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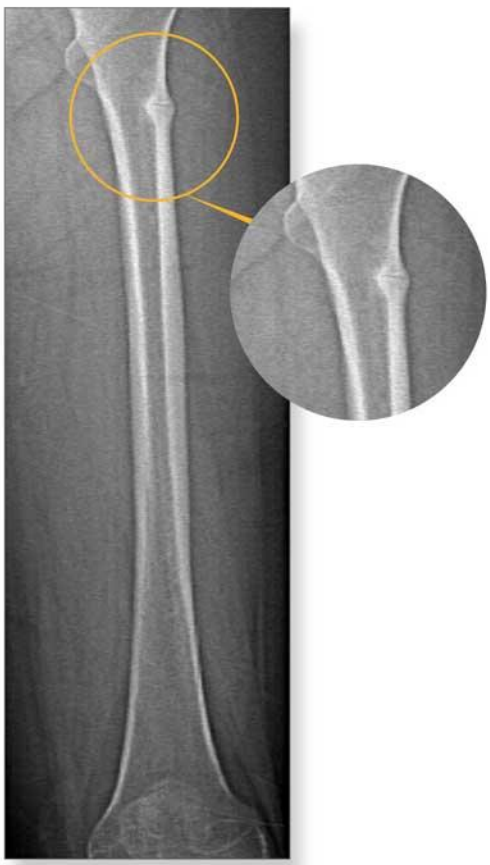

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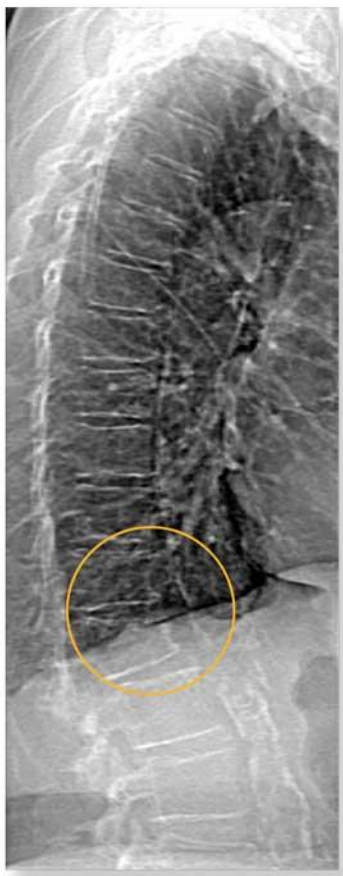

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ORIGINAL ARTICLE

JBMR

Does Osteoporosis Therapy Invalidate FRAX for Fracture Prediction?

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ABSTRACT

Ten-year fracture risk assessment with the fracture risk assessment system (FRAX) is increasingly used to guide treatment decisions. Osteoporosis pharmacotherapy reduces fracture risk, but the effect is greater than can be explained from the increase in bone mineral density (BMD). Whether this invalidates fracture predictions with FRAX is uncertain. A total of 35,764 women (age $\geq$50 years) and baseline BMD testing (1996–2007) had FRAX probabilities retroactively calculated. A provincial pharmacy database was used to identify osteoporosis medication use. Women were categorized as untreated, current high adherence users [medication possession ratio (MPR) $\geq$0.80 in the year after BMD testing], current low adherence users (MPR $<$0.80), and past users. Fractures outcomes to 10 years were established form a population-based health data repository. FRAX and femoral neck BMD alone stratified major osteoporotic and hip fracture risk within untreated and each treated subgroup (all p-values $<$0.001) with similar area under the receiver operating characteristic curve. In untreated and each treated subgroup, a stepwise gradient in observed 10-year major osteoporotic and hip fracture incidence was found as a function of the predicted probability tertile (all p-values $<$0.001 for linear trend). Concordance (calibration) plots for major osteoporotic fractures and hip fractures showed good agreement between the predicted and observed 10-year fracture incidence in untreated women and each treated subgroup. Only in the highest risk tertile of women highly adherent to at least 5 years of bisphosphonate use was observed hip fracture risk significantly less than predicted, though major osteoporotic fracture risk was similar to predicted. In summary, this work suggests that the FRAX tool can be used to predict fracture probability in women currently or previously treated for osteoporosis. Although FRAX should not be used to assess the reduction in fracture risk in individuals on treatment, it may still have value for guiding the need for continued treatment or treatment withdrawal. © 2012 American Society for Bone and Mineral Research.

KEY WORDS: OSTEOPOROSIS; BONE DENSITOMETRY; TREATMENTS; POPULATION STUDIES; EPIDEMIOLOGY

Introduction

Osteoporosis predisposes to fragility (low trauma) fractures and has large public health implications. Pain, reduced function, impaired quality of life, institutionalization, and death are consequences to the individual, with a large societal burden resulting from economic costs.[1–4] Fortunately, the last 2 decades have found an expanding armamentarium of therapeutic agents that can halt the loss of bone mineral density (BMD) and significantly reduce fracture risk.[5,6] Although approved medications are generally well tolerated, side effects may occur with all treatment modalities and safety concerns have been raised.[7] Therefore, it is incumbent upon the clinical practitioner to identify patients in whom treatment will result in the greatest benefit while avoiding treatment of low-risk individuals where the expectation of benefit is small.

The fracture risk assessment system (FRAX), developed by the WHO Collaborating Centre for Metabolic Bone Diseases, allows for the estimation of individual fracture risk based upon that individual's risk factor profile.[8] The adoption of 10-year fracture risk reporting in clinical practice has been shown to beneficially impact on prescribing practices by physicians through better alignment of treatment initiation with the patient's actual risk when compared with a BMD T-score alone.[9] Notwithstanding the substantial impact of FRAX on clinical practice and its increasing use in clinical practice guidelines,[6,10–12] questions remain on how to improve FRAX and better inform those who use FRAX in clinical practice. Some of these questions were

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recently addressed by a set of joint Task Forces and position statements from the International Osteoporosis Foundation (IOF) and the International Society for Clinical Densitometry (ISCD).[13]

FRAX is intended to identify patients for treatment. Whether FRAX can be used to assess fracture risk in patients receiving concurrent treatment for osteoporosis has not been studied to date. The antifracture benefit from osteoporosis therapy is consistently greater than can be explained from the increase in BMD alone, and the latter typically accounts for only a minority of the antifracture benefits found in clinical trials.[14,15] It is therefore presumed that in those receiving treatment for osteoporosis, FRAX might overestimate fracture probability because treatment effects are not accommodated in the model.[13] A strict application of this statement would lead to the suggestion that fracture risk not be reported at all in individuals currently receiving treatment for osteoporosis. However, because many individuals were initiated on treatment before the availability of FRAX, this potentially limits the use of important information for advising patients on their need for continued treatment, or whether treatment could potentially be withdrawn. Furthermore, BMD is only one of the risk factors included in the FRAX model, and most other risk factors would not be expected to change as a result of osteoporosis therapy. Therefore, the impact of osteoporosis therapy on fracture prediction with FRAX, and more specifically whether osteoporosis therapy invalidates use of FRAX for fracture prediction, remains uncertain. To address this issue, we examined a large clinical cohort that was linked to population-based databases to determine medication prescriptions and fracture outcomes.

Methods

Patient population

The study population consisted of all women aged 50 years and older at the time of baseline femoral neck BMD measurement with Dual-emission X-ray absorptiometry (DXA) performed between 1996 and 2007 with 10-year fracture probability measurements from the Canadian FRAX tool (version 3.1).[16] We excluded individuals with earlier BMD testing, as the provincial retail pharmacy database system was only established in 1995. Women were required to have at least 1 year of medical coverage from Manitoba Health during the observation period ending March 2008. Therefore, at least 12 months of medication prescription data were available for each individual before and after BMD measurement. We excluded all men and women younger than age 50 years as the criteria for treatment are less well developed, treatment rates are typically much lower, and individuals referred for BMD testing are less representative of the general population. For women 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 measurements

In the Province of Manitoba, Canada, health services are provided to virtually all residents through a single public healthcare system. Bone density testing with DXA has been managed as an integrated program since 1997; criteria and testing rates for this program have been published.[17] 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. The DXA database has been previously described with completeness and accuracy in excess of 99%.[18]

DXA scans were performed and analyzed in accordance with manufacturer recommendations. Hip *T*-scores were calculated from the NHANES III White female reference values.[19,20] Before 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 crosscalibrated using anthropomorphic phantoms and 59 volunteers. No clinically significant differences were identified (femoral neck *T*-score differences <0.1). Densitometers showed stable long-term performance [coefficient of variation (CV) $<0.5\%$] and satisfactory in vivo precision (CV $= 1.9\%$–2.4% for the femoral neck).[21]

Fracture probability calculations

Prior fracture and other conditions required for calculating fracture probability with FRAX were assessed through a combination of hospital discharge abstracts (diagnoses and procedures coded using the ICD-9-CM before 2004 and ICD-10-CA thereafter) and physician billing claims (coded using ICD-9-CM).[22] For purposes of the FRAX calculation, prior fragility fracture was taken to be a major osteoporotic fracture (hip, clinical vertebral, forearm, and humerus fracture) before BMD testing that was not associated with severe trauma as previously described.[23] A diagnosis of rheumatoid arthritis was taken from physician office visits or hospitalizations with a compatible ICD-9-CM/ICD-10-CA code in a 3-year period before BMD testing. Proxies were used for smoking [chronic obstructive pulmonary disease (COPD) diagnosis] and high alcohol intake (alcohol or substance abuse diagnosis) over the same time frame. Prolonged corticosteroid use (over 90 days dispensed in the year before DXA testing at a mean prednisone-equivalent dose of 7.5 mg per day or greater) was obtained from the provincial pharmacy system.[24] We adjusted for the effect of missing parental hip fracture information on FRAX probability estimates before 2005 using age- and sex-specific adjustment factors derived from 2005 to 2008 parental hip fracture responses as previously described.[25]

Ten-year probability of a major osteoporotic fracture or hip fracture was retroactively calculated for each subject by the WHO Collaborating Centre based on the Canadian FRAX tool (version 3.1) using the previously defined variables without knowledge of the fracture outcomes. The Canadian FRAX tool has been previously shown to accurately predict fracture risk in the Canadian population in two large independent cohort studies.[26,27] In sensitivity analyses we also assessed fracture probability generated with the U.S. White FRAX tool (version 3.1).[28,29]

Ascertainment of incident fractures was performed using previously reported methods. Briefly, longitudinal health service

records were assessed for the presence of hip, clinical vertebral, forearm, and humerus fracture codes (collectively designated as "major osteoporotic") after BMD testing that were not associated with trauma codes.[23] Incident fractures were defined as fractures that occurred after the index BMD measurement and generated two or more site-specific fracture codes in any diagnosis field (hospitalization or physician visit). We required that hip fractures and forearm fractures be accompanied by a site-specific fracture reduction, fixation, or casting code as this enhances the diagnostic and temporal specificity for an acute fracture event. To minimize potential misclassification of prior fractures as incident fractures, we required that there be no hospitalization or physician visit(s) with the same fracture type in the 6 months preceding an incident fracture diagnosis.

Osteoporosis medication use

Use of osteoporosis medications was 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 WHO.[24] Each prescription record contains the date dispensed and 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 as well as the prescription details.[30]

For purposes of the current analysis, osteoporosis therapy was defined as use of a bisphosphonate, raloxifene, salmon calcitonin, or systemic estrogen replacement therapy (ERT). ERT was included because this was a primary treatment for osteoporosis before release of the Women's Health Initiative (WHI) Study.[31] Anabolic therapy was not available throughout most of the study, and was very rarely used even in the later years.

The medication possession ratio (MPR) was calculated from osteoporosis drugs dispensed during the first year after BMD testing, and allowed for medication switching. Gaps in treatment were not considered. Medication use was categorized as follows:

- Untreated: no use in the year before or after BMD testing, and less than 6 months lifetime use for earlier years;
- High adherence current user: MPR $\geq$0.80 in the year after BMD testing;
- Low adherence current user: MPR $<$0.80 in the year after BMD testing;
- Past user: any use in the year before BMD testing or at least 6 months lifetime use for earlier years, with no use in the year after BMD testing.

Statistics

All results are reported as mean $\pm$ SD unless otherwise stated. Group comparisons for continuous data were with Student's *t*-test and for categorical data were with a chi-square test. Within each subgroup defined by osteoporosis medication use (untreated, high adherence current user, low adherence current user, past user), we estimated major osteoporotic and hip fracture incidence to 10 years as a function of the FRAX probability. FRAX estimates fracture probability adjusted for competing mortality; therefore, we adopted a competing mortality framework for estimation of major osteoporotic and hip fracture incidence.[32] Fracture discrimination was performed from area under the receiver operator characteristic curve (AUROC). Concordance between predicted 10-year fracture probability and estimated 10-year fracture incidence (calibration) were assessed for each medication use subgroup with probability stratified into risk tertiles. In sensitivity analyses we also assessed major osteoporotic fracture probability stratified by fixed risk categories ($<$10%, 10%–19%, and $\geq$20%),[6] treatment effects in women with high adherence in the year before and after BMD testing (both with MPR $\geq$0.80), and when analysis was limited to bisphosphonate users with 5 years of high adherence (MPR $\geq$0.80 for the 5 years after BMD testing). Cox proportional hazards models were used to examine linear trend in fracture risk according to risk tertile for each medication use subgroup. In a separate set of models we derived hazard ratios (HRs) for fracture predicted by femoral neck BMD within each medication use subgroup, adjusted for multiple FRAX covariates. The proportional hazard assumption was confirmed graphically from log[$-$log(survival)] versus log (time) plots. All statistical analyses were performed with Statistica (Version 10.0, StatSoft Inc, Tulsa, OK, USA) except for the AUROC analyses, which were performed with PASW for Windows (Version 18, SPSS Inc., Chicago, IL, USA).

Results

The study cohort available for analysis consisted of 35,764 women aged 50 years or older at the time of baseline assessment (Fig. 1). The population characteristics are summarized in Table 1. A total of 12,450 women were categorized as untreated, 9712 were highly adherent current users, 9126 were low adherence current users, and 4476 were past users. Currently treated women had significantly higher predicted fracture probabilities and a higher prevalence of densitometric osteoporosis than untreated women (*p*-value $<$0.001 by Tukey test), whereas women whose records showed past (but not current) treatment had significantly lower predicted fracture probabilities and a lower prevalence of densitometric osteoporosis than untreated women (*p*-value $<$0.001).

During mean 5.3 years of observation, 2276 individuals sustained incident major osteoporotic fractures, of which 474 were hip fractures. There were also 2342 (6.5%) deaths and 955 (2.7%) migrations out of province; for the latter, censoring occurred at the point of cancellation of health insurance coverage. Mean predicted 10-year major osteoporotic fracture probability estimated with BMD for all untreated women (10.6%) agreed very closely with the observed fracture incidence estimated to 10 years [10.0%, 95% confidence interval (CI) = 8.8%–11.2%], consistent with a well-calibrated prediction tool. Similarly, mean predicted 10-year major hip fracture probability estimated with BMD for all untreated women (1.9%) agreed very closely with the observed fracture incidence estimated to 10 years (1.9%, 95% CI = 1.4%–2.5%). Before BMD

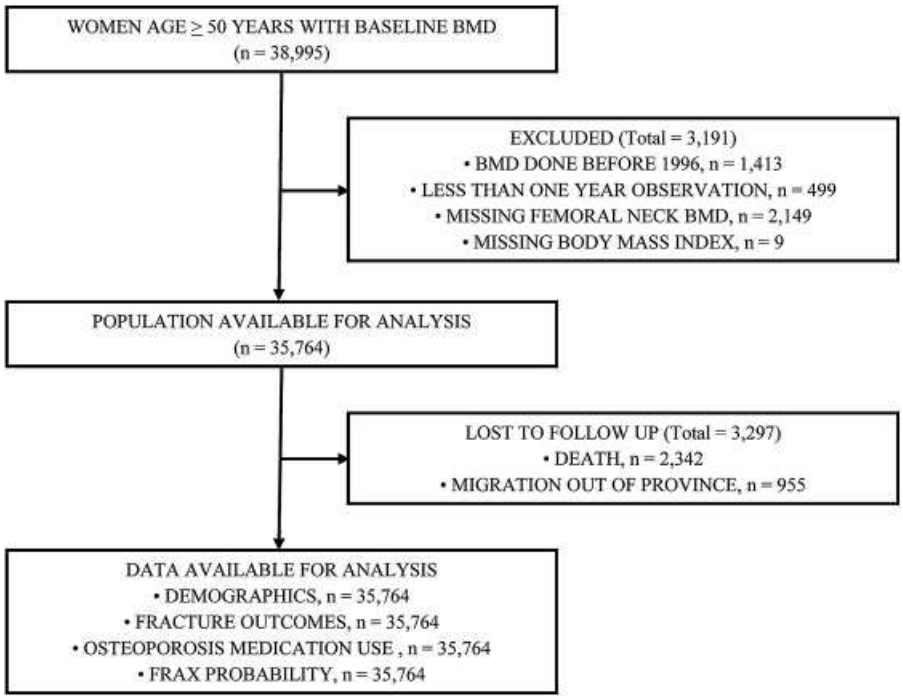

Fig. 1. Study cohort selection flow diagram.

testing, systemic ERT was responsible for the vast majority of osteoporosis medication use (88.9%), but this shifted to non-ERT medications after BMD testing (72.8%). The preponderance of non-ERT medication use was bisphosphonates (89.1%). For women not receiving treatment in the year after BMD testing (untreated or past treatment), treatment rates remained low throughout the period of observation (average combined ERT and non-ERT use less than 4 months). Women receiving treatment in the year after BMD testing tended to maintain a similar treatment pattern (average cumulative ERT and non-ERT use 4.5 years for high adherence current users and 2.2 years for low adherence current users).

Table 2 shows that FRAX stratified major osteoporotic and hip fracture risk in untreated women and each treatment subgroup (all $p < 0.001$), and that fracture discrimination was similar for each subgroup. For example, among untreated women, the AUROC for FRAX major osteoporotic fracture probability estimated without BMD was 0.64 (95% CI = 0.61–0.65) compared

Table 1. Study Population Baseline Characteristics ($N = 35,764$)

	Untreated	High adherence current treatment (MPR ≥0.8)	Low adherence current treatment (MPR <0.8)	Past treatment
	$n = 12,450$	$n = 9712$	$n = 9126$	$n = 4476$
Age	65.1 ± 10.0	66.6 ± 9.7	66.7 ± 10.0	63.4 ± 8.2
BMI (kg/m^2)	27.8 ± 5.5	25.7 ± 4.9	26.0 ± 4.9	27.8 ± 5.3
Prior fragility fracture	1371 (11.0)	1571 (16.2)	1465 (16.1)	415 (9.3)
Parental hip fracture[a]	429 (12.6)	204 (13.9)	251 (13.9)	219 (13.1)
Rheumatoid arthritis	313 (2.5)	407 (4.2)	432 (4.7)	123 (2.7)
Current corticosteroid use	337 (2.7)	562 (5.8)	483 (5.3)	108 (2.4)
COPD diagnosis	830 (6.7)	876 (9.0)	814 (8.9)	297 (6.6)
Substance abuse diagnosis	236 (1.9)	246 (2.5)	251 (2.8)	105 (2.3)
Femoral neck *T*-score	−1.2 ± 0.9	−1.8 ± 1.0	−1.7 ± 1.0	−1.0 ± 0.9
Femoral neck *T*-score -2.5 SD or lower (%)	738 (5.9)	2166 (22.3)	1962 (21.5)	154 (3.4)
Major fracture probability without BMD (%)	10.6 ± 7.2	12.8 ± 8.5	12.8 ± 8.7	9.3 ± 6.0
Major fracture probability with BMD (%)	9.5 ± 5.8	12.9 ± 8.2	12.7 ± 8.2	8.3 ± 4.9
Hip fracture probability without BMD (%)	3.0 ± 4.3	4.2 ± 5.6	4.3 ± 5.8	2.1 ± 3.4
Hip fracture probability with BMD (%)	1.9 ± 3.1	3.8 ± 5.2	3.7 ± 5.2	1.3 ± 2.5

Data are mean ± SD, or *N* (%). BMI = body mass index; COPD = chronic obstructive pulmonary disease; MPR = medication possession ratio.
[a]Percentages based upon total $n = 8339$.

Table 2. Area Under the Receiver Operating Characteristic Curve for Fracture Prediction

	Untreated	High adherence current treatment (MPR ≥0.8)	Low adherence current treatment (MPR <0.8)	Past treatment
	Prediction of major osteoporotic fractures			
Major fracture probability without BMD	0.63 (0.61–0.65)	0.67 (0.65–0.69)	0.69 (0.67–0.71)	0.67 (0.62–0.72)
Major fracture probability with BMD	0.66 (0.64–0.68)	0.64 (0.62–0.66)	0.71 (0.70–0.73)	0.69 (0.64–0.74)
Femoral neck BMD	0.65 (0.62–0.67)	0.65 (0.63–0.67)	0.69 (0.67–0.71)	0.66 (0.61–0.71)
	Prediction of hip fractures			
Hip fracture probability without BMD	0.78 (0.74–0.82)	0.76 (0.72–0.79)	0.83 (0.80–0.86)	0.83 (0.80–0.86)
Hip fracture probability with BMD	0.82 (0.79–0.85)	0.80 (0.77–0.83)	0.85 (0.83–0.88)	0.85 (0.83–0.88)
Femoral neck BMD	0.78 (0.74–0.83)	0.77 (0.73–0.8)	0.82 (0.79–0.85)	0.79 (0.70–0.88)

Data are AUROC (95% CI). MPR = medication possession ratio; BMD = bone mineral density.

with 0.67 for highly adherent current users, 0.69 for low adherence current users, and 0.67 for past users. Fracture discrimination was improved in all subgroups when major fracture probability was estimated with BMD, but again, there was no evidence that fracture discrimination in the treated subgroups was inferior to that found in untreated women. Comparable results were found for prediction of hip fractures using FRAX hip fracture probability, and for risk stratification based upon femoral neck BMD alone. Gradient of risk for femoral neck BMD to predict incident fractures in shown in Table 3. Femoral neck BMD strongly predicted major osteoporotic fractures and hip fractures, and this was unaffected by medication use (p-interaction >0.1).

In untreated and each treated subgroup, a stepwise gradient in observed 10-year major osteoporotic and hip fracture incidence was found as a function of the predicted probability tertile (all p-values <0.001 for linear trend). Concordance plots for major osteoporotic fractures (Fig. 2) and hip fractures (Fig. 3) showed good agreement between the predicted and observed 10-year fracture incidence in the untreated women (reference subgroup), with the 95% CI (reference area) largely containing the line of identity indicating perfect concordance. None of the 95% CIs for the treated subgroups fell below the line of identity. Sensitivity analyses performed using the U.S. White FRAX tool, risk categorization using fixed major osteoporotic fracture probability cutoffs (<10%, 10%–19%, and ≥20%) and in the 3462 women with high adherence to osteoporosis treatment in the year before and after BMD testing gave similar results (data not shown).

Treatment effects were also assessed in 3047 women with high adherence to at least 5 years of bisphosphonate use (MPR ≥0.80). The only subgroup where incident fractures were significantly less than predicted was for hip fractures in the highest risk tertile (observed/predicted ratio 0.61, 95% CI = 0.40–0.83, p-value <0.001), although there was still good concordance between observed and predicted major osteoporotic fractures (observed/predicted ratio 0.92, 95% CI = 0.78–1.06, p-value = 0.280).

Discussion

This analysis found that FRAX, used for the prediction of major osteoporotic and hip fractures, performed similarly in untreated, currently treated and previously treated women. Only in the relatively small subgroup of women in the highest risk tertile with high adherence to at least 5 years of bisphosphonates was observed hip fracture risk significantly less than predicted, with a treatment effect that approximated the risk reduction reported in clinical trials of bisphosphonates.[5,6,33,34] Risk stratification (based upon AUROC) and concordance (agreement between predicted fracture probability and observed fracture incidence) was similar for untreated and treated women, indicating that osteoporosis therapy does not invalidate the use of FRAX for fracture prediction. This potentially expands the clinical role of FRAX as a tool for advising patients on their need for continued treatment, and whether treatment could potentially be withdrawn. Given concerns about serious side effects from

Table 3. Adjusted Hazard Ratios (HR) for Fracture per Standard Deviation Decrease in Femoral Neck T-Score

	Untreated	High adherence current treatment (MPR ≥0.8)	Low adherence current treatment (MPR <0.8)	Past treatment
Prediction of major osteoporotic fractures	1.53 (1.43–1.65)	1.52 (1.34–1.72)	1.64 (1.50–1.79)	1.53 (1.40–1.67)
Prediction of hip fractures	2.33 (1.99–2.72)	2.26 (1.74–2.93)	2.32 (1.93–2.79)	2.18 (1.81–2.62)

Data are HR (95% CI) from Cox proportional hazards models adjusted for age, BMI, prior fragility fracture, rheumatoid arthritis, recent corticosteroid use, COPD diagnosis, and substance abuse diagnosis. p-interaction for BMD*treatment status nonsignificant (>0.1).

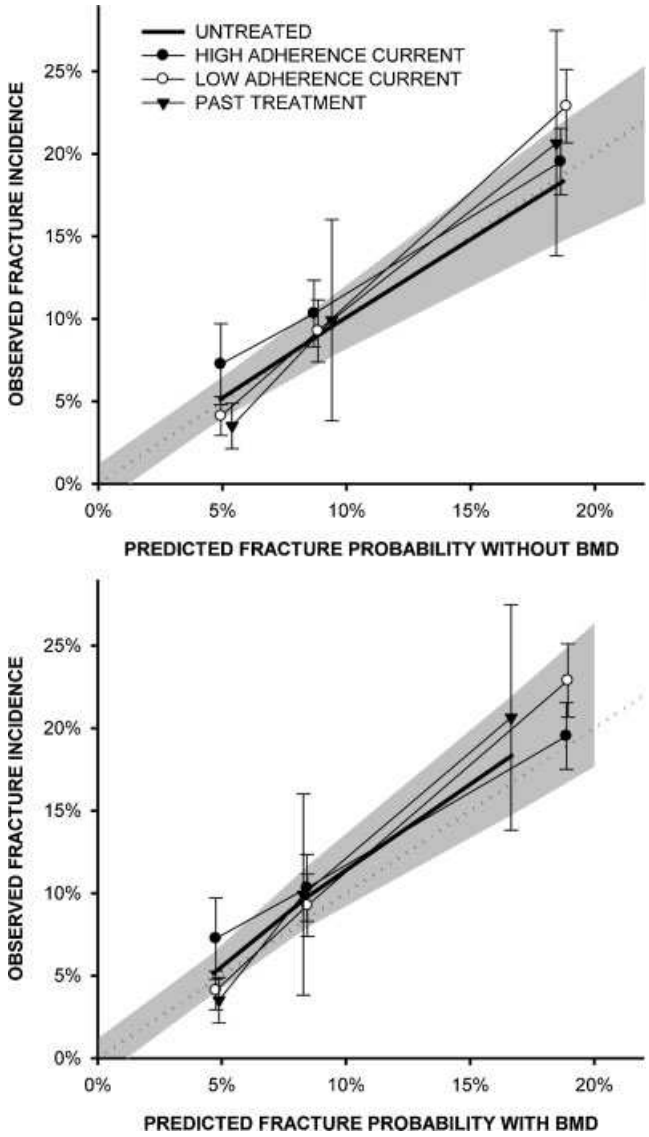

Fig. 2. Predicted 10-year major osteoporotic fracture probability from FRAX versus observed fracture incidence estimated to 10 years, according to risk tertile. Results are stratified by osteoporosis treatment status with the reference group being untreated women (heavy solid line with 95% CI shaded area); 95% CI bars are shown for the treated subgroups. The dotted line indicates the line of identity (perfect concordance between observed and predicted fracture incidence).

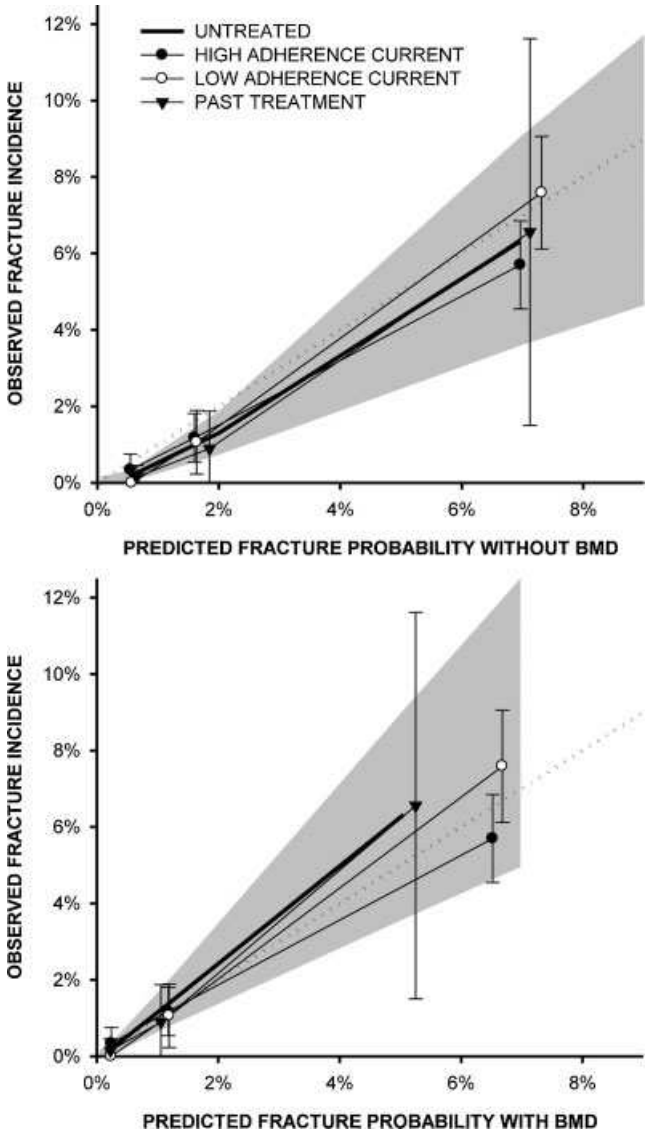

Fig. 3. Predicted 10-year hip fracture probability from FRAX versus observed fracture incidence estimated to 10 years, according to risk tertile. Results are stratified by osteoporosis treatment status with the reference group being untreated women (heavy solid line with 95% CI shaded area); 95% CI bars are shown for the treated subgroups. The dotted line indicates the line of identity (perfect concordance between observed and predicted fracture incidence).

treatment, this may be particularly important when treatment was initiated in a low-risk individual.[7]

Our observation that treatment status did not appear to interfere with fracture prediction should not be taken to mean that treatment was ineffective. Indeed, extensive clinical trials have documented the antifracture benefit of approved therapies and is supported by meta-analysis and systematic reviews.[5,6] Channeling bias could be a factor, with selection of women for treatment who had risk factors not included in FRAX (eg, discordantly low lumbar spine *T*-score, recurrent falls) or with more severe degrees of positivity in risk factors that are included in FRAX (eg, more than one prior fracture, heavier smoking alcohol exposure).[9] Such individuals would have higher fracture risk than that predicted by FRAX, and therefore effective treatment may be manifested by fracture rates roughly equal to those in untreated women. Furthermore, there are large CIs for the fracture incidence in the subgroups examined which reduces the power to determine a significant antifracture benefit. Moreover, the preponderance of major osteoporotic fractures are nonvertebral with a relatively small number of clinically diagnosed vertebral fractures (25.3% in our study), whereas in clinical trials the antifracture effect on vertebral fractures is consistently greater than for nonvertebral fractures.[35] Some medications have no evidence of efficacy for nonvertebral fractures.[5,6] This would make it more difficult to identify a treatment effect on the combined end-point of major osteoporotic fractures. Finally, selection of patients for treatment, persistence and compliance differ in clinical practice from

clinical trials. Randomized controlled trials remain the best way to establish treatment efficacy because they are conducted under optimal conditions for demonstrating treatment efficacy, but effectiveness at the community level may be more difficult to demonstrate.[36] Indeed, we were able to demonstrate a lower high fracture risk in women highly adherent to bisphosphonate use for at least 5 years.

Strengths and weaknesses of this analysis are acknowledged. Although based upon a large cohort, the clinical referral nature could introduce biases. Fracture ascertainment from administrative data sources may be incomplete, particularly for vertebral fractures, although similar algorithms have proven useful for both vertebral and nonvertebral fracture identification.[37,38] We used a FRAX tool that has been directly validated in the Canadian population,[26,27] but there was incomplete information on some of the baseline clinical risk factors (eg, parental hip fracture), and for others proxies were used (eg, smoking, alcohol intake) as previously described.[25] Despite these limitations, predicted 10-year fracture probability agreed very closely with the observed fracture incidence estimated to 10 years among untreated women, suggesting reasonably complete ascertainment of fractures and risk factors. Although the provincial retail database system is highly complete and accurate for prescribed medications, nonprescription drug use (eg, calcium and vitamin D), nonpharmacological interventions (eg, falls prevention and exercise), and patient behavior (eg, following the correct procedure for medication administration) cannot be assessed. We also combined all forms of osteoporosis therapy, whereas these may differ in terms of vertebral and non-vertebral fraction prevention[5,6] and FRAX probability dependency[39–42] for specific classes and agents. Some treatments appear to show efficacy in those at highest risk with little or no efficacy in those at lower fracture risk (such as clodronate,[39] bazedoxifene,[40] and denosumab[43]), whereas others show antifracture effect that is independent of baseline fracture risk (such as raloxifene[41] and strontium[42]). Finally, current medication use was defined from the first 12 months after BMD testing. Individuals who started or stopped treatment after this time would potentially be misclassified. However, the same is true in clinical practice where physicians are unable to predict long-term adherence, or which patients will need treatment initiated at some future date.

In summary, this work suggests that the FRAX tool can be used to predict fracture probability in women currently or previously treated for osteoporosis. However, it may overestimate hip fracture probability in highly adherent long-term bisphosphonate users. Although FRAX should not be used to assess the reduction in fracture risk in individuals in treatment, it may still have value for guiding the need for continued treatment or treatment withdrawal.

Disclosures

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