To Treat or Not to Treat: Reducing Fracture Risk in Postmenopausal Women

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Of the many unmet needs in the management of osteoporosis, perhaps the most fundamental is a general failure to identify patients at high risk for fracture who are likely to benefit from pharmacological intervention.

To help identify patients at high risk for fracture, the National Osteoporosis Foundation (NOF) has developed comprehensive evidence-based clinical practice guidelines[1] for the prevention and treatment of osteoporosis. An important component of the NOF guidelines is the use of the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX)[2] to provide a 10-year probability of fracture. (Additional information on the management of postmenopausal osteoporosis and FRAX is available in the 2010 Position Statement by The North American Menopause Society.[3])

FRAX

Background

There is a robust relationship between bone mineral density (BMD) and fracture risk, with approximately a doubling of fracture risk for every 1 standard deviation decrease in BMD.[4] However, exclusive reliance on a diagnostic classification of osteoporosis (T-score ≤ –2.5) will miss many patients who go on to fracture, most of whom have a T-score greater than –2.5.[5] Although fracture risk rises as BMD declines, there are many more patients with T-scores above –2.5 than at or below, resulting

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in a greater total number of fractures in those patients who do not have a densitometric classification of osteoporosis. Hence, a combination of clinical risk factors (CRFs), particularly advanced age and previous fracture,[6] and BMD is a more accurate predictor of fracture risk.[7]

Due to the limited availability of dual-energy x-ray absorptiometry (DXA) in some world regions and the imperative to reduce the burden of osteoporotic fractures, WHO embarked on a massive project to analyze data from 12 large prospective epidemiological studies involving about 60,000 men and women in different world regions, with over 250,000 person-years of observation and more than 5,000 fractures reported.

The result of this project was FRAX, a computer-based algorithm for estimating the 10-year probability of major osteoporotic fracture (ie, clinical spine, hip, proximal humerus, distal forearm). The input for FRAX is the patient's age, sex, height, weight, femoral neck BMD if available, and a "yes" or "no" answer for 7 CRFs:

- Previous "spontaneous" or fragility fracture as an adult
- Parent with hip fracture
- Current tobacco smoking
- Use of chronic glucocorticoids (at least 5 mg prednisolone for at least 3 months)
- Confirmed rheumatoid arthritis
- Secondary osteoporosis, such as type 1 diabetes, osteogenesis imperfecta in adults, untreated longstanding hypothyroidism and hypogonadism, or premature menopause
- Alcohol intake greater than 3 units per day

FRAX is continually upgraded to correct errors, enhance its usability, and incorporate new data.

FOCUSPOINT

The use of FRAX provides a quantitative estimation of fracture risk that is based on robust data in large populations of men and women with ethnic and geographic diversity.

Benefits

The use of FRAX provides a quantitative estimation of fracture risk that is based on robust data in large populations of men and women with ethnic and geographic diversity. Expression of fracture risk as a probability offers greater clinical utility than relative risk. When combined with cost-utility analysis, a fracture risk level at which it is cost-effective to treat can be derived. FRAX can be used to estimate fracture probability without femoral neck BMD, providing a helpful clinical tool when DXA testing is not available or accessible.

Limitations

The selection of FRAX input requires good clinical judgment. For example, a patient may report a diagnosis of rheumatoid arthritis when the actual diagnosis is osteoarthritis. An informed health care professional must take care that only correct responses are used. FRAX may underestimate or overestimate fracture risk due to the dichotomous (yes or no) input for risk factors, which in reality are associated with a range of risk that vary according to dose or severity. For example, taking prednisone 40 mg per day for the past 5 years certainly imparts a greater fracture risk than a history of prednisone 5 mg per day for 6 months in the remote past, yet the FRAX input of "yes" is the same for both.

FRAX is only validated in untreated patients, with uncertainty as to how long, if ever, a patient must be removed from treatment in order to be considered

untreated. FRAX is validated for four US ethnicities, with uncertainty as to the application of FRAX for patients of other ethnicities or a mix of ethnicities. The selection of risk factors for secondary osteoporosis may not be clear, and it may not be recognized by some that this is a "dummy" risk factor that plays no role in the calculation of fracture probability when the femoral neck BMD is entered in FRAX.

The range of error for fracture probability is not known. For example, if the calculated 10-year probability of major osteoporotic fracture is 18%, it is not clear whether that value is really ± 2%, ± 4%, or something else. Not all risk factors for fracture are considered. For example, frailty and falls are major concerns in the pathogenesis of hip fractures in the elderly but are not included in the fracture risk calculation since they are not likely to be altered by drug therapy. Since the BMD input for FRAX is for the femoral neck only, FRAX may underestimate fracture risk in patients with a low lumbar spine BMD and a comparatively good femoral neck BMD. These limitations must be recognized when using FRAX to make clinical decisions.

NOF Guidelines

Background

The NOF's *Clinician's Guide to Prevention and Treatment of Osteoporosis*[1] is a helpful desktop reference to assist health care professionals in all aspects of managing osteoporosis. The guide applies to postmenopausal women and men aged 50 and older of all ethnicities. The NOF developed the guide through a review of the best available medical evidence, with establishment of thresholds for initiating pharmacological therapy to reduce fracture risk based on cost-utility analyses that considered the cost-effectiveness of treatments and competition for resources in the United States.[8,9]

The guide also provides information on the epidemiology of osteoporosis, consequences of osteoporotic fractures, and evaluation of patients at risk for fracture. Recommendations are given on lifestyle measures to improve bone health, calcium and vitamin D intake, fall risk reduction, and evaluation of patients for secondary causes of osteoporosis.

Benefits

The NOF guide applies to a broad range of patients who may be candidates for treatment. By incorporating FRAX into the decision-making process for untreated patients with osteopenia, it allows for quantitative estimation of fracture risk to play a role, displacing some of the "guesswork." By combining validated and easily obtainable CRFs and BMD in a quantitative manner, patients at high risk are more easily identified. Since high-risk patients are most likely to benefit from therapy, this directs limited health care resources toward those who need it the most. It is likely that use of the NOF guide will result in more elderly postmenopausal women with slightly low BMD being treated and fewer early postmenopausal women being treated.

FOCUSPOINT

By combining validated and easily obtainable clinical risk factors and bone mineral density in a quantitative manner, patients at high risk are more easily identified.

Limitations

The NOF guide may identify some elderly patients with slightly low BMD as candidates for treatment, although there is no evidence that patients with T-scores greater than –1.5 will benefit from fracture risk reduction. Despite repeated statements that the recommendations are intended to be a helpful clini-

cal tool and not the final determinant in making treatment decisions, there is a risk that health care policymakers, regulators, and payers will select portions of the guide to restrict care in those who might actually benefit from therapy.

FIGURE 1. Estimation of fracture risk with the Fracture Risk Assessment Tool (FRAX). A 55-year-old postmenopausal white woman with no clinical risk factors for fracture has a femoral neck T-score of –1.9. Since she has osteopenia, FRAX is used to evaluate the 10-year probability of fracture. The calculated values are below the National Osteoporosis Foundation (NOF) thresholds for treatment, suggesting that the patient may be managed with nonpharmacological therapy. Treatment decisions should consider all clinical factors as well as the NOF treatment thresholds.
FRAX website accessed November 20, 2011. Reproduced with permission from the World Health Organization.[2]

The NOF treatment recommendations, which are based on cost-effectiveness modeling that includes assumptions on the cost of drugs, may not apply to situations where drugs (eg, generic alendronate) are much less expensive than considered in the analysis. In such cases, the traditional method of making treatment decisions based on a risk/benefit analysis may be most appropriate.

Managing Patients to Reduce Fracture Risk

Evidence-based medicine is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[10] Clinical practice guidelines are recommendations intended to influence the clinical decisions of health care providers,[11] usually based on the best available medical evidence evaluating the efficacy, safety, and necessity of an intervention, and sometimes considering health care policy, cost-effectiveness, and expert opinion.

Treatment decisions require the application of clinical skills in addition to knowledge of medical research and guidelines.[12] For example, most patients treated for osteoporosis in clinical practice would probably not qualify for participation in the pivotal clinical trials that demonstrated efficacy and safety of the drugs used to treat them.[13] Medical evidence alone does not provide the answers to many clinical questions that arise in the care of individual patients.

When evaluating the skeletal health status of patients, all available clinical information should be considered. The treatment of a postmenopausal woman with a T-score of –2.5 or less or a clinical diagnosis including a personal history of fragility fracture regardless of T-score is generally supported by the evidence and probably very appropriate. However, a T-score of –2.4 is not significantly different than –2.5, even though the diagnostic classification is different and guidelines may suggest a different approach to management. Thus, slavish adherence to cutoffs in guidelines may not always be in the best interest of our patients.

A major challenge in clinical practice is making treatment decisions for a patient with osteopenia (T-score between –1.0 and –2.5) when fracture risk may be low or high depending on age and other CRFs. FRAX is helpful in estimating the 10-year probability although an informed clinician must be aware of potential factors that may result in underestimation or overestimation of fracture risk. The clinical utility of FRAX is illustrated in Figures 1 and 2. The early postmenopausal woman with osteopenia whose data is entered into FRAX (Figure 1) does not

meet the NOF guidelines for initiation of pharmacological therapy, while an older woman with the same T-score (Figure 2) has a much higher risk of fracture that does meet the NOF guidelines for starting treatment. Here, FRAX is able to discriminate differences in fracture risk despite identical T-scores, resulting in different treatment recommendations. (The fracture risk assessment tool can be found online at http://www.shef.ac.uk/FRAX.)

Other important factors include the presence of medical conditions that may affect fracture risk (eg, frailty), response to therapy (eg, malabsorption), or choice of drug (eg, esophageal stricture), as well as the patient's past drug experiences, fears, medication affordability and availability.

Finally, the patient's desire to be treated and willingness to accept pharmacological therapy should be evaluated. If the patient has not fully accepted the idea of treatment, compliance and persistence may be poor and the desired clinical outcome (fracture risk reduction) may not be achieved. When the patient has a good understanding of the disease state, the goal of therapy, and the possibility of side effects, then long-term clinical outcomes are likely to be much better.

FIGURE 2. Estimation of fracture risk with the Fracture Risk Assessment Tool (FRAX). This is a 76-year-old postmenopausal white woman with no risk factors for osteoporosis and the same T-score (–1.9) as the younger woman in Figure 1. When FRAX is used to calculate the 10-year probability of fracture, the value for hip fracture (3.1%) exceeds the National Osteoporosis Foundation (NOF) intervention threshold for initiation of pharmacological therapy. This suggests that it is cost-effective to start drug therapy and illustrates the effect of age on fracture risk, independently of T-score. Treatment decisions should consider all clinical factors as well as the NOF treatment thresholds. *FRAX website accessed November 20, 2011. Reproduced with permission from the World Health Organization.*[2]

Conclusions

FRAX estimation of 10-year fracture probability provides a better estimation of fracture risk and greater clinical utility than previous qualitative methods and those using relative risk of fracture. The NOF guide is a comprehensive desktop reference for managing skeletal health, with recommendations that identify high-risk patients who are most likely to benefit from therapy.

Appropriate use of these tools requires a thorough understanding of their limitations as well as their benefits. The final decision to treat, and the selection of treatment, rests in the hands of a well-informed health care professional who uses these tools wisely and considers all other available clinical information.

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For a **PATIENT HANDOUT** on reducing fracture risk in midlife women, see page 47.

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