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FRAX based intervention thresholds for Pakistan

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Abstract

Summary We compared, for women in Pakistan, the utility of intervention thresholds either at a T-score ≤−2.5 or based on a FRAX probability equivalent to women of average body mass index (BMI) with a prior fragility fracture. Whereas the FRAX-based intervention threshold identified women at high fracture probability, the T-score threshold was less sensitive, and the associated fracture risk decreased markedly with age.

Purpose The fracture risk assessment algorithm FRAX® has been recently calibrated for Pakistan, but guidance is needed on how to apply fracture probabilities to clinical practice.

Methods The age-specific ten-year probabilities of a major osteoporotic fracture were calculated in women with average BMI to determine fracture probabilities at two potential intervention thresholds. The first comprised the age-specific fracture probabilities associated with a femoral neck T-score of -2.5. The second approach determined age-specific fracture probabilities that were equivalent to a woman with a prior fragility fracture, without bone mineral density (BMD). The parsimonious use of BMD was additionally explored by the computation of upper and lower assessment thresholds for BMD testing.

Results When a BMD T-score ≤−2.5 was used as an intervention threshold, FRAX probabilities in women aged 50 years were approximately two-fold higher than in women of the same age but with no risk factors and average BMD. The relative increase in risk associated with the BMD threshold decreased progressively with age such that, at the age of 80 years or more, a T-score of -2.5 was actually protective. The 10-year probability of a major osteoporotic fracture by age, equivalent to women with a previous fracture, rose with age from 2.1% at the age of 40 years to 17%, at the age of 90 years, and identified women at increased risk at all ages.

Conclusion Intervention thresholds based on BMD alone do not effectively target women at high fracture risk, particularly in the elderly. In contrast, intervention thresholds based on fracture probabilities equivalent to a ‘fracture threshold’ target women at high fracture risk.

Keywords FRAX · Fracture probability · Guidelines · Intervention threshold · Osteoporosis · Epidemiology · Pakistan

Introduction

Osteoporosis is a common, chronic, and costly condition; its major clinical consequence is fracture, with an annual cost exceeding €55.3 billion in Europe in 2019 [1]. This cost accounts for approximately 3.5% of all healthcare spending, indicating a very substantial impact of fragility fractures on present healthcare budgets. Disability due to fragility fractures was greater than that caused by any single cancer, with the exception of lung cancer, and was comparable or greater than that caused by a variety of chronic noncommunicable diseases, such as rheumatoid arthritis, asthma or high blood pressure related heart disease [2]. Fortunately, a wide variety of treatments is available that favourably affect bone mass and thereby decrease the risk of fractures associated with osteoporosis [3]. The use of such interventions by health care practitioners is assisted by techniques that assess patients' fracture risk to optimise clinical decisions about prevention and treatment.

In many countries, intervention thresholds have historically been based on the T-score for bone mineral density (BMD) and/or the presence of a prior fragility fracture. These strategies seem intuitively sound because they cover the operational definition of disease and/or its clinical expression. For example, the National Osteoporosis Foundation (NOF) in the United States recommends BMD assessment in women and treatment is advised in women with a T-score of <–2.5 [4]. Treatment is also recommended in women with a prior spine or hip fracture. More recently, the use of tools designed to calculate fracture risk are increasingly used to improve identification of those at highest risk who would benefit from appropriate treatment. Of these, the FRAX® tool (www.sheffield.ac.uk/FRAX) is most widely used globally. FRAX computes the 10-year probability of a major osteoporotic fracture (MOF, comprising a hip, spine, forearm or humerus fractures) or hip fracture alone from simple, easily captured clinical risk factors (CRFs) with the optional incorporation of femoral neck BMD measured by dual-energy X-ray absorptiometry (DXA) [5, 6]. FRAX models are available for 73 countries covering more than 80% of the world population at risk [7] and have been incorporated into more than 100 guidelines worldwide [8].

A country specific FRAX model for Pakistan was developed and launched in 2020 [9]. Whereas the model should enhance accuracy of determining fracture probability among the Pakistani population, guidance is not yet available to make decisions about treatment [10]. The aim of the present study was to investigate BMD and FRAX-based intervention thresholds for Pakistan.

Methods

Intervention thresholds

The FRAX model for Pakistan is a surrogate model that used the ethnic-specific incidence of hip fracture in Indian men and women living in Singapore, combined with the death

risk for Pakistan. The need for a surrogate model arises because of a dearth of epidemiological data on osteoporosis and fragility fractures [11]. The surrogate model gives somewhat lower 10-year fracture probabilities for men and women at all ages compared to the model for Indians from Singapore, reflecting a higher mortality risk in Pakistan. Two intervention thresholds were tested using the Pakistan FRAX model applied to postmenopausal women. The first was based on BMD measurements from DXA with a threshold for intervention set at a T-score of -2.5. The ten-year probabilities of a major osteoporotic fracture were calculated by age (in 5-year increments from the age of 40 to 90 years) in women at the threshold of osteoporosis (i.e., with a T-score set at -2.5). The age of 40 years was chosen to accommodate women with an early menopause. Women were assumed to have no other clinical risk factors that might contribute to fracture probability.

Many guidelines recommend treatment in women with a previous fragility fracture [3, 4, 8, 12, 13, 14, 15]. For this reason, a second intervention threshold was calculated over the same age intervals, set as the age-specific FRAX probability of major osteoporotic fracture in women with a prior fracture but no other clinical risk factors, using the Pakistan-specific FRAX tool without BMD, and body mass index (BMI) set at 25 kg/m^2, which approximates the mean value for women at the age of 50 years in Pakistan [16].

Assessment thresholds for BMD testing

The intervention threshold based on the fracture probability in women with a prior fracture and no other clinical risk factors was determined without the use of BMD. However, the inclusion of BMD in the assessment calculation of probability improves the accuracy of the assessment [17] but the value of BMD in a clinical context is greatest in individuals in whom fracture probabilities lie close to the intervention threshold [17]. Thus, where access to BMD testing is limited, the use of BMD can be optimised by only testing those individuals in whom probabilities are close to the intervention threshold [18, 19, 20]. In other words, testing is confined to those in whom there is a reasonable likelihood that individuals at high (or low) risk would be reclassified at low (or high) risk on the basis of the BMD test. On this basis, we calculated two assessment thresholds which were applied to the intervention threshold described above [5, 10, 20]:

The threshold probability below which neither treatment nor a BMD test should be considered (lower assessment threshold).

The threshold probability above which treatment may be recommended without the need for BMD (upper assessment threshold).

The lower assessment threshold was based on the 10-year probability of a major osteoporotic fracture equivalent to women without clinical risk factors (and a body mass index of 25kg/m^2 and without BMD). This is consistent with a view in most practice guidelines that individuals without clinical risk factors should not be considered eligible

for assessment [3]. The upper assessment threshold was set at 1.2 times the intervention threshold as used in the UK [20].

FRAX also computes the 10-year probability of hip fracture which can also be used to determine eligibility for treatment. Indeed, guidelines commonly recommend that eligibility for treatment should be predicated on whether the intervention threshold is exceeded for the probability of a major osteoporotic fracture or that for a hip fracture [3, 4, 12]. For the present report, we consider the use of thresholds based on the probability of a major osteoporotic fracture but provide assessment and intervention thresholds for hip fracture probability. These were derived on the same basis as those for a major osteoporotic fracture.

Results

In women with no clinical risk factors, 10-year major osteoporotic fracture probability rose with age from 0.9% at the age of 50 years to 10.6% at the age of 90 years (Figure 1). The increase in fracture probability with age was non-linear and began to flatten off after the age of 80 years due to the competing effect of mortality.

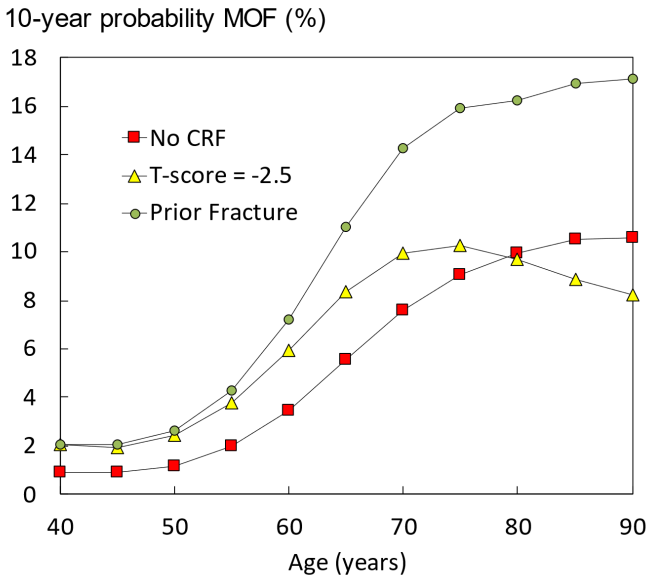

Fig. 1 10-year probabilities of a major osteoporotic fracture (MOF; hip, clinical spine, humerus and forearm) calculated with the Pakistani FRAX model for women.

T-score threshold

In women aged 40 years at the threshold of osteoporosis (a BMD T-score of -2.5), fracture probability was approximately two-fold higher than in women of the same age with no clinical risk factors and an average BMD for such women. The 10-year fracture probability rose progressively with age from 2.1% at the age of 40 years to 10.3% at the

age of 75 years. Thereafter, fracture probability decreased with age and, at the age of 90 years, was comparable to the risk at 65 years (see Figure 1). Indeed, at the age of 90 years, the fracture probability was lower than in women of the same age but with no risk factors (8.2% vs. 10.6%, respectively). Thus, the BMD threshold became less and less clinically appropriate with advancing age.

Prior fracture threshold

The 10-year major osteoporotic fracture probabilities equivalent to women with a previous fragility fracture are shown in Figure 1. The 10-year probability rose with age, from 2.1% at the age of 40 years to 16%, at the age of 75 years and was relatively stable thereafter due to the competing effect of mortality on the fracture risk. Fracture probabilities at this threshold were consistently higher than in women with no clinical risk factors and in women with a T-score of -2.5.

BMD assessment thresholds

The lower assessment threshold, below which BMD tests are of limited value, is shown in Table 1, representing the age-specific probabilities in women with no clinical risk factors. The upper assessment was set at 1.2 times the intervention threshold. The intervention threshold together with the two assessment thresholds is shown in Figure 2. BMD testing (where available) is recommended for fracture probabilities that lie between the upper and lower assessment thresholds.

At the age of 65 years, for example, a BMD test would not be recommended in an individual with a fracture probability below 5.5%. At the same age, a BMD test would be recommended with a fracture probability that lay between 5.5 and 13%. Treatment would be recommended without the requirement of a BMD test (for fracture risk assessment, though it may still be useful for monitoring of treatment) in individuals with a fracture probability that exceeded 13%. Amongst individuals in whom a BMD test was undertaken, treatment would be recommended in those with a fracture probability that was 11% or greater.

Table 1 Ten-year probability of a major osteoporotic fracture (%) and hip fracture (%) by age at the intervention threshold, lower and upper assessment thresholds calculated with FRAX for Pakistan.

	Major osteoporotic fracture			Hip fracture		
Age (years)	Intervention threshold[a] (%)	Lower assessment threshold[b] (%)	Upper assessment threshold[c] (%)	Intervention threshold[a] (%)	Lower assessment threshold[b] (%)	Upper assessment threshold[c] (%)
40	2.07	0.92	2.48	0.04	0.19	0.23
45	2.03	0.91	2.44	0.05	0.25	0.30
50	2.63	1.19	3.16	0.11	0.42	0.50

55	4.28	1.98	5.14	0.24	0.82	0.98
60	7.18	3.43	8.62	0.59	1.71	2.05
65	11.03	5.54	13.24	1.24	3.06	3.67
70	14.24	7.59	17.09	2.06	4.34	5.21
75	15.94	9.07	19.13	3.05	5.49	6.59
80	16.25	9.95	19.50	4.16	6.40	7.68
85	16.94	10.50	20.33	4.64	7.11	8.53
90	17.10	10.57	20.52	4.00	6.14	7.37

[a] The threshold is the probability for a woman with a previous fracture and no other clinical risk factors without BMD.
[b] The lower assessment is the probability for a woman with no clinical risk factors without BMD
[c] The upper assessment was set at 1.2 times the intervention threshold.

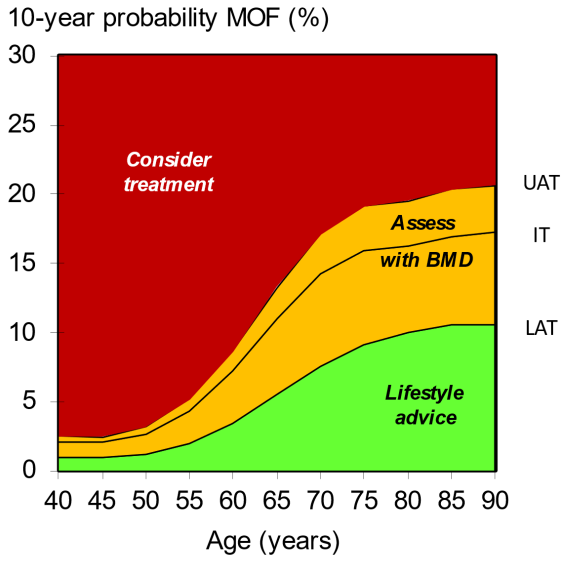

Fig. 2 10-year probability (%) of a major osteoporotic fracture corresponding to the lower assessment threshold (LAT) and upper assessment threshold (UAT) for Pakistan. The red area is where the treatment would normally be recommended, the amber area shows the limits of fracture probabilities for the assessment of BMD, and the green area is where treatment would not normally be recommended. The line within the amber area represents the intervention threshold (IT).

For completeness, Table 1 also provides assessment and intervention thresholds based on hip fracture probability.

Discussion

In this study, we examined two scenarios for the assessment and treatment of women at high fracture risk based on the hybrid Pakistan FRAX tool. The first examined the scenario in which intervention could be recommended with a BMD T-score of -2.5 or less. A fixed threshold based on the T-score of -2.5 has the advantage of simplicity and universality, but it also has important limitations. The present study showed that fracture risk is approximately doubled in women age 40-50 years with a T-score of -2.5 compared to women of the same age with no clinical risk factors (see Figure 1) but, with advancing age, the difference is attenuated. Indeed, from the age of 80 years, a T-score of -2.5 is protective, in the sense that the fracture probability is lower than that of the population with no clinical risk factors at that age. A similar phenomenon is reported in the use of FRAX models elsewhere [21, 22, 23, 24, 25]. The explanation is that the average T-score in the elderly is less than -2.5 since the T-score of the general population decreases with age. Thus, at the age of 50 years the relative risk (RR) of hip fracture in a woman at the threshold value for osteoporosis (T score = -2.5) = 2.9. At the age of 75 years the RR is < 1.0 [26]. Also, a low BMD is associated with an increased mortality which decreases fracture probability. These considerations suggest that fixed intervention thresholds based on the T-score alone become less and less appropriate with advancing age.

A number of additional problems have been identified with the use of BMD as the gateway for fracture risk assessment [23]. Problems of accuracy arise when the T-score is variously calculated based on different referents. Although low BMD is a strong risk factor for fracture, many studies have shown that half or more of all patients presenting with a fragility fracture have BMD T-scores at the lumbar spine or the hip greater than −2.5, i.e., are not osteoporotic [27]. Thus, a BMD-based policy for risk assessment can only capture a minority of the population at high risk of fracture. The policy is also problematic in that it assumes that all prospective patients should have a BMD test and the availability of BMD equipment is limited in Pakistan and elsewhere [28].

In this report, we also present intervention thresholds and BMD assessment thresholds based on fracture probability using FRAX. The approach used was similar to that first adopted by the National Osteoporosis Guideline Group (NOGG) in the UK, and thereafter in many counties of Europe, Eurasia, Latin America [3, 6, 13, 29] and applied in the present study to the FRAX model for Pakistan. Thus, the intervention threshold was set at the fracture probability equivalent to a woman from Pakistan with a prior fragility fracture. The rationale is that if women with a prior fragility fracture are considered eligible for treatment, as commonly recommended, then women without fracture but

with equivalent probabilities should also be eligible for treatment. In contrast to the fixed T-score, a prior fracture was associated with a marked increase in fracture probability over all ages and thus, appears to represent the more suitable intervention threshold.

On this basis, the following management algorithm can be proposed for postmenopausal women. Women with a prior fragility fracture should be considered for treatment. Where there are facilities for BMD assessment, this can be undertaken as a baseline to monitor treatment (commonly by DXA at the lumbar spine). The starting point in the assessment of women without a prior fragility fracture is the presence of a clinical risk factor that alerts the physician to consider osteoporosis. The sentinel clinical risk factor might include one of those used in FRAX but could also include others such as thoracic kyphosis, height loss, disorders associated with osteoporosis etc. The opportunistic case finding strategy arises because screening the general population is not widely recommended in Asia or Europe, though advocated in North America [14, 15]. In those eligible for assessment, FRAX probabilities should be calculated without the inclusion of BMD (Figure 3). Those individuals with fracture probabilities equivalent or lower than women with no clinical risk factors (as used in FRAX) would not be assessed by BMD. At the other extreme, BMD testing is not universally recommended in individuals at high risk. Thus, BMD is reserved for those at intermediate risk. The rationale is that reclassification of risk with the addition of a BMD test (from high risk to low risk and vice versa) is high when fracture probabilities estimated without BMD are close to the intervention threshold, but the likelihood of reclassification decreases the further away the probability estimate is from the intervention threshold [18]. The approach used has been well validated in the UK and Canada [15, 19, 25, 26, 30, 31, 32].

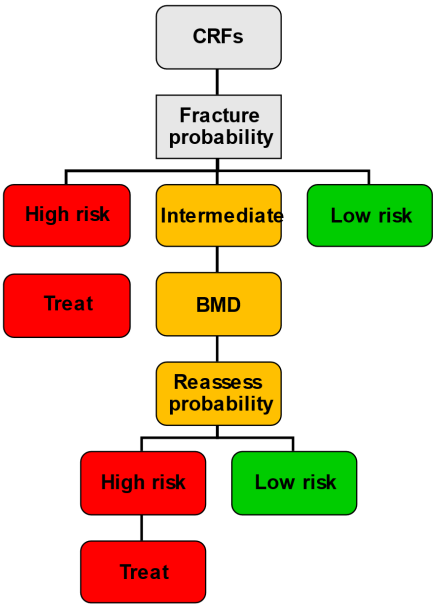

Fig. 3 Management algorithm for the assessment of individuals at risk of fracture (adapted from Kanis 2008 [20] with kind permission from Springer Science and Business Media). CRFs, clinical risk factors.

The attraction of this approach is that this makes efficient use of BMD resources, or indeed can be implemented in the absence of access to DXA facilities as is the case in Pakistan, thereby enfranchising treatment in those without such access. The strategy implies, that patients at high risk, but identified without BMD, would respond to pharmacological intervention. The available evidence suggests that such patients respond to treatment [19, 33, 34, 35, 36, 37 ,38]. A principal reason is that BMD values are low in patients identified with FRAX but without a BMD test [32, 33].

In the present study we have focused on intervention thresholds based on 10-year probabilities of a major osteoporotic fracture. There is, in principle, no reason why a strategy should not be based on the probability of hip fracture. Indeed, screening on this basis has recently been shown to decrease the incidence of hip fracture in the UK [39]. We have also assumed that measurements of BMD are included in the strategy. Where facilities for BMD testing are wanting, FRAX without BMD provides similar predictive value as BMD without FRAX [17]. Nevertheless, the combination of FRAX with BMD where appropriate provides the optimal strategy. A caveat is that FRAX has its own limitations [8] and should not be used to replace clinical judgement.

The approach to intervention thresholds is based on the principles of case finding and do not consider a health economic perspective. Although the approach has been shown to be cost-effective in a UK setting [40, 41], cost-effectiveness will necessarily differ in the Pakistan setting because of different fracture risks and cost. It will be important therefore to underpin these guidelines with an economic assessment. Overcoming these hurdles will, however, improve the delivery of health care to those most at need.

Conflicts of interest G Naureen, H Johansson, E Liu, L Vandenput, M Lorentzon, NC Harvey, E. McCloskey and JA Kanis declare that they have no competing interests in relation to this paper. HJ, EM, NCH, and JAK are the architects of FRAX in which they have no financial interest. JAK is editor in chief of the European office of Osteoporosis International. The manuscript was independently reviewed by the US office.

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