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Independent Clinical Validation of a Canadian FRAX Tool: Fracture Prediction and Model Calibration

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ABSTRACT

A FRAX model for Canada was constructed for prediction of osteoporotic and hip fracture risk using national hip fracture data with and without the use of femoral neck bone mineral density (BMD). Performance of this system was assessed independently in a large clinical cohort of 36,730 women and 2873 men from the Manitoba Bone Density Program database that tracks all clinical dual-energy X-ray absorptiometry (DXA) test results for the Province of Manitoba, Canada. Linkage with other provincial health databases allowed for the direct comparison of fracture risk estimates from the Canadian FRAX model with observed fracture rates to 10 years (549 individuals with incident hip fractures and 2543 with incident osteoporotic fractures). The 10-year Kaplan-Meier estimate for hip fractures in women was 2.7% [95% confidence interval (CI) 2.1–3.4%] with a predicted value of 2.8% for FRAX with BMD, and in men the observed risk was 3.5% (95% CI 0.8–6.2%) with predicted value of 2.9%. The 10-year estimate of osteoporotic fracture risk for all women was 12.0% (95% CI 10.8–13.4%) with a predicted value of 11.1% for FRAX with BMD, and in men, the observed risk was 10.7% (95% CI 6.6–14.9%) with a predicted value of 8.4%. Discrepancies were observed within some subgroups but generally were small. Fracture discrimination based on receiver operating characteristic curve analysis was comparable with published meta-analyses with area under the curve for osteoporotic fracture prediction of 0.694 (95% CI 0.684–0.705) for FRAX with BMD and for hip fractures 0.830 (95% CI 0.815–0.846), both of which were better than FRAX without BMD or BMD alone. Individual risk factors considered by FRAX made significant independent contributions to fracture prediction in one or more of the models. In conclusion, a Canadian FRAX tool calibrated on national hip fracture data generates fracture risk predictions that generally are consistent with observed fracture rates across a wide range of risk categories. © 2010 American Society for Bone and Mineral Research.

KEY WORDS: BONE MINERAL DENSITY; DUAL X-RAY ABSORPTIOMETRY; OSTEOPOROSIS; FRACTURES; FRAX; ADMINISTRATIVE DATA; HISTORICAL COHORT STUDY

Introduction

Osteoporosis is a common condition affecting up to 16% of women and 7% of men over age 50 years in Canada.[1] The consequences of fracture include increased mortality, morbidity, institutionalization, and economic costs.[2,3] An individual with a hip fracture has a one in four risk of death in the year following fracture, and this excess risk continues into subsequent years independent of age and comorbidity.[4] Those with vertebral fractures are also at substantially increased risk of death.[4–6] Moreover, all osteoporosis-related fractures can lead to significant long-term disability and decreased quality of life.[7,8]

The ability to accurately gauge fracture risk is critical in identifying cost-effective thresholds for intervention.[9,10] The WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield recently has identified a set of seven clinical risk factors [ie, prior fragility fracture, a parental history of hip fracture, smoking, use of systemic corticosteroids, excess alcohol intake, body mass index (BMI), and rheumatoid arthritis] that, in addition to age and sex, contribute to fracture risk independent of bone

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mineral density (BMD).[10,11] The fracture risk assessment (FRAX) tool (www.shef.ac.uk/FRAX), released in 2008, computes individualized 10-year probability of hip and osteoporotic fracture (ie, composite of hip, clinical spine, distal forearm, and proximal humerus).[12] The FRAX tool has been endorsed by several countries and organizations, including the US National Osteoporosis Foundation.[11,13–16] Since fracture rates are known to vary by more than an order of magnitude worldwide,[17] calibration for the FRAX tool is population- and country-specific. To date, over 20 FRAX tools have been developed, but none has independently confirmed the accuracy of the predictions for both hip and osteoporotic fractures.

This report describes construction of the Canadian FRAX tool, with direct assessment of its calibration and fracture discrimination in a large clinical cohort from the Manitoba Bone Density Program database. The latter was linked to other provincial health databases for comparison of observed osteoporotic fracture rates to 10-year risk estimates from the Canadian FRAX model.

Methods

Construction of the Canadian model

National hip fracture data for 2005 and national mortality data for 2004 (the most recent available) were used to construct the Canadian FRAX tool using previously described data sources.[18] Ideally, detailed fracture epidemiology for major nonhip fracture sites (ie, clinical spine, forearm, and humerus) are also used in FRAX tool construction, but these were not available at a national level. Therefore, nonhip fracture rates were imputed based on the assumption that the ratios would be similar to those for the United States, as recently described in construction of the updated US FRAX tool.[19–21]

Briefly, the Canadian Institute for Health Information (CIHI) collects and analyzes information on health and health care in Canada and makes this publicly available. The Hospital Morbidity Database (HMDB), a database housed at CIHI, includes administrative, clinical, and demographic information on hospital inpatient events and provides national discharge statistics from Canadian health care facilities by diagnoses and procedures. The HMDB is comprised of a subset of the Discharge Abstract Database (DAD) data, and it appends data from provinces/territories that are not participating in DAD in order to provide a national database. Hospital discharges in the HMDB for 2005 were coded using the *Tenth International Classification of Diseases, Canadian Enhancement* (ICD-10-CA) system following standardized and mandatory coding methods.[22,23] CIHI ensures a high quality of information in the HMDB through a data quality enhancement program.[22,23] We identified all 2005 hospitalizations from the HMDB in which the most responsible diagnosis was a hip (proximal femoral) fracture using the following diagnosis codes: ICD-10-CA S72.0 through S72.2. The annual number of hip fractures was tabulated by sex and age (5-year intervals). The denominator was stratified in the same fashion using national census data.

Using methods that have been described previously,[12] the WHO Collaborating Centre constructed 10-year fracture risk predictions for the hip and any osteoporotic site with and without femoral neck BMD using the standard FRAX risk factors. Briefly, Poisson models were used to calculate the hazard functions of fracture and death. Age-specific fracture and mortality hazards were computed. The relationship between the hazard functions was used to calculate the 10-year probability of fracture for a combination of given risk factors.[11] The independent contribution of each risk factor was used to compute probabilities of fracture in the absence of clinical risk factors or in the presence of any combination.

Patient population and bone density measurements

The population for this historical cohort study consisted of all women and men in the Province of Manitoba, Canada, aged 50 years or older at the time of baseline femoral neck dual-energy X-ray absorptiometry (DXA) between January 1990 and March 2007. Subjects were required to have medical coverage from Manitoba Health during the observation period ending March 2008 without other exclusions. 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 the Health Information Privacy Committee of Manitoba.

Bone density testing with DXA has been available in Manitoba since 1990 and has been managed as an integrated program since 1997 using targeted case-finding and standard criteria, as described previously.[24,25] The program maintains a database of all DXA results that can be linked with other population-based computerized health databases through an anonymous personal identifier.[26] The DXA database has been described previously with completeness and accuracy in excess of 99%. DXA scans were performed and analyzed in accordance with manufacturer recommendations. All subjects were required to have a valid femoral BMD measurement. In addition, trochanter BMD was available in 100% of the subjects, total hip BMD in 93.9%, and lumbar spine BMD in 91.8%. Hip *T*-scores were calculated using the NHANES III white female reference values. Lumbar spine *T*-scores were calculated using the manufacturer's US white female reference values after vertebral levels affected by artifact were excluded by experienced physicians using conventional criteria.[27] The minimum *T*-score was calculated from all available measurement sites. Prior to 2000, DXA measurements were performed with a pencil-beam instrument (Lunar DPX, GE Lunar, Madison, WI, USA), and after this date, a fan-beam instrument was used (Lunar Prodigy, GE Lunar). Instruments were cross-calibrated using anthropomorphic phantoms and 59 volunteers. No clinically significant differences were identified (femoral neck *T*-score differences < 0.2). Therefore, all analyses are based on the unadjusted numerical results provided by the instrument. Absorptiometers showed stable long-term performance [coefficient of variation (CV) $< 0.5\%$] and satisfactory in vivo precision.[28]

Definitions of fractures and other clinical risk factors

Fractures and other medical diagnoses can be assessed through a combination of hospital discharge abstracts (ie, diagnoses and procedures coded using the ICD-9-CM prior to 2004 and

ICD-10-CA thereafter) and physician billing claims (ie, coded using ICD-9-CM).[29] Use of systemic corticosteroids and other medications can be obtained by linkage to the provincial Drug Program Information Network (DPIN) database, with drugs classified according to the Anatomical Therapeutic Chemical (ATC) system of the World Health Organization (WHO).[30] Each prescription record contains the date of dispensation, an exact identification of the dispensed drug (including substance, strength, route, and dosage form), the number of doses provided, the anticipated duration of the prescription in days, and a code for prescribing physician and dispensing pharmacy. The pharmacy database is accurate both for capture of drug dispensations and for the prescription details.[31]

Longitudinal health service records were assessed for the presence of hip, clinical vertebral, forearm, and humerus fracture codes (collectively designated as "osteoporotic") before and after BMD testing that were not associated with trauma codes.[32] We required that hip and forearm fractures be accompanied by a site-specific fracture reduction, fixation, or casting code, which enhances the diagnostic and temporal specificity for an acute fracture. For purposes of the FRAX calculation, prior fragility fracture was taken be an osteoporotic fracture prior to BMD testing based on the preceding definition. A diagnosis of rheumatoid arthritis testing was taken from physician office visits and/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 [chronic obstructive pulmonary disease (COPD) diagnosis] and high alcohol intake (alcohol or substance abuse diagnosis). Prolonged corticosteroid use (over 90 days dispensed in the year prior to DXA testing at a mean prednisone-equivalent dose of 7.5 mg/day or greater) was obtained from the provincial pharmacy system. Parental hip fracture information was collected only in the last two years (2005 and onwards) and therefore was missing for earlier cases. 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 kg) divided by height squared (in m). Secondary causes of osteoporosis, other than rheumatoid arthritis, do not contribute to the probability of fracture as calculated by FRAX when information on BMD is present and therefore was not considered in this analysis.

FRAX predictions

The WHO Coordinating Centre calculated 10-year fracture risk for hip and osteoporotic sites (with and without femoral neck BMD) for each case using the Canadian FRAX tool without knowledge of the fracture outcomes. To adjust for the effect of missing parental hip fracture information on FRAX estimates prior to 2005, age- and sex-specific estimates of the effect of a positive response were determined using the later years of data (2005–2007). This averaged effect incorporates both the prevalence of a positive response and the relative change in risk. The risk-adjustment factor ranged from 1.00 to 1.25 for hip fractures and 1.06 to 1.11 for osteoporotic fractures. These ratios then were used to adjust the FRAX risk estimate for those years of data where parental hip information was not available.

Statistics

Descriptive statistics for demographic and baseline characteristics are presented as mean $\pm$ SD for continuous variables or count (percent) for categorical variables. Univariate comparisons of women and men were performed with the χ^2 test (for categorical data) and the nonparametric Mann-Whitney test (for continuous data). Individuals were grouped into risk quintiles based on the hip and osteoporotic FRAX estimates using BMD, with men and women categorized separately. Ten-year fracture risk with 95% confidence interval (CI) was estimated using the Kaplan-Meier product-limit method for each subgroup, with death considered a competing hazard (ie, a person who died during follow-up was included in the analysis analogous to the handling of death risk in FRAX). Within each subgroup, the average predicted 10-year risk then was compared with the observed 10-year risk using graphic methods and linear regression with the intercept at the origin. In a well-calibrated risk prediction system, predicted and observed rates should track the line of identity.[33–37] Parallel analyses were performed for osteoporotic fractures and hip fractures. Cox proportional hazards models were constructed for osteoporotic and hip fracture prediction to assess the contributions of the individual FRAX variables. Receiver-operating characteristic (ROC)/area under the curve analyses were conducted to explore the fracture risk stratification using FRAX (with and without BMD) versus BMD alone (femoral neck *T*-score or minimum site). Statistical analyses were performed with Statistica (Version 6.1, StatSoft, Inc., Tulsa, OK, USA) and SPSS for Windows (Version 16.0, SPSS, Inc., Chicago, IL, USA).

Results

Population

The final study population consisted of 36,730 women and 2873 men (combined 39,603). Baseline characteristics, summarized in Table 1, are consistent with greater clinical selection bias in men referred for BMD testing. Men were slightly older than women (mean age 68.2 ± 10.1 versus 65.7 ± 9.8, $p < .001$) and had a higher mean BMI and greater frequency of prior fragility fracture, rheumatoid arthritis, corticosteroid use, COPD, and substance abuse. Women had a lower mean femoral neck *T*-score (-1.5 ± 1.0 versus -1.2 ± 1.1, $p < .001$) and had a higher frequency of parental hip fracture. FRAX risk estimates for osteoporotic fracture were greater for women than for men with and without BMD and for hip fracture without BMD (all $p < .001$).

Fracture risk by quintile

Incident hip fractures were identified in 506 women and 43 men (combined 549). The 10-year Kaplan-Meier estimate of hip fractures for all women was 2.7% (95% CI 2.1–3.4%) with a mean predicted risk of 2.8% for FRAX with BMD. For men, the 10-year hip fracture risk was 3.5% (95% CI 0.8–6.2%) with a mean predicted risk of 2.9% for FRAX with BMD. When stratified by risk quintile, observed 10-year hip fracture rates showed very close agreement with the FRAX predictions for women (ie, 95% CI for the observed risk included the line of identity; Fig. 1). The

Table 1. Baseline Characteristics and Canadian FRAX Tool Risk Estimates of the Study Population

	Women ($n = 36{,}730$)	Men ($n = 2873$)	p Value
Age	65.7 ± 9.8	68.2 ± 10.1	<.001
BMI	26.8 ± 5.2	27.1 ± 4.4	.004
Prior fragility fracture	4984 (13.6)	431 (15)	.031
Parental hip fracture[a]	1,110 (13.2)	86 (10.6)	.036
Rheumatoid arthritis	1,311 (3.6)	219 (7.6)	<.001
Current or recent corticosteroid use	1,542 (4.2)	634 (22.1)	<.001
COPD (smoking proxy)	2,928 (8.0)	521 (18.1)	<.001
Substance abuse (alcohol use proxy)	874 (2.4)	122 (4.2)	<.001
Femoral neck *T*-score (white female)	−1.5 ± 1.0	−1.2 ± 1.1	<.001
Minimum *T*-score (white female)	−1.9 ± 1.1	−1.5 ± 1.2	<.001
Osteoporotic BMD (minimum *T*-score ≤ −2.5)	11,335 (30.9)	555 (19.3)	<.001
Canadian FRAX tool estimates[b]			
Hip with BMD	2.8% ± 4.4%	2.9% ± 3.9%	.243
Osteoporotic with BMD	11.1% ± 7.4%	8.4% ± 5%	<.001
Hip without BMD	3.6% ± 5.1%	2.8% ± 3.3%	<.001
Osteoporotic without BMD	11.6% ± 8.0%	7.6% ± 4.0%	<.001

[a]For data from 2005–2007 ($n = 8439$ women, 814 men).
[b]Adjusted for incomplete parental hip fracture information.

estimated regression slope for women was 1.03 (95% CI 1.02–1.04). The smaller number of men with hip fractures limited analysis, but there was reasonable agreement between observed and predicted hip fracture rates and a regression slope of 0.92 (95% CI 0.57–1.27).

Calibration plots were generated based on 2380 women and 163 men with incident osteoporotic fractures (combined 2543). The 10-year Kaplan-Meier estimate of osteoporotic fractures for all women was 12.1% (95% CI 10.8–13.4%) with a mean predicted risk of 11.3% for FRAX with BMD. For men, the 10-year osteoporotic fracture risk was 10.7% (95% CI 6.6–14.9%) with a mean predicted risk of 8.4% for FRAX with BMD. When women were stratified by risk quintile, the Canadian FRAX tool gave risk predictions that were within the 95% CI for the observed risk in the lowest three quintiles, but the observed rate slightly exceeded the predicted rate for the second highest risk quintile (15.0%, 95% CI 13.3–16.7%, versus 12.8%) and the highest risk quintile (26.5%, 95% CI 24.4–28.6%, versus 23.5%). The regression slope for women was 1.13 (95% CI 1.08–1.19). Results for men were more variable owing to the smaller numbers of events, and the wider confidence intervals included the line of identity in all subgroups except for the middle quintile, in which the observed rate (13.2%, 95% CI 8.2–18.3%) exceeded the predicted rate (7.2%). The regression slope for men was 1.24 (95% CI 1.00–1.48).

Fracture risk by category

Calibration for osteoporotic fractures with and without BMD was next evaluated in women and men combined using three pres-

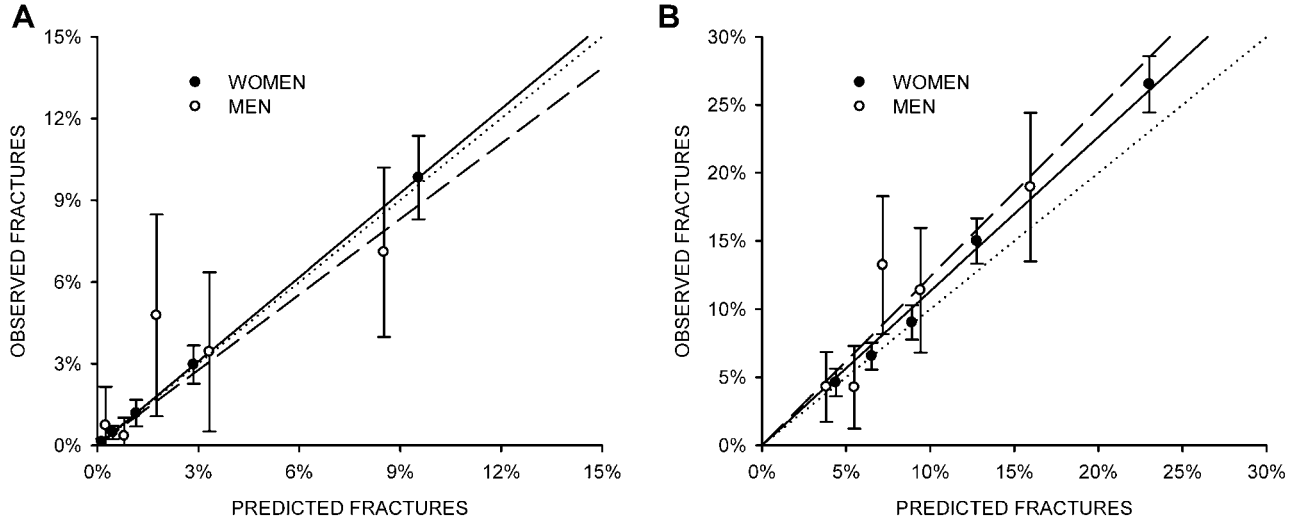

Fig. 1. Predicted 10-year fracture risk from Canadian FRAX tool with BMD (*x* axis) versus observed Kaplan-Meier 10-year fracture rates (*y* axis) by risk quintile for women (*solid line*) and men (*dashed line*). The dotted line depicts the line of identity. (*A*) Hip fractures. (*B*) Osteoporotic fractures. 95% error bars are shown.

pecified absolute risk categories: low, less than 10%; moderate, 10% to 20%; and high, greater than 20% (Fig. 2). The weighted mean ratio for observed versus predicted fractures was 1.12 for FRAX with BMD and 1.09 for FRAX without BMD. Deviations from the line of identity were noted for the moderate-risk category (observed-predicted ratio 1.18 with BMD and 1.11 without BMD) and high-risk category (observed-predicted ratio 1.14 with BMD and 1.16 without BMD). The regression slopes were 1.14 (95% CI 1.11–1.18) for FRAX with BMD and 1.16 (95% CI 1.08–1.23) for FRAX without BMD.

ROC analyses

As shown in Table 2, the FRAX estimates using BMD and clinical risk factors were superior to BMD alone or clinical risk factors alone for both osteoporotic fractures and hip fractures. For osteoporotic fractures, FRAX with BMD gave an area under the curve of 0.694 (95% CI 0.684–0.705) versus FRAX without BMD of 0.663 (95% CI 0.652–0.674) and femoral neck *T*-score alone of 0.679 (95% CI 0.668–690). For hip fractures, FRAX with BMD gave an area under the curve of 0.830 (95% CI 0.815–0.846) versus FRAX without BMD of 0.793 (95% CI 0.775–0.810) and femoral neck *T*-score alone of 0.801 (95% CI 0.783–0.819). There was no improvement in fracture prediction when minimum *T*-score was used instead of the femoral neck *T*-score alone.

Cox proportional hazards models

As shown in Table 3, age, prior osteoporotic fracture, rheumatoid arthritis, recent corticosteroid use, COPD diagnosis (smoking proxy), substance abuse diagnosis (alcohol proxy), and BMD all were independent predictors of osteoporotic fractures. Sex and BMI were not associated with osteoporotic fractures after adjustment for the other covariates. When BMD was not included in the model, BMI in addition to all other clinical risk factors except sex were independent predictors of osteoporotic fractures (Table 4).

Femoral neck BMD showed a larger gradient of risk for hip fracture prediction [hazards ratio (HR) = 2.186, 95% CI 1.968–2.429] than for osteoporotic fractures (HR = 1.577, 95% CI 1.499–1.659). Age, prior osteoporotic fracture, rheumatoid arthritis diagnosis, recent corticosteroid use, COPD diagnosis (without BMD), and substance abuse diagnosis all were independent predictors of hip fractures. Sex showed an apparent effect on hip fracture risk in the model with BMD (HR = 1.388, 95% CI 1.005–1.917) but not when BMD was excluded (HR = 1.068, 95% CI 0.776–1.47).

Discussion

A Canadian FRAX model has been constructed for prediction of osteoporotic and hip fracture risk using national hip fracture data, with incident fracture discrimination and model calibration assessed in a large clinical population. To date, no similarly detailed assessment of FRAX calibration has been performed in a population completely independent from that used for the initial tool construction. For prediction of hip fracture and any osteoporotic fracture in Canadians, the Canadian FRAX tool was reasonably well calibrated, with overall risk estimates that were close to observed fracture rates, particularly among women for whom the data are more robust. Discrepancies were observed within some subgroups but generally were small.

It is notable that our assessment was performed in a clinical population, whereas population-based hip fracture and mortality data were used in construction of the model. Clinical populations would be expected to show a greater prevalence of clinical risk factors for low BMD and fracture because these are fundamental to the targeted case-finding strategy used widely in osteoporosis clinical practice guidelines. Therefore, our analysis complements population-based assessments of fracture prediction. Despite clinical referral bias, which was particularly evident among men, this did not appear to compromise the overall performance of FRAX significantly. Men referred for BMD testing clearly differed from the general population, with higher prevalences of prior

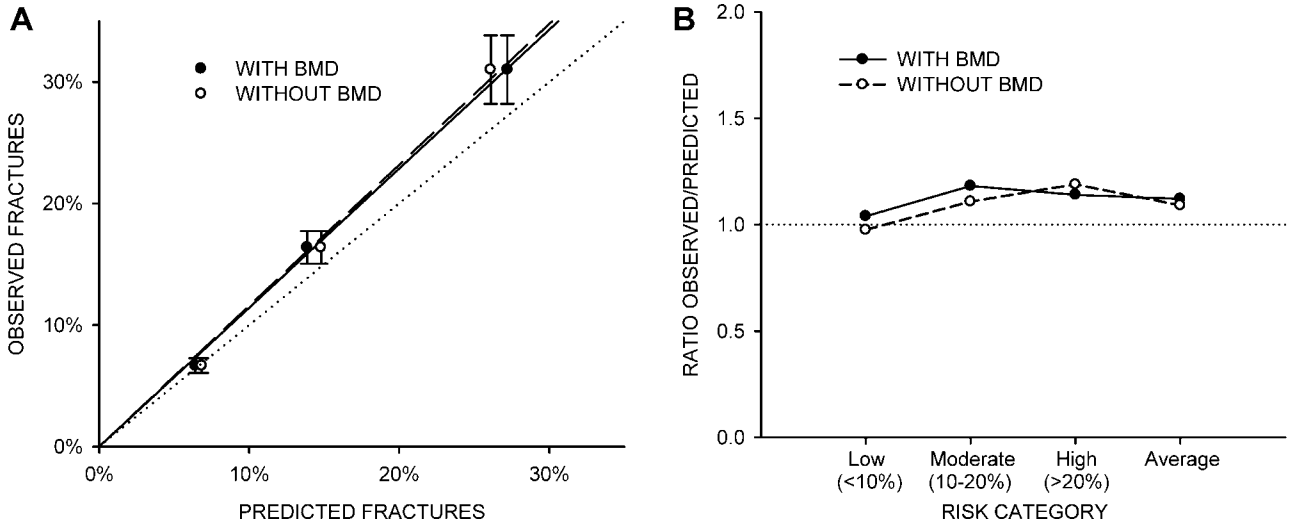

Fig. 2. Predicted 10-year fracture risk from Canadian FRAX tool with and without BMD (*x* axis) versus observed Kaplan-Meier 10-year fracture rates (*y* axis) by risk category (low, less than 10%; moderate, 10% to 20%; and high, greater than 20%) with BMD (*solid line*) and without BMD (*dashed line*). The dotted line depicts the line of identity. (*A*) Osteoporotic fractures (95% error bars are shown). (*B*) Calibration ratios for women and men combined.

Table 2. ROC Area Under the Curve (AUC) Analyses for Osteoporotic Fractures and Hip Fractures

	Hip fractures			Osteoporotic fractures		
	AUC	95% CI	*p* Value	AUC	95% CI	*p* Value
FRAX with BMD	0.830	0.815–0.846	<.001	0.694	0.684–0.705	<.001
FRAX without BMD	0.793	0.775–0.810	<.001	0.663	0.652–0.674	<.001
Femoral neck *T*-score	0.801	0.783–0.819	<.001	0.679	0.668–0.690	<.001
Minimum *T*-score	0.770	0.753–0.787	<.001	0.675	0.665–0.686	<.001

osteoporotic fracture, rheumatoid arthritis, and corticosteroid use than women. The fact that FRAX still performs satisfactorily in this highly selected population should enhance confidence in the robustness of the FRAX system because FRAX must perform well in diverse clinical settings and not simply in healthy populations.

The individual risk factors that are considered by FRAX were found to make significant independent contributions to fracture prediction in one or more of the models. As expected, age and femoral neck BMD were strongly associated with osteoporotic and hip fracture risk. BMI was noncontributory when BMD was used but was strongly predictive when BMD was not included in the risk assessment. Prior osteoporotic fracture, physician-diagnosed rheumatoid arthritis, and corticosteroid use showed HRs comparable with those which have been reported in previous meta-analyses.[10,38,39] Although we did not have smoking history or information on alcohol consumption, proxy variables (ie, physician diagnosis of COPD or substance abuse) showed a similar effect.[10,40,41] Interestingly, sex did not independently modify osteoporotic fracture risk and had an inconsistent effect on hip fracture risk (significant in the FRAX model with BMD but not in the FRAX model without BMD). Since the femoral neck *T*-scores were calculated based on female reference data (NHANES white reference population), as recommended by the WHO Collaborating Centre, this would support the view that men and women have similar fracture risk at the same absolute BMD level.[42,43]

Fracture discrimination as determined by ROC area under the curve analysis is consistent with a previous validation study from the WHO Collaborating Centre using the initial derivation cohorts in addition to multiple new cohorts.[12] Area under the curve for osteoporotic fracture prediction with BMD in the current study was 0.694, which compares favorably with the value of 0.63 obtained in the original WHO cohorts. Similarly, the original WHO cohorts showed hip fracture area under the curve of 0.78 with BMD compared with 0.830 in the Manitoba cohort. Since the performance of the Canadian FRAX tool was tested in a population completely independent from the national data sources used for construction and calibration of the FRAX tool, there should not be any appreciable optimism in the assessment.

The FRAX system is calibrated for femoral neck BMD measurements and does not consider additional measurement sites that are used in clinical practice, such as the lumbar spine. Investigations from the WHO Collaborating Centre, as well as others, have not found an improvement in fracture risk prediction when the minimum *T*-score is used rather than the femoral neck *T*-score.[44,45] Our analyses are consistent with this finding and actually found that the ROC area under the curve for minimum *T*-score was no better than for femoral neck *T*-score and actually worse for hip fracture prediction.

Some limitations to this study are acknowledged. Reliance on administrative data for fracture ascertainment is less reliable than direct radiographic review, particularly for vertebral fractures, because the majority are not clinically diagnosed.[46] Nonetheless, hip fractures are reported accurately, and our previous analyses have shown good detection of nonhip fractures (including clinical vertebral fractures).[32] Additional limitations include the incomplete parental hip fracture information and use of proxy variables for smoking and high alcohol intake. Since diagnosed COPD and substance abuse are likely to reflect the most extreme forms of smoking and alcohol consumption, this may have unpredictable effects in terms of model

Table 3. Hazard Ratios (HRs) for Fracture Based on Individual FRAX Variables Including Femoral Neck BMD

	Hip fractures			Osteoporotic fractures		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Sex (men vs women)	1.388	1.005–1.917	.046	1.051	0.893–1.238	.547
Age (per decade)	2.230	2.021–2.462	<.001	1.395	1.335–1.458	<.001
BMI (per 5 kg/m^2)	0.799	0.719–0.888	<.001	0.999	0.957–1.043	.972
Prior osteoporotic fracture	1.353	1.119–1.636	.002	1.829	1.672–2.000	<.001
Rheumatoid arthritis	1.458	1.045–2.032	.026	1.502	1.274–1.772	<.001
Recent corticosteroid use	1.496	1.103–2.029	.010	1.224	1.047–1.432	.011
COPD (smoking proxy)	1.261	0.996–1.598	.054	1.278	1.136–1.438	<.001
Substance abuse (alcohol proxy)	1.902	1.222–2.961	.004	1.599	1.297–1.971	<.001
Femoral neck *T*-score (per SD)	2.186	1.968–2.429	<.001	1.577	1.499–1.659	<.001

Note: Data are from a multivariable Cox proportional hazards model with death considered a competing hazard.

Table 4. Hazard Ratios (HRs) for Fracture Based on Individual FRAX Variables Without BMD

	Hip fractures			Osteoporotic fractures		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Sex (men vs women)	1.068	0.776–1.47	.686	0.888	0.755–1.045	0.152
Age (per decade)	2.801	2.54–3.089	<.001	1.616	1.554–1.681	<.001
BMI (per 5 kg/m^2)	0.604	0.542–0.672	<.001	0.865	0.832–0.9	<.001
Prior osteoporotic fracture	1.742	1.443–2.103	<.001	2.128	1.948–2.324	<.001
Rheumatoid arthritis	1.655	1.184–2.314	.003	1.640	1.391–1.934	<.001
Recent corticosteroid use	1.602	1.182–2.17	.002	1.283	1.097–1.501	0.002
COPD (smoking proxy)	1.446	1.145–1.826	.002	1.377	1.224–1.549	<.001
Substance abuse (alcohol proxy)	1.948	1.251–3.034	.003	1.672	1.356–2.062	<.001

Note: Data are from a multivariable Cox proportional hazards model with death considered a competing hazard.

performance. A direct comparison of the Canadian FRAX tool with other FRAX tools has not been performed, and therefore, it is unclear whether equivalent results could be obtained using another country's FRAX tool. Detailed fracture epidemiology was available only for hip fractures on a national level, and therefore, nonhip fractures (ie, clinical spine, forearm, and proximal humerus) that contribute to the osteoporotic FRAX model were imputed based on an untested assumption that hip to nonhip fracture ratios in the United States and Canada would be similar. It also has been reported that women referred for BMD testing may differ from the general population in terms of their underlying mortality risk, with lower mortality (and consequently higher fracture risk) seen in the very elderly.[47] Although FRAX considers some of the risk factors associated with death (eg, age, sex, BMI, smoking, corticosteroid use, and BMD and the interaction between sex and age), this may not fully account for all factors leading to lower mortality among persons referred to BMD testing and could contribute to the finding of slightly higher osteoporotic fracture risk in some subgroups than is predicted by FRAX.

In conclusion, a Canadian FRAX tool calibrated on national hip fracture epidemiology generates fracture risk predictions that are generally consistent with observed fracture rates across a wide range of risk categories. Satisfactory performance of FRAX was documented in both men and women, with fracture discrimination comparable with that reported in the derivation and validation of the cohorts studied by the WHO Collaborating Centre.[12] Although this analysis was based on a single Canadian province, a recent publication indicates that hip fracture rates show minimal differences between Canadian provinces, and in particular, Manitoba hip fracture rates are very close to the national average.[18] Therefore, the Canadian FRAX tool is considered suitable for clinical use in Canada.

Disclosures

In the past 3 years, WDL has received speaker fees and unrestricted research grants from Merck Frosst Canada, Ltd. and unrestricted research grants from Sanofi-Aventis, Procter & Gamble Pharmaceuticals Canada, Inc., Novartis, Amgen Pharmaceuticals Canada, Inc., Innovus 3M, and Genzyme Canada and has served on advisory boards for Genzyme Canada, Novartis, and Amgen Pharmaceuticals Canada, Inc. In the past 3 years, LML has received unrestricted research grants from Amgen Pharmaceuticals Canada, Inc.., and Innovus 3M. In the past 3 years, EMC has received speaker fees and/or unrestricted research grants from Novartis, Amgen, AstraZeneca, Pfizer, Bayer, Procter & Gamble, Lilly, Roche, Servier, and Hologic. JAK states that he has nothing to declare for FRAX and the context of this article but has had numerous ad hoc consultancies for 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 & 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; and Wyeth, USA, as well as the National Institute for Health and Clinical Excellence (NICE), UK; the International Osteoporosis Foundation; INSERM, France; the Ministry of Public Health, China; the Ministry of Health, Australia; the National Osteoporosis Society (UK); and WHO. All the other authors state that they have no conflicts of interest

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