 years between tests) and according to osteoporosis treatment adherence as defined by the MPR during the entire interval (untreated versus MPR <50% versus MPR 50% to 79% versus MPR ≥ 80%). We repeated these analyses using median change in FRAX score for hip fracture. We also examined percent change in BMD at the femoral neck, lumbar spine, and total hip.

Second, we examined risk of major fracture reclassification rates among untreated women and the treated subgroup of highly adherent (MPR ≥80%) women, and determined the proportion of these women who had clinically important reductions in FRAX score. As per the National Osteoporosis Foundation (NOF),[2] 10-year major fracture risk of ≥20% or hip fracture risk ≥3% or more was designated "high risk." We defined a clinically meaningful reduction in predicted fracture risk as a greater than 4% absolute reduction in major fracture risk and a greater than 1% absolute reduction in hip fracture risk because these values correspond to the risk reduction that would be seen at the NOF intervention cut-offs for an increase in femoral neck BMD equal to the 95% least significant change (LSC).[2] Essentially, these predefined clinically important reductions could be considered the most important (albeit minimal) "goal" of osteoporosis treatment.[4,5]

Third, we used multivariable logistic regression analyses to determine the association between osteoporosis treatment and change in FRAX score for major fractures. Similar analyses were then performed for the FRAX hip fracture score. Models compared the women in the lowest quartile of change in median FRAX score with the women in the highest quartile of change (reference group, the quartile of women who had the greatest increase in FRAX score over time). Because the updated input variables for starting osteoporosis treatment between DXA scans and change in *T*-score between DXA scans were collinear, we could not include both variables simultaneously into our models. Because FRAX responsiveness to osteoporosis treatment was the focus of our study, we included treatment (MPR) rather than BMD (*T*-score) in our models. All models were adjusted for the seven available FRAX input variables and either one of MPR or *T*-score; hereafter whenever we refer to "adjusted," this is what we mean. The adjusted odds ratios (aOR) generated by these models can be interpreted as a measure of "responsiveness." In these analyses, aOR >1 indicates that osteoporosis treatment (the exposure of interest) has a greater likelihood of attenuating or abolishing the expected increase in FRAX score than nonexposure, with larger positive values of the aOR associated with greater responsiveness.

Fourth, we used multivariable Cox proportional hazards analyses to determine the independent association between change in FRAX score over time and incident major fractures, overall and then stratified by osteoporosis treatment status. We repeated this analysis for incident hip fractures. Models were adjusted for values of the seven FRAX input variables available at the time of the second DXA. The time from the second DXA scan to the end of follow-up was the at-risk period then analyzed. Subjects were censored at death, disenrollment, or study end on March 30, 2011. Proportional hazards assumptions were examined with visual inspection of log-minus-log survival plots and analysis of rescaled Schoenfeld residuals; no violations of these assumptions were noted. All analyses were conducted using Statistica Version 10 (StatSoft Inc., Tulsa, OK, USA).

Results

There were 11,049 previously untreated women who had at least two DXA scans more than 1 year apart in the final study cohort (median interval between the first and second scans 3.8 years, interquartile range [IQR] 2.9:5.3). A total of 6534 (59%) of the women initiated osteoporosis treatment after their initial DXA scan, whereas 5473 (50%) of the women met one or more of the NOF criteria for treatment (35% osteoporotic *T*-score, 5% prior spine or hip fracture, 13% major fracture score ≥20%, and 33% hip fracture score ≥3%). At the time of the first (versus second) DXA scan, mean age was 64.5 (versus 68.8) years, mean BMI was 26.2 (versus 26.3) kg/m^2, mean femoral neck *T*-score was −1.6 (versus −1.7), and 12% (versus 16%) had experienced previous fractures (Table 1). Median change in BMI was 0.0 kg/m^2 (IQR −0.9:1.2) and median change in femoral neck *T*-score was 0.0 (IQR −0.2:0.2). For the presence of other clinical risk factors (ie, prior fracture, smoking, alcohol use, glucocorticoid use, and rheumatoid arthritis), 81% remained the same between DXA scans, and no single risk factor increased (indicating a new risk factor) or decreased (indicating a resolved risk factor) by more than 5% between DXA scans (Fig. 1). Of the clinical risk factors that did change between the first and second DXA scans, more changes were in the direction of higher rather than lower fracture risk (11% versus 8%).

Change in fracture risk and BMD over time

The median FRAX score for major fractures was 8.2% (IQR 5.8:12.2) at the first DXA scan and 9.6% (IQR 6.9:14.2) at the second; for hip fractures it was 1.1% (IQR 0.4:2.8) at the first and 1.6% (IQR 0.7:3.4) at the second. Between the first and second scans, FRAX scores for the entire study cohort increased despite stable femoral neck BMD. Overall, the FRAX-predicted risk of major fracture increased by median 1.1% (IQR 0.4:2.3) and the risk of hip fracture increased 0.3% (IQR 0.0:0.8), whereas femoral neck BMD showed little change over time (−0.1%, IQR −3.8:3.4; Table 1).

Change in fracture risk and osteoporosis treatment over time

Of the women who initiated prescription osteoporosis treatment, 2621 (40%) were highly adherent (≥MPR 80%). Table 2 presents median change in FRAX score and percent change in BMD according to DXA testing interval and according to categories of osteoporosis treatment adherence. Although osteoporosis treatment did not decrease the median FRAX scores for major fracture or hip fracture below baseline values calculated at the first DXA scan, greater adherence to treatment was associated with smaller increases in risk over time ($p < 0.001$ for linear trend for major fractures and for hip fractures, Table 2). Conversely, FRAX scores increased more for those with longer intervals between the DXA scans compared with shorter intervals, even for highly adherent women. BMD decreased in untreated women, whereas greater treatment adherence was associated with larger gains in BMD at the femoral neck (2.8% to 3.0%), lumbar spine (5.6% to 7.8%), and total hip (2.9% to 3.7%) ($p < 0.001$ for linear trend at all sites, Table 2).

Table 1. Characteristics of the 11,049 Women at the Time of Their First and Second DXA Examinations

	First examination	Second examination
Clinical risk factors		
Age (years)	64.5 ± 8.7	68.8 ± 8.8
BMI (kg/m^2)	26.2 ± 4.9	26.3 ± 4.9
Prior major fracture	1329 (12)	1766 (16)
COPD (smoking proxy)	866 (8)	770 (7)
Prior glucocorticoid use	483 (4)	546 (5)
Rheumatoid arthritis	421 (4)	405 (4)
High alcohol use	159 (1)	129 (1)
Bone mineral density		
Femoral neck *T*-score	−1.6 ± 0.9	−1.7 ± 0.8
Lumbar spine *T*-score	−1.7 ± 1.4	−1.7 ± 1.3
Total hip *T*-score	−1.2 ± 1.1	−1.3 ± 1.0
FRAX scores		
Major fracture probability with BMD	8.2 (5.8:12.2)	9.6 (6.9:14.2)
Hip fracture probability with BMD	1.1 (0.4:2.8)	1.6 (0.7:3.4)
Change in FRAX score between DXA scans		
Major fracture probability with BMD	—	1.1 (0.4:2.3)
Hip fracture probability with BMD	—	0.3 (0.0:0.8)

Mean ± standard deviation or frequency (percentage) or median (interquartile range).

Reclassification of fracture probabilities during followup

In analyses restricted to the 2621 women highly adherent to treatment (MPR ≥ 80%), only 57 (2.2%) had a 4% or greater decrease in major fracture probability, whereas 235 (9.0%) had a 1% or greater decrease in hip fracture probability. Conversely, among the 4515 women not treated for osteoporosis, only 21 (0.5%) had a clinically important decrease in major fracture probability and only 55 (1.2%) had an important decrease in hip fracture probability.

Responsiveness of FRAX to changes in risk factors and treatment

Fig. 2 shows that, when stratified by osteoporosis treatment adherence categories, FRAX major osteoporotic and hip fracture scores change very little over time with median and interquartile ranges that essentially overlap. In multivariable logistic regression analyses of FRAX scores for major fractures, comparing the quartile of subjects that changed least over time (lower risk) with the quartile of subjects whose FRAX score worsened most over time (higher risk), we observed a dose-gradient in the aOR across osteoporosis treatment adherence categories (untreated = 1.0 reference): aOR = 2.3 (95% CI 1.8–2.9) for MPR <50% versus 7.3 (95% CI 5.6–9.6) for MPR 50% to 79% versus 12.0 (95% CI 9.5–15.1) for MPR ≥80% or more with $p < 0.001$ for linear trend. Findings were similar when examining the dose-gradient for adherence categories and FRAX score for hip fracture (untreated = 1.0 reference): aOR = 3.3 (95% CI 2.6–4.3) for MPR <50% versus 9.2 (95% CI 7.0–12.1) for MPR 50% to 79% versus 15.3 (95% CI 12.1–19.5) for MPR ≥80% or more with $p < 0.001$ for linear trend.

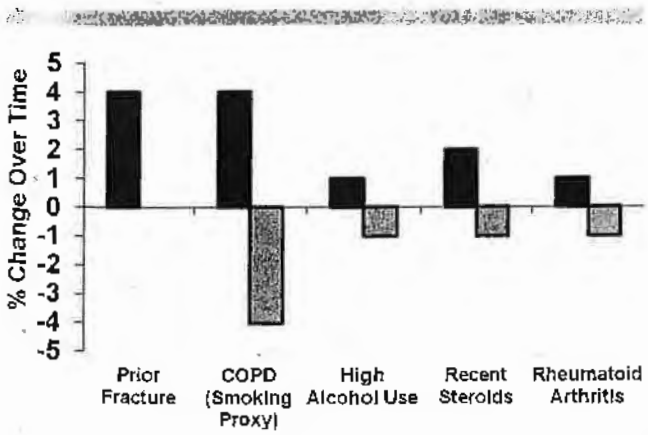

Fig. 1. Percentage increases or decreases in the prevalence of FRAX clinical risk factors between DXA scans.

Change in fracture probability and incident fracture

Over a median of 4.0 years follow-up (IQR 1.9:6.1) after the second DXA scan, 620 (6%) women sustained one or more incident major fractures (152 hip fractures). FRAX score for the risk of major fracture, calculated with updated BMD and other inputs from the second DXA scan, was strongly predictive of subsequent major fractures (adjusted hazard ratio [aHR] per standard deviation [SD] increase in FRAX score = 1.78, 95% CI 1.65–1.92). However, in Cox proportional hazards models that first adjusted for the FRAX score at the time of the second DXA scan, change in FRAX score was not independently associated with incident major fractures: smallest increase quartile versus largest increase (reference) aHR = 1.05 (95% CI 0.81–1.35) with $p = 0.8$ for linear trend across quartiles (Table 3). An even stronger relationship than that observed with major fractures was seen when using FRAX score for predicting the probability of hip fractures (aHR per SD increase in FRAX score = 4.54, 95% CI 3.65–5.65). In multivariable models that first adjusted for the FRAX score at the time of the second DXA scan, change in FRAX score was not independently associated with incident hip fracture: smallest increase quartile versus largest increase (reference) aHR = 1.14 (95% CI 0.69–1.91) with $p = 0.3$ for linear trend across quartiles (Table 3).

Table 2. Change in Major and Hip Fracture Probability and BMD According to DXA Testing Interval and Osteoporosis Treatment

Interval	Treatment	*n*	Major fracture probability with BMD	Hip fracture probability with BMD	Femoral neck BMD	Lumbar spine BMD	Total hip BMD
			Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
1–3 years	None (MPR = 0)	1277	0.7 (0.3:1.3)	0.2 (0:0.5)	−1.3% (−4.2:1.3)	−1.2% (−3.9:1.7)	−1.5% (−4:0.6)
	MPR <0.50	528	0.7 (0.1:1.5)	0.2 (−0.1:0.6)	0.2% (−3.1:3.3)	0.8% (−2.3:5.3)	−0.2% (−2.7:2.5)
	MPR 0.50–0.79	384	0.5 (−0.3:1.2)	0 (−0.2:0.4)	2% (−0.9:5.1)	3.7% (1.3:7.3)	2.3% (0:4.7)
	MPR ≥0.80	845	0.3 (−0.5:0.9)	0 (−0.4:0.3)	2.9% (0.1:5.9)	5.6% (2.4:9.1)	3.3% (1.1:5.4)
3–5 years	None (MPR = 0)	1866	1.2 (0.7:2.1)	0.3 (0.1:0.8)	−2.2% (−5.2:0.7)	−1.1% (−4.2:1.9)	−2.3% (−5:0)
	MPR <0.50	1000	1.2 (0.6:2.2)	0.3 (0.1:0.8)	−0.5% (−3.8:2.6)	0.8% (−3.3:4.9)	−0.9% (−3.8:1.9)
	MPR 0.50–0.79	709	0.8 (0:1.6)	0.1 (−0.1:0.6)	2.2% (−0.8:5.4)	5% (1.6:8.5)	2.5% (−0.3:5)
	MPR ≥0.80	1259	0.6 (−0.2:1.4)	0.1 (−0.2:0.5)	3% (0.3:5.9)	6.6% (3.1:10.4)	3.7% (1.1:6.2)
>5 years	None (MPR = 0)	1372	2.2 (1.4:3.5)	0.6 (0.2:1.2)	−3.5% (−7.3:0)	−1.6% (−5.7:2.2)	−3.9% (−7.5:−0.7)
	MPR <0.50	923	2.4 (1.4:4.4)	0.7 (0.2:1.7)	−2.2% (−5.8:2)	−0.1% (−4.6:5.1)	−2.7% (−6.5:0.9)
	MPR 0.50–0.79	369	1.8 (0.9:3.4)	0.5 (0.1:1.4)	1.6% (−2.9:5.1)	5.2% (0.4:10.9)	1.4% (−2.1:5.2)
	MPR ≥0.80	517	1.5 (0.4:3)	0.4 (0:1.3)	2.8% (−0.4:7.3)	7.8% (3.1:12.6)	2.9% (−0.9:6.9)
Overall		11,049	1.1 (0.4:2.3)	0.3 (0:0.8)	−0.1% (−3.8:3.4)	1.6% (−2.6:6.3)	−0.3% (−3.8:3.1)

BMD = bone mineral density; Interval = time between DXA scans; MPR = medication possession ratio; IQR = interquartile range.

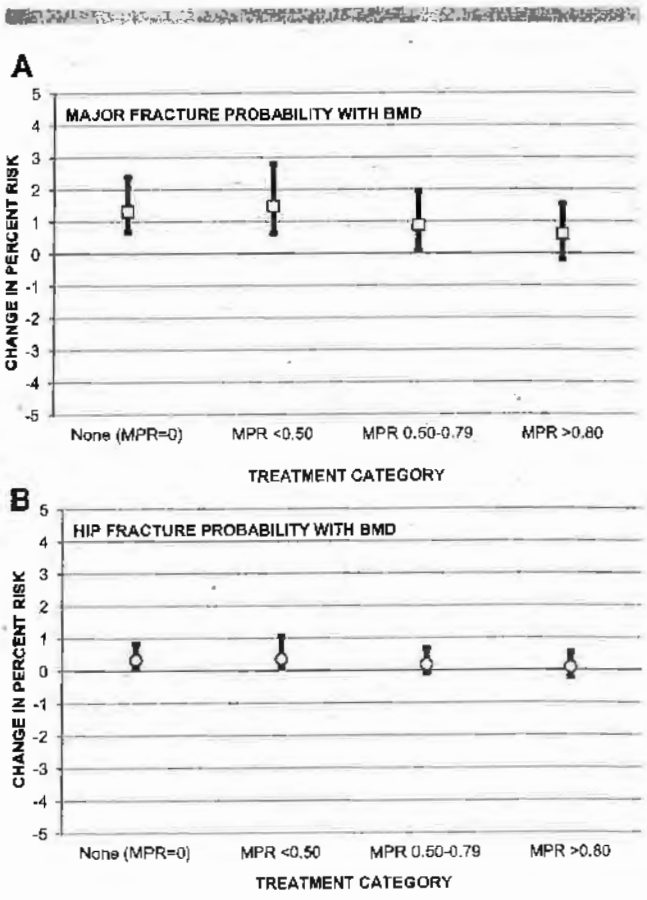

Fig. 2. Change in FRAX score between DXA scans according to osteoporosis treatment. (*A*) Major fractures. (*B*) Hip fractures. Data are median values with interquartile range. MPR = medication possession ratio.

Discussion

In a cohort study of more than 11,000 previously untreated older women who had serial DXA scans, we found that FRAX scores increased over time for both major fractures (1.1% absolute increase) and hip fractures (0.3% absolute increase) despite a high rate of osteoporosis treatment initiation (59% between the DXA scans), whereas femoral neck BMD remained stable. More than 80% of FRAX clinical risk factors were unchanged over time in our study, and of the variables that changed, most (but not all) were in the direction associated with increased fracture risk. Even in the subgroup of women highly adherent to osteoporosis treatment, we noted a negligible clinically important reclassification of fracture risk: 98% of these women had the same or greater risk of major fracture according to FRAX as they did before therapy, and treatment only seemed to attenuate the universal increase in FRAX scores over time. Indeed, we found that, after accounting for the FRAX score at the time of the second DXA scan, change in FRAX score was not independently associated with incident major fractures or hip fractures over the next 4 years.

Perhaps it is unsurprising that FRAX would be poorly responsive to changes in clinical risk factors given that they remained mostly stable over time. Furthermore, BMD itself only provides a modest contribution to FRAX prediction, and it has been previously demonstrated that change in BMD over time may not predict future fracture.[5,8] If this is so, it also helps explain why osteoporosis treatment itself did not affect FRAX scores over the study period, given that the only mechanisms whereby treatment could alter FRAX calculations would be via changes in fracture rates or BMD. A limitation of our study sample is that we did not include newer, more potent osteoporosis treatments that might have much larger effects on BMD and thus might have differentially impacted on BMD and fracture rates and thence FRAX responsiveness.[19]

In aggregate, these findings illustrate that although FRAX scores do tend to slowly increase with age and time, FRAX itself is poorly responsive to change in BMD and osteoporosis treatment

Table 3. Probability of Incident Fractures According to Change in FRAX Scores Between DXA Scans: Multivariable Cox Proportional Hazards Analysis

	Hazard ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
	All women ($N = 11,049$)		Untreated women ($n = 4515$)		Highly adherent treated women ($n = 2621$)	
Probability of incident major fractures according to change in FRAX scores between DXA scans						
1st quartile (smallest change)	1.05 (0.81:1.35)	0.763	1.52 (0.89:2.60)	0.299	0.74 (0.46:1.17)	0.296
2nd quartile	1.00 (0.78:1.29)	0.921	1.13 (0.73:1.75)	0.362	0.70 (0.43:1.12)	0.596
3rd quartile	0.97 (0.76:1.23)	0.684	0.76 (0.49:1.17)	0.055	0.69 (0.42:1.11)	0.556
4th quartile (largest change)	1	referent	1	referent	1	referent
Linear trend across quartiles		0.806		0.298		0.084
Probability of incident hip fractures according to change in FRAX scores between DXA scans						
1st quartile (smallest change)	1.14 (0.69:1.91)	0.205	0.97 (0.31:3.04)	0.890	2.17 (0.79:6.00)	0.093
2nd quartile	0.84 (0.41:1.71)	0.360	1.40 (0.42:4.63)	0.873	0.97 (0.29:3.27)	0.938
3rd quartile	1.17 (0.71:1.93)	0.560	1.68 (0.72:3.92)	0.406	0.70 (0.22:2.25)	0.366
4th quartile (largest change)	1	referent	1	referent	1	referent
Linear trend across quartiles		0.271		0.567		0.140

HRs adjusted for FRAX probabilities estimated from the second DXA examination. "Quartiles" refers to ordinal categories of change in FRAX scores between DXA scans, with largest change in FRAX over time as the reference group for all analyses.

status. Thus, serial FRAX measurements are unlikely to be useful in making decisions about treatment initiation or duration or cessation and it would not serve the "treat-to-target" paradigm well.[5] In essence, change in FRAX scores do not fulfill the standard criteria for being a valid "surrogate measure," ie, change in the measure are strongly and independently associated with clinically relevant endpoints: quality of life (fracture), function, or survival.[10,11] To our knowledge, there are no validated surrogate measures in osteoporosis, although some believe that bone marker turnovers may eventually fill this niche.[4,20,21] This is an area of ongoing and much needed research.

This clinical study has several limitations that need to be considered. First, updated input variables for FRAX and BMD from the second DXA scan were used for predicting incident fracture, and thus variables were not updated in a time-varying fashion (eg, new starts or stops of osteoporosis medications after the second scan). In fact, that we even used updated FRAX input variables is a strength compared with prior studies. Furthermore, given how little change there was observed between the first and second DXA scan, this is unlikely to be an important limitation. Second, although FRAX predicts 10-year risk of fractures, our follow-up time was shorter. It is unlikely that a longer follow-up would show greater responsiveness of FRAX because age would continue to be a major determinant of change. In fact, among highly adherent women, FRAX scores increased more (not less) for those with more than 5 years between the DXA scans compared with shorter intervals. Third, there are important risk factors that we did not capture, such as propensity to fall or frailty or diabetes, and these may have affected our findings. Of course, these risk factors are also not directly captured within FRAX itself.[1,12] We may have also slightly underestimated FRAX scores because of missing parental hip fracture information and reliance on proxy variables for smoking and high alcohol intake. Fourth, the DXA scans and interscan intervals were all based on routine clinical practice and not standardized as part of a study protocol. Along these lines, there might be concern about selection bias (in terms of how physicians choose patients for DXA) and the fact that we only studied women. Last, we did not have access to any laboratory data and in particular did not have any markers of bone turnover.

In conclusion, we found that although FRAX scores were strongly predictive of incident major fractures and of hip fractures, they also tended to increase over time and were not particularly responsive to changes in risk factors, BMD, or osteoporosis treatments. Thus, changes in FRAX score are a poor surrogate measure for treatment response and cannot be recommended as a target for goal-directed therapy. Until more responsive measures are available and validated, our findings support the current osteoporosis management paradigm:[2,3,6] Treat those at high risk of fracture based on BMD and clinical risk factors; consider as treatment failures those who lose bone density or fracture on treatment; and continue successful treatment for the safest duration of time known for the therapy being used.

Disclosures

All authors state that they have no conflicts of interest.

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