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A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX

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ABSTRACT

Trabecular bone score (TBS) is a gray-level textural index of bone microarchitecture derived from lumbar spine dual-energy X-ray absorptiometry (DXA) images. TBS is a bone mineral density (BMD)-independent predictor of fracture risk. The objective of this meta-analysis was to determine whether TBS predicted fracture risk independently of FRAX probability and to examine their combined performance by adjusting the FRAX probability for TBS. We utilized individual-level data from 17,809 men and women in 14 prospective population-based cohorts. Baseline evaluation included TBS and the FRAX risk variables, and outcomes during follow-up (mean 6.7 years) comprised major osteoporotic fractures. The association between TBS, FRAX probabilities, and the risk of fracture was examined using an extension of the Poisson regression model in each cohort and for each sex and expressed as the gradient of risk (GR; hazard ratio per 1 SD change in risk variable in direction of increased risk). FRAX probabilities were adjusted for TBS using an adjustment factor derived from an independent cohort (the Manitoba Bone Density Cohort). Overall, the GR of TBS for major osteoporotic fracture was 1.44 (95% confidence interval [CI] 1.35–1.53) when adjusted for age and time since baseline and was similar in men and women ($p > 0.10$). When additionally adjusted for FRAX 10-year probability of major osteoporotic fracture, TBS remained a significant, independent predictor for fracture (GR = 1.32, 95% CI 1.24–1.41). The adjustment of FRAX probability for TBS resulted in a small increase in the GR (1.76, 95% CI 1.65–1.87 versus 1.70, 95% CI 1.60–1.81). A smaller change in GR for hip fracture was observed (FRAX hip fracture probability GR 2.25 vs. 2.22). TBS is a significant predictor of fracture risk independently of FRAX. The

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findings support the use of TBS as a potential adjustment for FRAX probability, though the impact of the adjustment remains to be determined in the context of clinical assessment guidelines. © 2015 American Society for Bone and Mineral Research.

KEY WORDS: TRABECULAR BONE STRUCTURE; TBS; FRACTURE; RISK; FRAX; META-ANALYSIS

Introduction

Osteoporosis is conceptually defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] The operational definition of osteoporosis is based on dual-energy X-ray absorptiometry (DXA), although clinically the presence of a fragility fracture with or without DXA corroboration is commonly used as a diagnostic criterion and an intervention threshold.[2] Although bone mineral density (BMD) measured by DXA is a major determinant of bone strength and fracture risk,[3] most individuals with a fragility fracture will have BMD values in the osteopenic or even normal range.[2,4,5] Thus, factors other than BMD influence bone strength and fracture risk, including microarchitectural deterioration of bone tissue as implied from the conceptual definition of osteoporosis. Additional skeletal and extraskeletal factors such as bone geometry, microdamage, mineralization, bone turnover, age, family history of fracture, prior fracture, and fall risk contribute to the overall assessment of fracture risk.[6–10]

Several of these additional factors are captured by FRAX, which estimates the 10-year probability of hip and major osteoporotic fracture based on the individual's risk factor profile.[11] FRAX does not, however, capture all skeletal determinants of bone strength that improve upon or are independent of BMD or prior fracture.[12] Several such determinants are the subject of clinical research with one of the most recent and extensively studied being the trabecular bone score (TBS).[13–19]

TBS is a gray-level textural measurement derived from lumbar spine DXA images. It appears to be an index of bone microarchitecture that provides skeletal information additional to the standard BMD measurement.[19] Several cross-sectional studies have shown that TBS is associated with osteoporotic fractures independently of lumbar spine BMD measurements in postmenopausal women.[20–24] Prospective studies have also shown that TBS predicts fracture in postmenopausal women and older men.[25–30]

Preliminary data have shown an incremental improvement in fracture prediction when lumbar spine TBS is used in combination with FRAX variables.[30,31] The study comprised more than 33,000 women aged 40 to 100 years from Manitoba (mean age 63 years) with baseline DXA measurements of lumbar spine TBS and femoral neck BMD. The association between TBS, the variables used in FRAX, and the risk of major osteoporotic fracture or death was examined using an extension of the Poisson regression model. For each standard deviation reduction in TBS, there was a 36% increase in major osteoporotic fracture risk (hazard ratio [HR] = 1.36, 95% confidence interval [CI] 1.30–1.42, $p < 0.001$) and a 32% increase in death (HR = 1.32, 95% CI 1.26–1.39, $p < 0.001$). When adjusted for significant clinical risk factors and femoral neck BMD, lumbar spine TBS was still a significant predictor of major osteoporotic fracture (HR = 1.18, 95% CI 1.12–1.23) and death (HR = 1.20, 95% CI 1.14–1.26). Models for estimating major osteoporotic fracture probability, accounting for competing mortality, showed that low TBS (10th percentile) increased risk by 1.5- to 1.6-fold compared with high TBS (90th percentile) across a broad range of ages and femoral neck *T*-scores.[31] Data from this cohort have been used to derive potential correction factors for the adjustment of FRAX-derived probabilities to take account of TBS.[32]

The primary aim of the present meta-analytical study in independent cohorts was to validate the FRAX-independent contribution of TBS to fracture risk prediction and, using the FRAX adjustments derived from the Manitoba study described elsewhere,[32] to examine the impact of applying the adjustment factor for TBS to FRAX probabilities.

Materials and Methods

Cohorts studied

We used baseline and follow-up data from 14 prospective population-based cohorts comprising the Canadian Multicenter Osteoporosis Study (CaMos), the Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF), the Geelong Osteoporosis Study (GOS), the Os des Femmes de Lyon (OFELY) cohort, the Osteoporosis and Ultrasound Study (OPUS), the Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) study, the Japanese Population-based Osteoporosis Study (JPOS), the Structure of Aging Men's Bones (STRAMBO) cohort, MrOS Hong Kong cohort, MsOS Hong Kong cohort, MrOs Sweden cohort, the Rotterdam study (RS-I and RS-II) and the Salt Osteoporosis Study (SOS). Details of each of the cohorts are published elsewhere and summarized briefly below and in Table 1.

The Canadian Multicenter Osteoporosis Study (CaMos) is an ongoing population-based, prospective age-stratified cohort of men and women aged 25 years and older. Subjects residing within a 50-km radius of one of nine designated clinical centers were contacted at random by phone. Data from seven recruitment centers were available for the present study. BMD for the lumbar spine and proximal femur was measured at year 10 using cross-calibrated Hologic (QDR 4500; Hologic, Inc., Waltham, MA, USA) and GE Lunar (Prodigy; Madison, WI, USA) devices.[33]

The Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) study is an ancillary study of a larger prospective cohort study. BMD measurement was undertaken using a Hologic QDR 4500 device.[34]

The Geelong Osteoporosis Study (GOS) is an ongoing population-based, prospective age-stratified cohort of men and women aged 20 years and older. Subjects were randomly selected from electoral rolls of the Barwon Statistical Division that includes the Geelong region in southeastern Australia. The GOS was launched in 1993, but only the BMD data for men have been included in this analysis because their BMD was measured with a DXA suitable for TBS (GE Lunar Prodigy Pro) with sufficient follow-up period for identifying fractures.[35]

The Japanese Population-based Osteoporosis Study (JPOS) is a multicenter population-based study launched in 1996 to produce a BMD reference database using DXA (Hologic QDR 4500 device) to evaluate bone turnover markers in the Japanese women and to determine risk factors related to osteoporotic fractures.[36]

Table 1. Characteristics of the Cohorts Included in the Study and the Number of Incident Fractures Observed Within Each

Cohort	*n*	Women (%)	Follow-up (years) mean (max)	Age (years) mean (range)	BMD FN *T*-score mean (SD)	TBS mean (SD)	Incident fractures (*n*)	
							Hip	MOP
CaMos	2863	70	4.7 (6.9)	69 (40–90)	−1.89 (1.07)	1.28 (0.11)	43	157
FORMEN	1523	0	4.2 (6.1)	73 (65–90)	−0.98 (0.90)	1.27 (0.08)	2	20
GOS	597	0	5.0 (7.2)	69 (40–90)	0.52 (0.88)	1.29 (0.11)	8	30
JPOS	977	100	15.0 (16.7)	63 (50–80)	−1.62 (0.79)	1.31 (0.09)	27	114
MsOs Hong Kong	1953	100	8.8 (11.3)	73 (65–90)	−2.31 (0.79)	1.26 (0.08)	67	225
MrOS Hong Kong	1924	0	9.9 (12.2)	72 (65–90)	−1.44 (0.88)	1.28 (0.08)	61	132
MrOs Sweden	1781	0	5.3 (7.8)	77 (70–89)	−0.94 (0.91)	1.26 (0.11)	39	108
OFELY	496	100	11.5 (13.4)	67 (50–88)	−1.38 (0.77)	1.28 (0.10)	15	76
OPUS	937	100	5.9 (8.2)	66 (55–80)	−1.21 (0.91)	1.29 (0.10)	4	57
SOS	2364	100	1.6 (3.1)	74 (62–90)	0.19 (1.00)	1.24 (0.09)	17	65
Rotterdam RS-I	914	100	3.5 (4.7)	74 (65–90)	−1.59 (0.78)	1.25 (0.10)	12	39
Rotterdam RS-II	240	100	2.2 (4.5)	68 (59–88)	−0.15 (0.42)	1.27 (0.10)	0	4
SEMOF	524	100	2.8 (3.7)	76 (70–82)	−1.58 (0.84)	1.23 (0.11)	3	41
STRAMBO	707	0	5.4 (7.0)	72 (60–88)	−0.73 (0.94)	1.28 (0.10)	0	41
Total	17809	59	6.1 (16.7)	72 (40–90)	−1.20 (1.21)	1.27 (0.10)	298	1109

BMD = bone mineral density; FN = femoral neck; TBS = trabecular bone score; MOP = major osteoporotic fracture; CaMos = Canadian Multicenter Osteoporosis Study; FORMEN = Fujiwara-kyo Osteoporosis Risk in Men; GOS = Geelong Osteoporosis Study; JPOS = Japanese Population-based Osteoporosis Study; OFELY = the Os des Femmes de Lyon; OPUS = Osteoporosis and Ultrasound Study; SOS = Salt Osteoporosis Study; SEMOF = the Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk; STRAMBO = Structure of Aging Men's Bones.

MrOS Hong Kong included Chinese men of Asian ethnicity aged 65 years and older who were enrolled between 2001 and 2003. This cohort was an age-stratified cohort giving 33% of subjects in each of the following age groups: 65 to 69, 70 to 74, and ≥75 years. Subjects were recruited in housing estates and community centers for the elderly. Subjects had BMD evaluation using Hologic QDR 4500 devices and were followed up for incidence of fractures for an average of 10 years.[37,38]

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The MrOS Sweden cohort is a multicenter prospective cohort of mainly white men aged 69 to 81 years. Subjects were enrolled in three sites (Malmo, Goteborg, and Uppsala) by identifying men using national population registers. Participant follow-up was 5.3 years on average after the baseline examination. Both Hologic QDR 4500 and GE Lunar Prodigy devices were used to measure BMD.[40]

The Os des Femmes de Lyon (OFELY) cohort is an age-stratified cohort composed of 1039 women (aged 31 to 89 years) randomly recruited from the affiliates of a large health insurance company from the Rhone district (Mutuelle Generale de l'Education Nationale, Lyon, France). Among them, a subset of postmenopausal white women who had BMD evaluation using Hologic QDR4500 devices between 2000 and 2001 was selected for the study because data from earlier visits were measured with a DXA machine not compatible with TBS analysis (Hologic QDR2000).[41]

The Osteoporosis and Ultrasound Study (OPUS) is a multicenter age-stratified population-based female cohort involving 5 centers from different European countries (Sheffield and Aberdeen in the UK; Berlin and Kiel in Germany; and Paris in France). Of these, data from Paris, Kiel, and Paris were used because BMD evaluation was made on a DXA device compatible with the TBS analysis (Hologic QDR 4500).[42]

The Rotterdam Study is a single-center population-based follow-up study conducted in the suburb of Ommoord in Rotterdam, where all inhabitants aged 55 years or older were invited. The baseline study comprised a home interview followed by two visits at the research center for clinical examinations. The initial cohort (RS-I) recruited men and women in 1990 with follow-up visits in 1994–1995, 1997–1999, 2002–2004, and 2009–2011. In 2000–2001, a second cohort was established (RS-II) with participants aged 55 years having follow-up examinations in 2004–2005 and 2011–2012. DXA scans (GE Lunar Prodigy) and BMD of the lumbar spine for the present analysis were in RS-I during the third follow-up (mean age 74 years) and in RS-II during the first follow-up (mean age 68 years). Incident clinical vertebral fractures occurring during follow-up (mean 3.03 SD 0.11 years) after DXA were extracted from computerized records of the general practitioners and hospital registries for both cohorts.[43,44]

In the Amsterdam Salt Osteoporosis Study (SOS), all women aged 65 to 90 years in 225 GP practices in the northern part of the Netherlands were invited to participate. For this meta-analysis, 1.5 to 2 years' follow-up data of women from the first 165 practices included between February 2010 and June 2012 were used. Women with at least one risk factor for fractures were randomized into a screening group and a control group. In the screening group, bone densitometry with TBS analyses and vertebral fracture assessment were performed with Hologic Discovery SL or a Hologic Discovery A at five different locations.[45]

The Swiss Evaluation of the Methods of Measurement of Osteoporotic Fracture Risk (SEMOF) study is a prospective study involving 10 centers in Switzerland involving women aged 70 years and older studied prospectively for a mean time of 2.9 years. In a subset, BMD evaluation was undertaken on a Hologic QDR 4500.[46]

The Structure of the Aging Men's Bones (STRAMBO) cohort is a single-center prospective cohort study evaluating skeletal fragility and its determinants in men. This cohort is the result of a collaboration between INSERM (National Institute of Health and Medical Research) and MTRL (MuTuelle de la Région Lyonnaise). Participants were recruited in 2006–2008 in Lyon.[47]

Fracture outcomes

In each cohort, information was obtained on the time of incident fractures, the site of fracture, and the time of death. Fracture outcomes for this study comprised major osteoporotic fractures (clinical spine, distal forearm, proximal humerus, and hip fracture).

TBS calculations

TBS measurements were performed in the Bone Disease Center at the Lausanne University Hospital (CHUV), Lausanne, Switzerland (TBS iNsight Software version 2.1, Medimaps, Merignac, France) using anonymized spine DXA files from the cohorts to ensure blinding of the assessment to all clinical parameters and outcomes. Within each cohort, the analysis was confined to those with both spine and hip BMD scans available, as well as most of the FRAX clinical risk factors. Patients with BMI outside the working range for TBS (15 to 37 kg/m^2) were also excluded, as well as outliers identified by Box and Whisker plots (beyond $\pm$ 1.5 interquartile range). A recent review reported TBS precision, as the coefficient of variation, to range from 1.12% to 2.1%.[19]

FRAX probabilities

FRAX calculations of major osteoporotic and hip fracture probabilities were undertaken using individual-level data in each cohort using country-specific models (FRAX v3.8) (www.shef.ac.uk/FRAX).[48] The FRAX models used comprised Australia (597 participants), Canada (2863 participants), Switzerland (524 participants), France (1477 participants), Germany (318 participants), Hong Kong (3877 participants), Japan (2509 participants), Sweden (1781 participants), The Netherlands (3518 participants), and the UK (345 participants). Probability of fracture was calculated from sex, age, body mass index (BMI), and BMD dichotomized risk variables that included a prior fragility fracture, including vertebral fractures where documented; parental history of hip fracture; current tobacco smoking; ever long-term use of oral glucocorticoids; rheumatoid arthritis; other causes of secondary osteoporosis; and daily alcohol consumption of 3 or more units daily.

When there were missing values for a dichotomized risk variable, the value was set to no when calculating the 10-year probability.

Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kilograms divided by height squared in meters. BMD at the femoral neck was assessed as detailed above, standardized, and converted[7] to a *T*-score using the NHANES young women as reference.[49]

Relationship between clinical risk factors, TBS, and fracture risk

FRAX provides an estimate of fracture probability that is based on the hazard of fracture and the competing hazard of death. Each FRAX model comprises segments that compute (a) the risk of hip fracture and the risk of death and (b) the risk of other major fractures (clinical vertebral, humerus, or forearm fracture) and the risk of death. Low values of TBS are also associated with increased risks of both fracture and mortality.[31] To explore the independence of the risk factors contained within FRAX, including BMD, and the effect of TBS, alone or with the clinical risk factors, on fracture risk, we deconstructed the FRAX-like model derived from an analysis of women in the Manitoba cohort to provide fracture hazards without any competing mortality hazard.[11,32] A fracture risk score was computed using the coefficients for clinical risk factors from the Manitoba cohort, and the fracture hazards were additionally adjusted for the accompanying TBS result using the coefficient derived from the same study.[32] For women in each validation cohort, the computed risk score was expressed as a sex-specific *Z*-score. The gradient of hip fracture and other osteoporotic fracture risk was examined for the use of TBS alone, FRAX, and the combination to provide a TBS-adjusted risk score.

Combination of TBS and FRAX fracture probability

The clinical utility of TBS requires an examination of whether TBS contributes to the prediction of hip and major fracture outcomes independently of FRAX outputs. To examine the potential impact of adjusting FRAX probabilities for the accompanying TBS result, the FRAX hip and major osteoporotic fracture probabilities were modified using the adjustment factor derived from the Manitoba study[32] to provide a TBS-adjusted 10-year probability. The gradient of risk for the latter was compared with that of TBS and FRAX probabilities alone and adjusted for each other. Comparisons were made in men and women separately and in both sexes combined to see if the same adjustment could be applied across both sexes.

Statistical methods

The association between TBS, FRAX probabilities, and the risk of fracture was examined using an extension of the Poisson regression model[50] in each cohort and for each sex. The observation period of each participant was divided in intervals of 1 month. The first major osteoporotic fracture or hip fracture per person was counted for each relevant outcome. Covariates included current age and time since start of follow-up. The β-coefficients from each cohort were weighted according to the variance and then merged to determine the weighted mean of the coefficient and its standard deviation (SD). The associations between TBS, FRAX, or the combination and risk of fracture were described as the gradient of risk (GR; hazard ratio [HR] for fracture per 1 SD change) in risk score together with 95% confidence intervals (CI). At the insistence of the referees and editor, the contribution of TBS to the clinical variables was also reported using the area under the curve (AUC), although there are reservations about this approach (see Discussion). TBS thresholds were also evaluated based on a tertile approach (low-, medium-, and high-risk groups).

The extended Poisson model is similar to Cox regression models. The output and input are the same. The benefit of using Poisson regression model instead of Cox regression model is that Poisson regression model can use the time since follow-up as a continuous variable in the model. Therefore, the effect of a predictive variable can be different for different times since baseline, and interactions between time since baseline and the baseline variables can be investigated. The Poisson distribution is relevant when the observation time, time between baseline, and endpoint/end of follow-up is divided into small pieces (eg, here 1 month). In this short interval, the distribution of the endpoint is

Poisson distributed and the probability of more than one endpoint in this small interval is so extremely low it is negligible.

Inconsistencies between cohorts were quantified and tested by means of the I^2 statistic.[51] No important inconsistency was found for TBS and its relation to major osteoporotic fracture outcome ($I^2 = 31\%$, 95% CI 0–62) or the hip fracture outcome ($I^2 = 5\%$, 95% CI 0–40). Low heterogeneity was also found for FRAX in relation to the major osteoporotic fracture outcome ($I^2 = 29\%$, 95% CI 0–61) and the hip fracture outcome ($I^2 = 0\%$, 95% CI 0–90). For this reason, a fixed-effect model was used.

Results

The 14 population-based cohorts from North America, Asia, Australia, and Europe contributed 17,809 persons to the present meta-analysis; 59% were women with only one cohort (CaMos) contributing both men and women to the analysis (Table 1).

At baseline, the mean age was 72 years with the mean age within cohorts ranging from 66 to 77 years. The mean BMD femoral neck *T*-score was –1.20 SD with the mean *T*-score within cohorts ranging from +0.52 to –2.83. The mean TBS in the cohorts ranged from 1.23 to 1.31 with a mean in the whole study population of 1.27. In the whole study population, TBS was negatively but weakly correlated with age ($r = -0.28$, 95% CI –0.26 to –0.29), and BMI ($r = -0.16$, 95% CI –0.15 to –0.17) but positively correlated with spine and femoral neck BMD ($r = 0.27$ and $r = 0.18$, respectively). TBS was weakly but negatively correlated with FRAX probabilities calculated with and without femoral neck BMD, with correlation coefficients ranging from –0.18 for FRAX hip probability without BMD to –0.24 for FRAX major fracture probability with BMD.

Using the tertile analysis, the two thresholds corresponded to TBS values of 1.23 and 1.31 with no differences between sexes. In the tertiles deemed to be high risk (ie, a TBS below 1.23) or intermediate risk (TBS 1.23 to 1.31), the GRs for major osteoporotic fracture were 2.12 (95% CI 1.53–2.94) and 1.67 (95% CI 1.35–2.10), respectively, compared with the lowest-risk tertile (TBS >1.31).

The average follow-up length was 6.1 years with a maximum of 16.7 years (Table 1). During follow-up, 298 persons experienced one or more hip fractures and 1109 persons sustained one or more major osteoporotic fractures (hip, spine, humerus, or forearm).

Relationship between clinical risk factors, TBS, and fracture risk

The GRs for the fracture risk score are shown in Table 2 for women aged 50 to 90 years. Results are shown for TBS alone, clinical risk factors contributing to FRAX, including BMD, and for the combination.

For hip fracture and for major osteoporotic fracture, lower TBS was associated with an increase in the risk of fracture at all ages. There was a small but not significant trend for the GR to decrease with age. For the combined clinical risk variables (ie, including BMD), gradients of risk were high for hip fracture outcomes and decreased progressively with age but remained significantly increased over all ages. At all ages, the GR for hip fracture of the FRAX variables exceeded the GR for TBS. In the case of other major osteoporotic fractures (clinical spine, distal forearm, or proximal humerus fracture), both TBS and clinical risk variables were significantly associated with fracture with no significant difference between the two risk variables.

The combination of TBS with the clinical risk variables consistently resulted in higher GRs (Table 2). For example, at the age of 70 years, the GR of TBS for hip fracture was 1.41 (95% CI 1.12–1.77). When using the clinical risk variables in the risk score, the GR for hip fracture was 2.41 (95% CI 1.54–3.77). When using both clinical risk factors and TBS in a risk score, the GR was 4.19 (95% CI 2.29–7.69). The interaction between age and risk scores were not statistically significant ($p > 0.30$ for other major osteoporotic fractures with and without TBS, $p > 0.18$ for hip fracture with and without TBS).

When expressed using the AUC, the combination of clinical risk factors and BMD had AUCs of 0.74 (95% CI 0.71–0.76) and 0.64 (95% CI 0.62–0.66) for the outcomes of hip fracture and

Table 2. Gradients of Fracture Risk per SD Change in Fracture Risk Score (With 95% Confidence Intervals) in Men and Women With the Use of TBS Alone, Clinical Variables Alone, and the Combination[a]

	Risk indicator		
Age (years)	TBS only	Clinical risk factors[b] + BMD	Clinical risk factors[b] + BMD + TBS
Hip fracture			
50	1.51 (0.89–2.55)	3.06 (1.58–5.94)	4.71 (2.14–10.40)
60	1.46 (1.01–2.11)	2.72 (1.59–4.64)	4.45 (2.27–8.73)
70	1.41 (1.12–1.77)	2.41 (1.54–3.77)	4.19 (2.29–7.69)
80	1.36 (1.18–1.57)	2.14 (1.39–3.28)	3.95 (2.16–7.24)
90	1.31 (1.06–1.62)	1.89 (1.17–3.08)	3.73 (1.91–7.28)
Overall	1.44 (1.28–1.62)	2.31 (2.07–2.57)	3.98 (2.90–5.45)
Other major osteoporotic fracture			
50	1.54 (1.18–2.00)	1.46 (1.09–1.96)	1.53 (1.14–2.06)
60	1.51 (1.26–1.79)	1.45 (1.15–1.83)	1.52 (1.20–1.91)
70	1.47 (1.32–1.64)	1.44 (1.18–1.75)	1.50 (1.23–1.83)
80	1.44 (1.29–1.61)	1.42 (1.16–1.75)	1.49 (1.22–1.83)
90	1.41 (1.18–1.68)	1.41 (1.10–1.81)	1.48 (1.15–1.89)
Overall	1.42 (1.33–1.53)	1.42 (1.33–1.52)	1.48 (1.38–1.58)

TBS = trabecular bone score; BMD = bone mineral density.

[a]The gradients are adjusted for age and time since baseline. Coefficients used to derive the fracture risk score for the clinical risk variables and TBS were those derived from a previous study in Manitoba.[32]

[b]Clinical risk factors included in FRAX.

Table 3. Gradient of Risk (Hazard Ratio per 1 SD) for the Association Between the Outcome of Major Osteoporotic Fracture and TBS or FRAX Probability Adjusted for Time Since Baseline and Age and Additionally Adjusted for Each Other, and FRAX Probability Incorporating TBS Adjustment Factor

	Men + women	Men	Women
	GR (95% CI)	GR (95% CI)	GR (95% CI)
TBS adjusted for			
Time since baseline and age	1.44 (1.35–1.53)	1.50 (1.36–1.66)	1.40 (1.30–1.52)
+FRAX probability[a]	1.32 (1.24–1.41)	1.35 (1.21–1.49)	1.31 (1.21–1.42)
FRAX probability[a] adjusted for			
Time since baseline and age	1.70 (1.60–1.81)	1.80 (1.64–1.98)	1.63 (1.50–1.77)
+TBS	1.60 (1.50–1.71)	1.69 (1.54–1.87)	1.54 (1.41–1.68)
TBS-adjusted 10-year probability[b] adjusted for			
Time since baseline and age	1.76 (1.65–1.87)	1.86 (1.70–2.04)	1.68 (1.55–1.82)

GR = gradient of risk; TBS = trabecular bone score; CI = confidence interval.
[a]Ten-year probability of major osteoporotic fracture calculated using BMD with FRAX.
[b]Ten-year probability adjusted using adjustment factor for TBS derived from McCloskey and colleagues.[32]

other major osteoporotic fractures, respectively. The addition of TBS to this combination resulted in a higher AUC of 0.79 (95% CI 0.77–0.82) for hip fracture and a small increase in AUC for other fractures (0.65, 95% CI 0.63–0.66).

Combination of TBS and FRAX fracture probability

Overall, the GR, expressed as the HR per 1 SD decrease of TBS for major osteoporotic fracture, was 1.44 (95% CI 1.35–1.53) when adjusted for age and time since baseline (Table 3). The GRs were similar in men and women with no significant difference between the sexes ($p > 0.10$). When additionally adjusted for FRAX 10-year probability of major osteoporotic fracture, the GR for TBS decreased somewhat to 1.32 (95% CI 1.24–1.41), but it remained a significant, independent predictor for fracture probability. The inclusion of TBS in the predictive model resulted in a small reduction in the GR for the FRAX probability from 1.70 (95% CI 1.60–1.81) to 1.60 (95% CI 1.50–1.71), whereas the adjustment of probability for TBS resulted in a small increase in the GR (1.76, 95% CI 1.65–1.87).

For incident hip fracture alone, the GR for TBS alone (GR 1.44, 95% CI 1.28–1.62) (Table 4) was similar to that for major osteoporotic fracture (Table 3). Further adjustment for the FRAX 10-year probability of hip fracture similarly reduced the GR for TBS, but it remained a significant predictor of hip fracture (1.28, 95% CI 1.13–1.45). The adjustment of FRAX model for TBS resulted in a small reduction in the GR for the FRAX probability of hip fracture from 2.22 (95% CI 2.00–2.47) to 2.13 (95% CI 1.91–2.38) and the use of TBS-adjusted probability resulted in a small increase in the GR. As for major osteoporotic fracture, the GRs of TBS and FRAX probabilities tended to be slightly higher for men than for women, but these differences were not statistically significant ($p > 0.20$) (Table 4).

For both hip fracture and major osteoporotic fracture, incorporation of the TBS-adjustment factor resulted in an improvement in the GR. For example, the GR for FRAX probability of major osteoporotic fracture (adjusted for age and time since baseline) in men and women was 1.70 (95% CI 1.60–1.81) and this increased to 1.76 (95% CI 1.65–1.87) when adjusted for TBS (Table 3). The impact for hip fracture was similar (GR = 2.22 and 2.25 without and with the TBS correction, respectively) (see Table 4).

The mean FRAX 10-year probability of a major osteoporotic fracture was 9.8%, ranging from 4.1% to 24.0% across the cohorts. When the adjustment factor for TBS was applied, the mean 10-year probability increased slightly to 10.3% and varied from 4.6% to 23.9% across the cohorts. The mean FRAX 10-year probability of hip fracture was 3.5% with a small increase to 3.7% when adding TBS.

Table 4. Gradient of Risk (Hazard Ratio per 1 SD) for the Association Between the Outcome of Hip Fracture and TBS or FRAX Probability Adjusted for Time Since Baseline and Age and Additionally Adjusted for Each Other, and FRAX Probability Incorporating TBS Adjustment Factor

	Men + women	Men	Women
	GR (95% CI)	GR (95% CI)	GR (95% CI)
TBS adjusted for			
Time since baseline and age	1.44 (1.28–1.62)	1.47 (1.23–1.75)	1.42 (1.21–1.67)
+FRAX probability[a]	1.28 (1.13–1.45)	1.27 (1.06–1.53)	1.29 (1.09–1.52)
FRAX probability[a] adjusted for			
Time since baseline and age	2.22 (2.00–2.47)	2.34 (2.02–2.72)	2.11 (1.81–2.45)
+TBS	2.13 (1.91–2.38)	2.28 (1.96–2.66)	1.99 (1.70–2.32)
TBS-adjusted10-year probability[b]			
Time since baseline and age	2.25 (2.03–2.51)	2.37 (2.04–2.75)	2.14 (1.84–2.49)

GR = gradient of risk; TBS = trabecular bone score; CI = confidence interval.
[a]Ten-year probability of hip fracture calculated using BMD with FRAX.
[b]Ten-year hip fracture probability adjusted using adjustment factor for TBS derived from McCloskey and colleagues.[32]

Discussion

A number of studies have consistently shown TBS to be associated with fracture risk in both cross-sectional and prospective designs.[19,20,24–27,30,31,52–55] The meta-analysis reported here is the largest study to date that has investigated the role of TBS in multinational cohorts. In both men and women, TBS was a consistent and significant predictor of fracture risk. Thus, the results of the present study have a key role in establishing the validity of TBS as a widely applicable predictive measure. The findings of the study support the use of TBS, not only as a standalone assessment of fracture risk but also, more importantly, as an independent contributor to a more global risk assessment that could permit its use alongside established risk assessment tools such as FRAX. This was reflected in the higher GRs and AUCs when TBS was combined with the FRAX clinical risk factors and BMD, particularly for hip fracture outcomes. The use of AUCs can be problematic; although it is widely accepted as a means of characterizing discriminatory variables, it can be influenced by factors such as the distribution of risk factors within different study populations and can change depending on the timeframe, a feature that frequently varies across studies. Lack of appreciation of these points can lead to incorrect comparison of predictive tools across populations.[56]

The analyses of each cohort showed that TBS was consistently an independent contributor to the assessment of fracture risk and that the relationship with other risk factors was robust across sex, diverse races, fracture incidences, and geographical regions. Using the fracture risk score coefficients derived from the Manitoba cohort,[32] the combination of TBS with the clinical risk factors (including BMD) showed enhanced gradients of risk for hip and non-hip major osteoporotic fractures compared with TBS or the FRAX risk factors alone. Similar results were observed for the combination of TBS with actual FRAX probabilities in models predicting major osteoporotic fractures or hip fractures alone.

This study has a number of limitations and strengths. That the measurements of TBS were undertaken at a single center might be regarded as both a limitation and a strength. It should be noted that the TBS analyses were blinded to the subsequent incidence of fracture and that a fully automated, operator-independent algorithm was used to calculate TBS from the DXA spine BMD image once the latter had been optimally processed for the measurement of BMD, ie, there was no further operator input once the image had been accepted for BMD measurement. All of the statistical analyses were undertaken independently of the provider of the TBS measurements. A further possible limitation is that although all subjects had measurements of spine and femoral neck BMD available, some of the FRAX variables were missing in some cohorts or participants. In this case, the risk variable input was set to zero so that the calculated probabilities are lower than might be expected. For example, data were incomplete on causes of secondary osteoporosis, but this variable is no longer weighted in models containing femoral neck BMD, and GRs were similar in models with and without BMD. One might also expect that missing information at baseline would be randomly distributed between those sustaining incident fractures and those remaining fracture-free so that the impact on the examination of relationships is minimized. On another note, we know that the risk identified by low lumbar spine BMD is reversible with treatment but it is not yet known if the same is true for TBS. The major strength of this meta-analysis relates to the use of individual-level data to enable the examination of interactions between TBS and other risk variables and the derivation of adjusted FRAX probabilities at an individual level.

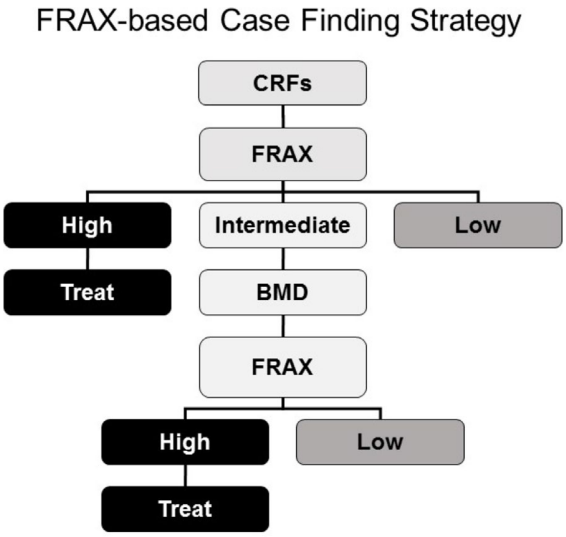

Fig. 1. An example of a case-finding strategy for the use of fracture probabilities. This necessitates the need for assessment thresholds (intermediate group) and intervention thresholds (assessment and high/low-risk groups; the latter represents the intervention threshold).

The clinical application of these findings with FRAX will vary from country to country depending on the FRAX model used and, more importantly, the manner whereby FRAX-generated probabilities are incorporated into clinical decision making. The use of FRAX in clinical practice demands a consideration of the fracture probability at which to intervene, both for treatment (an intervention threshold) and for BMD testing (assessment thresholds). A general approach is shown in Fig. 1.[57] The management process begins with the assessment of fracture probability and the categorization of fracture risk on the basis of age, sex, BMI, and the clinical risk factors. On this information alone, some patients at high risk may be offered treatment without recourse to BMD testing. Many guidelines recommend treatment in the absence of information on BMD in women with a previous fragility fracture (a prior vertebral or hip fracture in North America).[58–61] Many physicians would also perform a BMD test, but frequently this is for reasons other than to decide on intervention, for example, as a baseline to monitor treatment. There will be other instances where the probability will be so low that a decision not to treat can be made without BMD. An example might be the well woman at menopause with no clinical risk factors. Thus, not all individuals require a BMD test. The size of the intermediate category in Fig. 1 will vary in different countries. In the US, this will be a large category, whereas in a large number of countries with limited or no access to densitometry, the size of the intermediate group will necessarily be small. In other countries (eg, the UK), where provision for BMD testing is suboptimal, the intermediate category will lie between the two extremes.

It is evident, therefore, that the approach to the setting of intervention thresholds for BMD testing or for treatment varies markedly worldwide. The question arises how many patients would be reclassified from low risk to high risk and vice versa

with the consideration of TBS alongside FRAX or other risk instruments. It is likely that the number of individuals who would be reclassified after adjustment will be small because reclassification will be most frequent at probabilities close to the intervention threshold.[62] The findings are likely to be similar to those observed with use of the offset between lumbar spine and femoral neck BMD *T*-scores. In these studies, the proportion of patients reclassified across thresholds were typically small, ranging from 2.3% to 8.3%.[63,64] The quantum of effect of TBS remains, however, to be determined in the context of clinical assessment guidelines.

We conclude that TBS is a consistent and significant predictor of fracture risk and provides information independently of FRAX in men and women from independent, international cohorts including multiple ethnicities. The findings of the study support the use of TBS as a standalone assessment of fracture risk and, using adjustments derived from the Manitoba cohort, as a post hoc adjunct to risk assessment with FRAX.

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