

Identifying Patients at Risk for Osteoporotic Fracture: FRAX and the New NOF Guidelines

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With the recent development of a diverse therapeutic menu for osteoporosis, the need to develop cost-effective strategies to determine which patients would receive the greatest benefit from pharmacologic treatment has increased. The number of osteoporotic fractures among women in the US is increasing significantly over time. More therapy is being prescribed but, as pointed out by Professor John Kanis and colleagues,¹ societies cannot afford to treat all postmenopausal women and older men. The available treatments need to be targeted more effectively toward those individuals with a high risk of fracture, who need treatment, thereby avoiding unnecessary treatment, cost and side effects for individuals with a low fracture risk.

Diagnosing Osteoporosis

In 1994 the World Health Organization (WHO) developed operational criteria for diagnosis of osteoporosis based on measurement of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA), using the concept of *T*-scores.² *T*-scores were defined as the number of standard deviations (SDs) above or below the average peak bone density in young adults of the same sex. A *T*-score between -1 and -2.5 was classified as osteopenia (low bone mass) and -2.5 or lower was considered osteoporosis; a *T*-score of -2.5 or lower with a fragility fracture was considered severe, established osteoporosis. Although originally designed to be used in epidemiologic studies to compare prevalence across populations, *T*-scores are used as diagnostic criteria and were interpreted by third-

party payers and others to be intervention thresholds for pharmaceutical treatment.³

Predicting Fracture Risk

DXA measurements are specific but not sensitive. DXA measurements predict fracture with an increase in fracture risk of approximately 1.5- to 2-fold per SD decrease in BMD. This increase in relative fracture risk for each SD change is called the gradient of risk. Marshall et al⁴ found that each SD change at the hip was associated with a 2.6-fold increased risk of hip fracture, whereas each SD change at the lumbar spine was associated with only a 1.6-fold increased risk of hip fracture. This gradient of risk may help in detecting patients who need therapy; the greater the gradient of risk, the earlier risk of fracture can be predicted.

Unfortunately, DXA bone density measurement is not sufficient to identify all patients at risk. As stated above, DXA measurements are specific but not sensitive. Recent studies have shown that up to half of patients in the community with incident fractures have baseline BMDs above the WHO threshold of -2.5 . In the National Osteoporosis Risk Assessment (NORA), a large community study using peripheral densitometry, more than half the fractures in the community occurred in individuals with *T*-scores greater than -2.5 .⁵ Compared with patients who had normal BMDs, the relative fracture risk in patients with osteoporosis (*T*-score less than -2.5) was increased 2.3-fold, and the relative risk of patients with osteopenia was increased 1.6-fold. However, there were more patients with osteopenia, and therefore, more fractures occurred in the osteopenic group. This observation was reconfirmed by Wainwright et al⁶ using central DXA in the Study of Osteoporotic Fractures. This prospective study showed that 54% of patients who had a hip fracture had a total hip BMD *T*-score greater than -2.5 at baseline, 54% had a lumbar spine BMD *T*-score greater than -2.5 and 42% had both a total hip and lumbar spine *T*-score above -2.5 . This finding was also confirmed in the Rotterdam Study,⁷ a prospective, population-based cohort study of 5,794 men and

women. Only 44% of nonvertebral fractures occurred in women with a femoral neck *T*-score (on DXA) below -2.5 ; the comparable figure for men was 21%. In the OFELY study,⁸ in which 671 postmenopausal women were followed for 9 years, 8% of fractures occurred in women with normal BMDs (*T*-score greater than -1), 48% occurred in women with osteopenia (*T*-score -1 to -2.5) and 44% of fractures occurred in women with osteoporosis (*T*-score less than -2.5). Thus, if treatment decisions are based on BMD alone, about half of postmenopausal women who will experience fractures may not be considered for treatment before a fracture occurs.

Furthermore, BMD measurement may not be accessible worldwide. The US, with a population of about 300 million, has approximately 13,000 DXA machines, but China, a population of 1.3 billion, has only 300 central DXA devices, and India has fewer than 100 DXA machines for a population of 1 billion.⁹ Therefore, many women who will experience fractures in their lifetime will not be identified by BMD measurement.

The ability to predict fracture risk may be improved by understanding what risk factors, independent of BMD, predict fracture. The most important of these risk factors may be age and prior fracture. Looking at the 10-year probability of hip fracture in Sweden, Kanis et al¹⁰ have shown that although a *T*-score of -2.5 in the femoral neck predicts a 2.5% 10-year fracture risk in a 50-year-old, it predicts a risk of 12.5% in an 80-year-old. Prior fracture is also a significant predictor of future risk of fracture. During the Multiple Outcomes of Raloxifene Evaluations trial, the incident rate of vertebral fractures over 3 years in women in the placebo group was 2.5% in those without fracture at baseline, and was 12.5% in those with



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a prevalent fracture at baseline.¹¹ Similarly, in the Fracture Intervention Trial, individuals in the placebo group without prevalent fracture at baseline had a 1.6% risk of fracture over 3 years, compared with 8% in those with prevalent fracture.^{12,13}

Assessing Fracture Risk Using FRAX, the New WHO Fracture Risk Calculator

In an effort to identify candidate clinical risk factors that could be integrated in a clinically useful way, a WHO scientific group first reviewed the literature using meta-analysis to identify risk factors for fracture independent of BMD. Second, they combined data from 12 cohorts around the world, approximately 250,000 person-years, approximately 60,000 patients and more than 5,000 fractures. Using this analysis, candidate risk factors have been proposed. To be chosen, each of these risk factors needed to be validated in multiple

populations: adjustable for age, sex and type of fracture; intuitive; amenable to therapeutic manipulation; and readily accessible for primary practitioners. Thus, factors such as calcium deficiency and risk of falling, which would not be easy for primary care physicians to measure, were not considered.¹³

As listed in the Table, the risk factors that have been suggested by the

Table. Risk Factors Used in FRAX

Age
Femoral neck BMD or BMI
Fragility fracture since age 50
Parental history of hip fracture
Current smoking history
Alcohol use greater than 2 units daily*
Cortisone use [†]
Rheumatoid arthritis
Secondary osteoporosis [‡]

*Unit = one medium glass of wine or a half pint of beer.

[†]Defined as 5 mg or more for 3 months or more.

[‡]For example, type 1 diabetes, osteogenesis imperfecta in adults, longstanding hyperthyroidism, hypogonadism, premature menopause, chronic malabsorption and chronic liver disease.

WHO include age,¹⁰ prior fracture,¹⁴ BMD of the femoral neck¹⁵ or body mass index (BMI),¹⁶ past or present corticosteroid use,¹⁷ family history of fracture,¹⁸ current smoking,¹⁹ and ingestion of more than two units of alcohol per day,²⁰ as well as secondary osteoporosis associated with disorders such as rheumatoid arthritis.²¹ BMI may be used where there is limited access to DXA scanning, as low BMI is associated with significantly increased fracture risk. These clinical risk factors can be used to generate probabilities of fracture with or without BMD. The clinical risk factors may be added, but the sum would vary depending on the risk factors added because they have differing weights. These risk factors improve the prediction of fracture risk by improving the gradient of risk.²² If information on a patient's BMD is not available, these risk factors can still be used to estimate 10-year fracture risks.

This new WHO algorithm, or FRAX, predicts the probability that a patient will experience a hip fracture or any one of four major clinical fractures (clinical spine, forearm, hip or shoulder) over the next 10 years.²³ The intervention threshold depends on an individual country's fracture rates, costs, resources and willingness to pay.²³⁻²⁵ In the U.S. the intervention threshold has been set by National Osteoporosis Foundation (NOF) guidelines (see below).

Strengths of FRAX. FRAX represents a significant advance for the menopause practitioner as an easy-to-use calculator of fracture risk that can use clinical risk factors alone or in combination with BMD. FRAX is a fracture risk platform that can be used globally; the decision to treat will be based on regional willingness to pay using fracture risk rates, costs and intervention thresholds. While currently available only on the Internet ([http://](http://www.shef.ac.uk/FRAX)

www.shef.ac.uk/FRAX), FRAX will be available on updates to BMD software by central DXA manufacturers in the US later this year. Clinical risk information can be entered by bone

NOF Guidelines

In the first update since 1999, the NOF has issued new treatment guidelines using FRAX.²⁶ The guidelines suggest that among men and women

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density technologists. Future BMD printouts will include BMD, *T*-score and FRAX estimates of 10-year hip and any one of four fracture risks. Availability of FRAX will allow the clinician to reassure younger women with osteopenia and lower fracture risk that pharmacologic treatment may provide little benefit. Similarly, FRAX will allow the clinician to treat older patients who do not have osteoporosis but are at sufficiently high fracture risk to warrant drug intervention.

Limitations of FRAX. While FRAX has many strengths, it also has many limitations. Multiple candidate risk factors that are independent of BMD and have been associated in studies with fracture risk were not included. This was due to limitations of the epidemiologic data and was, in part, determined by the need to keep the model input simple. Some examples of data not included are ultrasound measurement of BMD, bone markers, and vertebral fracture and spine BMD measurements. The model does not account for the increased risk of multiple prevalent fractures versus single fractures, or the dose response of prednisone use higher than 5 mg daily for 3 months or alcohol use far greater than 3 units daily. The model uses only femoral neck BMD and ignores lumbar spine BMD. Lumbar spine BMD should be considered by clinicians, especially if it is considerably lower than hip BMD.

age 50 or older, those with one or more of the following criteria should be treated with FDA-approved pharmacologic therapy:

- 1) History of hip or radiographic or clinical vertebral fracture,
- 2) A *T*-score less than -2.5 at the femoral neck, total hip or lumbar spine, or
- 3) Low bone mass (ie, osteopenia: *T*-scores of -1 to -2.5 at the femoral neck, total hip or lumbar spine) and either:
 - A 10-year risk of hip fracture greater than 3% by FRAX,
 - A 10-year risk of major osteoporotic fracture (clinical spine, forearm, hip or shoulder) greater than 20% by FRAX

These recommendations are based on a cost-effectiveness analysis showing that drug treatment is "cost-effective" if the patient has a greater than 3% 10-year risk of hip fracture.²⁷ Treatment is cost-effective for any woman who meets any one of the NOF criteria.²⁷

Limitations of the NOF guidelines. As pointed out by Cummings et al,²⁸ there are multiple assumptions underlying the NOF cost-effectiveness analysis. The NOF guidelines assumed that drug therapy reduces the risk of all clinical fractures by 35%, regardless of bone density or presence of vertebral fracture. As Cummings and colleagues point out, although

bisphosphonates reduce the risk of vertebral fractures, we do not know if there will be significant reductions in the risk for other osteoporotic non-vertebral fractures in women who do not have vertebral fracture or osteoporosis by BMD measurement.^{29,30}

The NOF guidelines also recommend treatment of women with lumbar spine *T*-scores of less than -2.5 . However, the FRAX model currently includes only the femoral neck. Medications for osteoporosis vary with respect to cost, adverse effects and risk reduction. The NOF guidelines allow a physician to choose any drug for a patient who qualifies for treatment.

Strengths of the NOF guidelines. The new NOF guidelines represent a major paradigm switch in the treatment of osteoporosis; they now include use of fracture risk, not only BMD, and/or presence of one or more risk factors. Most older women and elderly men will be eligible for therapy. Many young women with osteopenia or low bone mass at low risk may not be eligible for treatment. We will need further randomized trials to confirm that individuals with low bone mass at high risk will benefit from existing therapies.

Conclusions

There has been a paradigm shift in terms of choosing which patients should receive pharmacologic treatment for osteoporosis. With this shift, treatment decisions will be based on fracture risk rather than BMD assessment alone. The level of fracture risk at which treatment will occur (ie, the intervention threshold) will be determined by regional willingness to pay. ■

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