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ORIGINAL ARTICLE

Prognosis of fracture: evaluation of predictive accuracy of the FRAX™ algorithm and Garvan nomogram

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Abstract
Summary We evaluated the prognostic accuracy of fracture risk assessment tool (FRAX™) and Garvan algorithms in an independent Australian cohort. The results suggest comparable performance in women but relatively poor fracture risk discrimination in men by FRAX™. These data emphasize the importance of external validation before widespread clinical implementation of prognostic tools in different cohorts.

Introduction Absolute risk assessment is now recognized as a preferred approach to guide treatment decision. The present study sought to evaluate accuracy of the FRAX™ and Garvan algorithms for predicting absolute risk of osteoporotic fracture (hip, spine, humerus, or wrist), defined as major in FRAX™, in a clinical setting in Australia.
Methods A retrospective validation study was conducted in 144 women (69 fractures and 75 controls) and 56 men (31 fractures and 25 controls) aged between 60 and 90 years. Relevant clinical data prior to fracture event were ascertained. Based on these variables, predicted 10-year probabilities of major fracture were calculated from the Garvan and FRAX™ algorithms, using US (FRAX-US) and UK databases (FRAX-UK). Area under the receiver operating characteristic curves (AUC) was computed for each model.
Results In women, the average 10-year probability of major fracture was consistently higher in the fracture than in the nonfracture group: Garvan (0.33 vs. 0.15), FRAX-US (0.30 vs. 0.19), and FRAX-UK (0.17 vs. 0.10). In men, although the Garvan model yielded higher average probability of major fracture in the fracture group (0.32 vs. 0.14), the FRAX™ algorithm did not: FRAX-US (0.17 vs. 0.19) and FRAX-UK (0.09 vs. 0.12). In women, AUC for the Garvan, FRAX-US, and FRAX-UK algorithms were 0.84, 0.77, and 0.78, respectively, vs. 0.76, 0.54, and 0.57, respectively, in men.
Conclusion In this analysis, although both approaches were reasonably accurate in women, FRAX™ discriminated fracture risk poorly in men. These data support the concept that all algorithms need external validation before clinical implementation.

Keywords Fracture risk · Prognostic models · Validation

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Introduction

Fragility fracture is an important public health problem because it is common and can result in serious clinical consequences. Among individuals aged 60 years, approximately one out of two women and one out of four men will sustain a fracture during their remaining lifetime [1]. In women, the lifetime of hip fracture is equivalent to or even greater than the lifetime of being diagnosed with breast cancer [2]. Hip fracture is the most serious consequence of osteoporosis because it incurs major health care costs and, like other osteoporotic fractures, is associated with increased risk of mortality [3, 4] and reduced quality of life [5]. At present, a major problem of osteoporosis management is that the majority of men and women who are at high risk of fracture are not diagnosed or treated [6, 7] despite the availability of safe and effective diagnostic tools and therapies. In an effort to help identify patients most likely to benefit from therapy and improve the uptake of treatment, prognostic models for predicting short-term (i.e., 5 to 10 years) fracture risk for an individual have been developed.

Fracture is the outcome of multiple risk factors, and this multiplicity should be taken into account in the assessment of fracture risk for an individual. During the past two decades, several studies have consistently demonstrated that low bone mineral density (BMD) is a major risk factor for fractures in men and women, and individuals with T-scores below −2.5 have progressively higher risk of fracture. However, despite differences in relative risk, most fractures occur in the much larger group of people with T-scores above −2.5 [8–10]. Thus, treatment strategies relying solely on the −2.5 T-score BMD threshold will miss many who are at risk for fracture. It is now clear that, apart from BMD, age, falls, and prior history of fragility fracture are important predictors of fracture risk [11–13].

There are currently two models available for predicting absolute risk of fractures. In 2007, we developed a prognostic nomogram for individualizing the risk of hip fracture, based on five factors identified from the Dubbo Osteoporosis Epidemiology Study data. Fracture outcome was markedly affected by age, BMD (or body weight), and history of prior fracture and falls [14]. In a subsequent study, we extended the model to predicting the 5- and 10-year risk of any fragility fracture [15]. In 2008, the World Health Organization Task Force introduced a country-specific Fracture Risk Assessment Tool (FRAX™), which estimates the 10-year probability of hip fracture or major osteoporotic fractures combined (hip, spine, humerus, or wrist) [16]. The FRAX™ model is based upon data collected from large international cohorts, including Australia, in which clinical risk factors, BMD, and fractures were evaluated. In addition to BMD, advancing age and prior history of fragility fracture as in the Dubbo data set, chronic glucocorticoid use, low body mass index (BMI), parental history of hip fracture, cigarette smoking, and excess alcohol intake were risk factors demonstrated to be most predictive of fracture. It has been validated in 11 independent cohorts, mainly comprised of women [16]. Both the Garvan nomogram and FRAX™ model are available online and being used widely in Australia.

Individualized prognosis is a critical step in the management of osteoporosis because it provides risk estimates for an individual and helps select appropriate intervention. However, it remains less clear whether available prognostic tools accurately predict risk of fracture in independent populations. Therefore, in this study, we sought to assess the ability of the Garvan nomogram and FRAX™ algorithm to predict osteoporotic fracture, defined as "major" in FRAX™, in an independent cohort of Australian men and women with and without fracture, who were not involved in developing either prognostic tool.

Materials and methods

Study design and subjects

The present study was a retrospective validation study in which men and women with a first osteoporotic fracture (cases), defined as major in FRAX™, were compared with individuals without a history of fracture (controls). Similar to the traditional case–control study, the hypothesis of this study was that cases have a higher probability of fracture than controls, as estimated by the FRAX™ and the Garvan prognostic model, given their risk profile prior to the event. This design was selected for the study of validation because fracture is a relatively uncommon event in any short time interval [17].

Medical records of patients attending outpatient Fracture and Bone and Calcium clinics at St. Vincent's Hospital, Sydney, were searched. Where the records were incomplete, patients were contacted to obtain relevant clinical information. Clinical data were obtained from 100 consecutive patients with recent fragility fracture of the hip, spine, humerus, or wrist and 100 consecutive patients without a history of fracture. Patients attending the fracture clinic, having presented to the emergency department and/or admitted under the orthopedics team with a fracture at St. Vincent's Hospital, were included as cases. Controls were men and women referred to the St. Vincent's Bone and Calcium Clinic for further investigation and management of clinical risk factors for fractures.

In total, 530 medical records were reviewed, dating back from July 2008. Patients were included if they were of Caucasian origin and aged between 60 and 90 years old. The age criteria (60–90 years) were based on 60 years

being the minimum age criterion for using the Garvan nomogram and 90 years the maximum age criterion for the FRAX™ algorithm. Fracture cases were included if they had a major osteoporotic fracture as defined in FRAX™, i.e., hip, spine, wrist, or humerus. Patients were excluded if they had been on bone-specific treatment for more than 3 months or had other metabolic bone disorders such as Paget's disease or skeletal metastases. Based on these inclusion and exclusion criteria, 330 records were discarded. In total, 200 people consisting of 144 women and 56 men were included in the analysis. Average duration of time from BMD scan to study entry was 1.7 years in the group with fractures and more than twice that time, 3.7 years, in the group without fractures. As the process of selecting patients involved reviewing medical records to ensure that the inclusion and exclusion criteria were met, the person abstracting the data could not be blinded to the case–control status of each patient.

Estimation of fracture risk

For each individual, relevant clinical information was obtained for estimating the risk of fracture. These information included age, BMI, history of falls in the last 12 months, prior history of fragility fracture, chronic glucocorticoid use (past or present exposure to prednisone equivalent dose of 5 mg or more for more than 3 months), parental history of hip fracture, results of investigation for secondary causes of osteoporosis, presence or absence of rheumatoid arthritis, current cigarette smoking, excess alcohol intake (three or more units of alcohol/day), and BMD measurements of the hip, using dual-energy X-ray absorptiometry (DXA; Table 1). In the fracture group, DXA scan had to be performed before or within 3 months of the incident fracture.

T-scores and relevant clinical data of each individual were entered online to obtain estimates of the 10-year absolute risk of osteoporotic fracture from the Garvan model and the FRAX™ algorithms in November 2008. As there is no available Australian database for FRAX™, UK and US databases were used instead. In men, estimates of fracture risk were calculated both before and after applying the formula converting male-referent T-scores to female-referent T-scores. When entering prior history of fracture data for the group with fractures, the incident fracture that led to study inclusion was not included.

Table 1 Clinical risk factors and predicted fractures included in Garvan nomogram and FRAX™ algorithm

Garvan nomogram	FRAX™ algorithm
Risk factors	Risk factors
Age	Age
Sex	Sex
Femoral neck bone mineral density[a]	Femoral neck bone mineral density
Body weight[a]	Body weight
History of prior fractures since age 50 years[b]	History of prior fractures
History of falls in the previous 12 months	Height
	Parental history of hip fracture
	Current smoking
	Chronic glucocorticoid use[c]
	Rheumatoid arthritis
	Secondary osteoporosis
	Alcohol (three or more units per day)
Fractures (5- and 10-year probability)	Fractures (10-year probability)
Hip	Hip
Clinical spine	Spine
Wrist	Wrist
Humerus	Humerus
Distal femur	
Proximal tibia/fibula	
Distal tibia/fibula	
Patella	
Pelvis	
Rib	
Sternum	
Hands and feet (excluding digits)	

[a] Either bone mineral density or body weight is used in the nomogram

[b] Excluding major trauma fractures

[c] Past or present exposure to prednisone equivalent dose of 5 mg or more for more than 3 months

Data analysis

Using the FRAX™ and FractureRiskCalculator.com websites, we calculated the 10-year risk of fracture for each individual. We then compared the average predicted probability between those who had fractures and those who had not sustained a fracture. The Hosmer–Lemeshow test was used to assess goodness of fit. To assess the discrimination of the prognostic test, we calculated the area under the receiver operating characteristic (ROC) curve (AUC), which reflects the model's ability to discriminate between those who will sustain a fracture from those who will not. An AUC of one represents perfect discrimination, and an AUC of 0.5 reflects discrimination that is no better than random chance. All database management and statistical analyses were performed via the R language system [18].

Results

The study included 56 men (31 cases and 25 controls) and 144 women (69 cases and 75 controls) with osteoporotic fractures defined as major in FRAX™ (Table 2). As expected, men and women who had sustained a major osteoporotic fracture were on average older than those in the control group (Table 2). BMD T-scores were significantly lower in women with a fracture compared with women who did not have a fracture; however, a similar difference was not observed in men. In addition, the prevalence of falls in the last 12 months was significantly higher in the fracture cases than in the controls for both genders. Although the prevalence of secondary causes of osteoporosis (vitamin D deficiency, hyperparathyroidism, hypogonadism, and premature menopause) was comparable between the two groups for either sex, use of corticosteroids was higher in the controls than in the fracture group, due in part presumably to referral bias.

All three algorithms show a high variability in the predicted probabilities of major fracture, with considerable overlap in the distribution between cases and controls (shown in Fig. 1 and summarized in Table 3). In women, the probability of fracture in the cases was consistently higher than in controls for all prognostic models, with $p<0.001$: Garvan (0.33 vs. 0.15), FRAX-US (0.30 vs. 0.19), and FRAX-UK (0.17 vs. 0.10). In men, the Garvan model yielded higher average probability of fracture in the cases than in the controls (0.32 vs. 0.14, $p<0.001$); however, neither FRAX-US nor FRAX-UK predicted higher probability of fracture in the fracture group: FRAX-US (0.17 vs. 0.19; $p=0.32$) and FRAX-UK (0.09 vs. 0.12; $p=0.20$).

Table 2 Baseline characteristics of study participants

	Women		Men	
	Fracture ($n=69$)	No fracture ($n=75$)	Fracture ($n=31$)	No fracture ($n=25$)
Age (years; mean, SD)	73 (8)	68 (8)*	75 (10)	68 (8)*
Body mass index (kg/m^2; mean, SD)	25 (5)	24 (4)	25 (4)	26 (3)
Femoral neck BMD T-score	−2.2 (0.8)	−1.7 (0.8)**	−2.1 (1.1)	−2.1 (0.8)
Antifracture therapy (<3 months)	7 (10%)	0	6 (19%)	0
Falls in the last 12 months	21 (30%)	1 (1%)**	8 (26%)	1 (4%)**
Prior fractures	33 (48%)	–	5 (16%)	–
Secondary causes of osteoporosis	47 (68%)	42 (56%)	19 (61%)	19 (76%)
Rheumatoid arthritis	2 (3%)	0	0	2 (8%)
Family history of hip fracture	0	4 (5%)	0	0
Corticosteroid use	3 (4%)	6 (8%)	3 (10%)	11 (44%)
Smoking	6 (9%)	1 (1%)	2 (6%)	1 (4%)
Alcohol consumption	2 (3%)	0	0	0
Fracture types				
Hip	12	–	9	–
Spine	4	–	3	–
Wrist	40	–	8	–
Humerus	13	–	11	–

Values are *n* (%) unless otherwise specified

n number of patients

*$p<0.01$

**$p<0.0001$

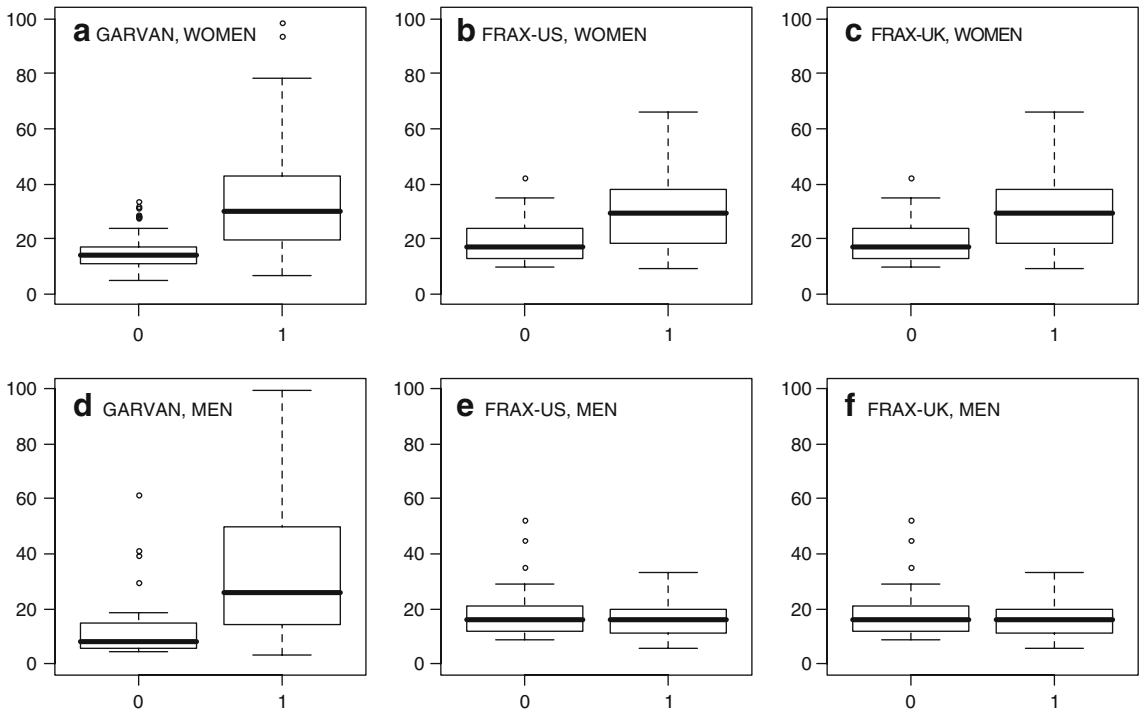

Fig. 1 Descriptive statistics of 10-year predicted probability of fracture for fracture cases (*1*) and controls (*0*) in women (*upper panel* **a**–**c**) and men (*lower panel* **d**–**f**). **a**, **d** Garvan model. **b**, **e** FRAX-US model. **c**, **f** FRAX-UK model

The AUC under the ROC curve for the Garvan model was significantly greater than that for FRAX-US and FRAX-UK in both sexes (Fig. 2). In men, on correcting for male-referent T-scores, the AUC of the FRAX-US model was 0.52, similar to that of the FRAX-UK at 0.55 and, hence, not much different from random allocation (AUC=0.5). Both remained significantly lower than the AUC for the Garvan model (0.76). Since the number of men on corticosteroids was greater in the controls than in the cases, in a subsequent analysis, we excluded this variable and recalculated the AUC. The results show the AUC of both FRAX™ algorithms increased slightly (FRAX-US, 0.63 and FRAX-UK, 0.57) but was still relatively poor.

The concordance in predicted probability between the three prognostic models was modest (Fig. 3). The correlation between the Garvan model and FRAX-US or FRAX-UK was 0.60, which was significantly lower than the correlation between the FRAX-US and FRAX-UK models with a correlation coefficient of 0.94. The difference in probability was mainly in those with high probability of fracture rather than in those with low probability. In the cases, the Garvan model consistently yielded a greater probability of fracture than either the FRAX-US or FRAX-UK model. However, the FRAX-UK model yielded a consistently lower probability of major osteoporotic fracture than the FRAX-US model.

Table 3 Ten-year predicted probability of fracture

Sex/model	Mean 10-year probability of fracture		AUC under the ROC curve
	Fracture	No fracture	
Women			
Garvan	32.8 (18.4)	15.1 (6.2)[a]	0.84 (0.03)
FRAX-US	30.1 (12.9)	18.7 (7.3)[a]	0.77 (0.04)
FRAX-UK	16.8 (8.2)	10.0 (3.9)[a]	0.78 (0.04)
Men			
Garvan	32.0 (23.5)	14.4 (14.0)[a]	0.76 (0.07)
FRAX-US	16.8 (7.1)	19.4 (10.9)	0.54 (0.08)
FRAX-UK	9.4 (4.9)	12.1 (9.0)	0.57 (0.08)

Values are mean (SD)

AUC area under the curve, *SE* standard error

[a] Statistically significant difference between fracture and no-fracture group at $p<0.001$ level

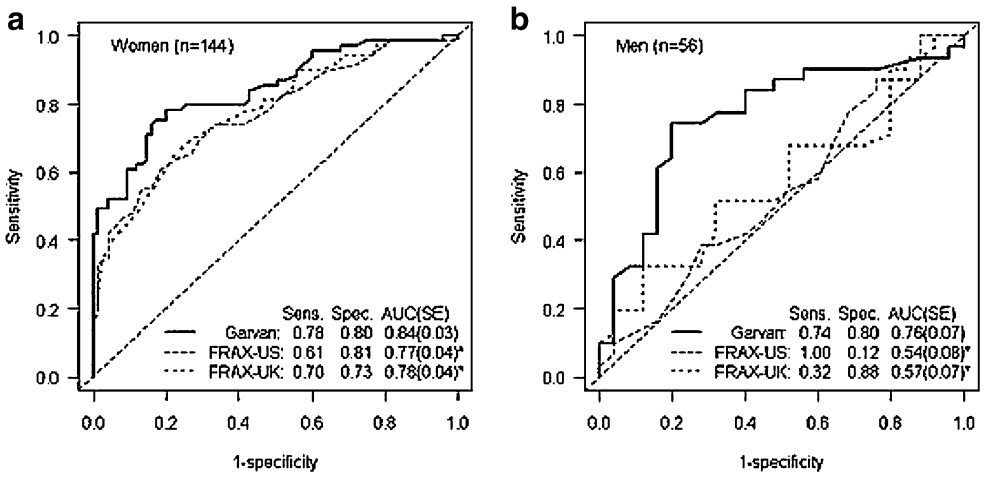

Fig. 2 Area under the curve (*AUC*) for the different prognostic models in women and men

Discussion

Absolute risk is gradually replacing the current T-score-based model in the assessment of fracture risk, as the latter is insufficient. More than 50% of women and 70% of men who sustain a fracture do not have an osteoporotic level of BMD (T-score≤−2.5) prior to the event. Combinations of BMD and non-BMD risk factors increase the reliability of prognosis of fracture (11–13). Therefore, any assessment of absolute risk should be ideally based on multiple risk factors, including BMD. The FRAX™ and Garvan models were developed with that view in mind, but the models

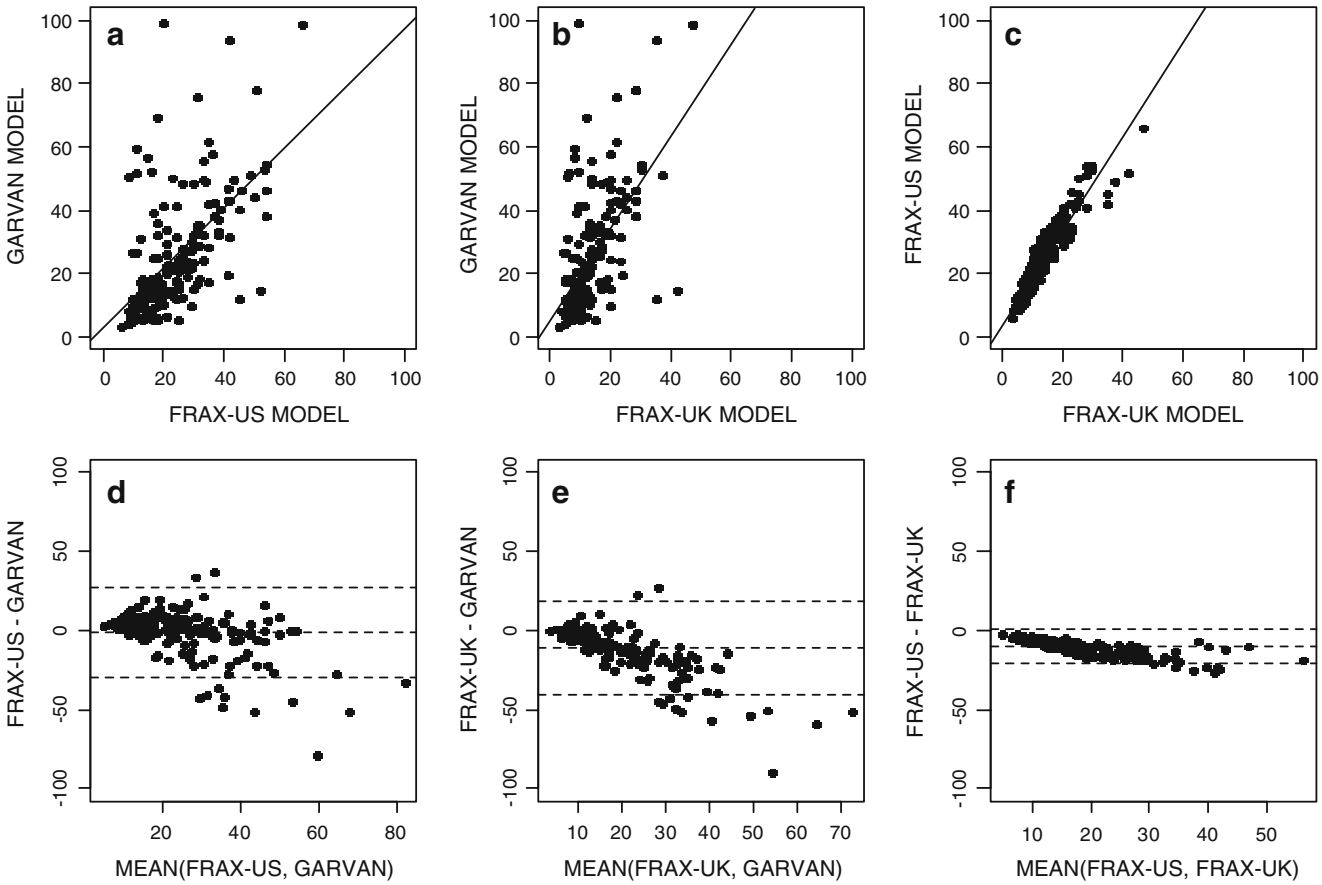

Fig. 3 Correlation between prognostic models in terms of fracture probability, comparing **a** Garvan model with FRAX-US model, **b** Garvan model with FRAX-UK model, and **c** FRAX-UK with FRAX-US model; and correlation between mean vs. difference in the predicted probabilities between prognostic models **d** Garvan and FRAX-US models, **e** Garvan and FRAX-UK models, and **f** FRAX-US and FRAX-UK models

have not been externally validated in independent populations. In this study, we evaluated the models' predictive accuracy in an Australian clinical setting and found that, while the Garvan model had good discriminatory performance in terms of osteoporotic fracture prediction in both men and women, discriminatory performances of the FRAX-US and FRAX-UK models were better in women than in men. These findings deserve reexamination in larger clinical data sets.

The prognostic models were developed from various data sources using different statistical methods, and risk estimates from one environment are not necessarily the same as in another. However, the difference in risk estimates from different models would be expected not to be large enough to be of clinical concern. Our findings suggest that, in an Australian outpatient group, the FRAX-UK consistently underestimated the risk of major osteoporotic fracture compared with FRAX-US or Garvan nomogram and hence appeared particularly unhelpful in men in this population group. The FRAX prognostic models did not perform any better in men on correcting for male-referent T-scores. A possible reason for this is that men were underrepresented in the population studies used to develop the models. In addition, the FRAX™ algorithm includes clinical risk factors that are not included in the Garvan nomogram, including a history of chronic glucocorticoid use. As more men in our control group were on corticosteroids than the fracture group, the multiplicative effect of this clinical variable could have resulted in a higher estimate of absolute fracture risk in men in the control group using the FRAX™ models. However, a reanalysis of the data in men, removing glucocorticoid use as a clinical variable, minimally altered performance of the FRAX-US and UK models.

Prior fracture is an important risk factor in both the FRAX™ and Garvan models, probably more so in the latter than in the former. The absence of prior fracture in the control group could underestimate the predicted probability of fracture, but this could not explain the differences between performance of the FRAX™ and Garvan models in men.

In addition, in this study, the average age of fracture cases was 73 years but that of the no-fracture controls was 68 years. In our original prospective study in which the Garvan nomogram was developed, men and women with fracture were on average 3 years older than those without a fracture (73 versus 70 years, respectively). So, the controls in our study were somewhat younger than the development cohort. However, in Garvan's model, each 8-year increase in age was associated with a 25% increase in the risk of any fracture. Therefore, we think that, while the difference in age could influence the study's results, the extent of this influence is minimal.

An ideal way to gain insight as to why the two models yield different predicted risks of fracture would be to compare the regression coefficients between the two prognostic models. While the regression coefficients of Garvan's nomogram have been published, the FRAX™ models' regression coefficients have not been published. Moreover, it seems the FRAX™ model utilizes interactions between risk factors, while Garvan's nomogram does not include interactive terms in the analyses.

One potential weakness of all prognostic models is that they do not take into account the possible time-related change in risk factors. For example, in the elderly, BMD is known to decline with advancing age, and this decline has been shown to be an independent risk factor for fracture [19]. Therefore, it could be argued that all current prognostic models underestimate the true risk of fracture.

It would be ideal to have a calculated probability of fracture of 1 or near 1 in the cases, considering this group of people had already sustained a fracture, and 0 or near 0 in the controls. However, given the small number of risk factors considered in these models, such a perfect discrimination is unlikely to be achieved. Although Garvan nomogram yielded the highest absolute risk of fracture for both men and women in the fracture group compared with the other prognostic models, the estimated 10-year absolute risk of osteoporotic fracture in our fracture group averaged 33% in women and 32% in men. In the control group, the 10-year absolute risk of osteoporotic fracture averaged 15% in women and 14% in men. Clearly, the estimated fracture risk in the fracture group was not as high as one would expect it to be. However, it should be noted that the predicted absolute risk is a continuous estimate of the risk of fracture in the next 10 years. Based on 35–50% risk reduction from antifracture treatment such as bisphosphonates, the 10-year fracture probability at which treatment becomes cost-effective (intervention threshold) seems reasonable at 20% or greater [20, 21]. This threshold is used in cardiovascular disease prevention [22] and has been recommended by a panel of osteoporosis experts. Based on our study results and the 20% intervention threshold, Garvan nomogram correctly discriminated between those who would benefit from treatment, i.e., the fracture group, from those who would probably not, i.e., the nonfracture group, in both genders.

The present results should be interpreted within the context of some potential strengths and weaknesses. A major strength of the study is that it was derived from an independent clinical representative population not involved in developing either of the prognostic tools. Therefore, the results provide an index of the usefulness of these prognostic models in the real-world primary care setting. The ascertainment of fracture was systematic to minimize misclassification. In addition, the control group had retrospective data for an average period of 3.7 years (from time of BMD scan up to study inclusion), during which

time, none of the control group sustained a fracture. However, the study was based on a modest sample size, particularly in men, which may be inadequate to delineate a small difference between cases and controls that might be seen in larger sample size studies. While the accuracy of a prognostic model is ideally validated in a longitudinal study, it is useful to evaluate prognostic values in a retrospective study as widely used in other fields [23–27]. An important dimension of prognosis is the passage of time, but the present study has not considered time in the analysis. A prospective study would allow a comparison to be made between observed and predicted risk of fracture.

In conclusion, these results imply that osteoporotic fracture is indeed a multifactorial disorder, making it difficult to discriminate those who will sustain a fracture from those who will not. However, our study demonstrates that, in an Australian outpatient setting, both the Garvan nomogram and the FRAX-US algorithm are reasonable tools for individualizing the risk of fracture for a woman. Furthermore, the predictive accuracy of the Garvan nomogram in men suggests that it can be used to individualize the risk of fracture in men. The current data suggest that the FRAX™ algorithm requires calibration with Australian data and revalidation before its use could be justified in the Australian context, especially for men. All prognostic models must be tested in independent populations before they are widely adopted in clinical practice. Nevertheless, these models have the potential to provide valuable clinical guidance for facilitating individualization of decision making for patients and their clinicians.

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Conflicts of interest John A. Eisman's research, including the Dubbo Osteoporosis Epidemiology Study, has been supported by and/or he has provided consultation to Amgen, deCode, Eli Lilly, GE-Lunar, Merck Sharp and Dohme, Novartis, Roche-GSK, Sanofi-Aventis, Servier and Wyeth Australia. He was the editor-in-chief for the *Journal of Bone and Mineral Research* between 2003 and 2007 and serves in the following committees: Department of Health and Aging, Australian Government and Royal Australasian College of General Practitioners.

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