

ASK THE EXPERT

The Facts on FRAX

A new fracture-risk assessment tool developed by the World Health Organization is poised to dramatically reduce the number of people experiencing bone fractures as a result of osteoporosis. Adding to the tool's clinical credibility is that it has received the endorsement of the International Osteoporosis Foundation and the Washington-based National Osteoporosis Foundation.

Called FRAX, the computer-based algorithm incorporates bone mineral density (BMD) and several specific clinical risk factors to generate models for the 10-year probability of fracture in men and women. To use the tool, clinicians enter a patient's age and body mass index into an online interface, along with answers to a series of questions regarding previous fracture history, parental fracture history, smoking status, alcohol consumption, long-term use of oral glucocorticoids, and history of diseases such as rheumatoid arthritis that increase osteoporosis risk. If available, femoral neck BMD, entered as either a z score or T score, can also be entered. In seconds, "FRAX generates a 10-year fracture-probability estimate that can be used alone or with BMD to enhance fracture risk prediction," said Dr. John A. Kanis, professor emeritus at the University of Sheffield (England). Dr. Kanis developed the algorithm along with colleagues in the WHO Collaborating Centre for Metabolic Bone Diseases at the university. He is director of the center.

"In addition to fracture risk, the algorithm derives hazard functions of death

and fracture using Poisson regression. These hazard functions are continuous as a function of time, which permit the calculation of the 10-year probability of hip, spine, shoulder, or wrist fracture, and the 10-year probability of hip fracture."

FRAX (online at www.shef.ac.uk/FRAX/reference.htm) was developed using information from the primary data of nine different population-based cohorts from

Europe, North America, Asia, and Australia, and it was validated in 11 independent cohorts with a similar geographic distribution, said Dr. Kanis. "The use of primary data for the model construct permits the interaction of each of the risk factors to be determined," he noted, providing the accuracy necessary for computing fracture probability.

In this month's column, Dr. Kanis talks about incorporating FRAX into clinical practice, as well as the clinical advantages and limitations of the tool.

Rheumatology News: What are the advantages of FRAX compared with existing risk assessment tools?

Dr. Kanis: FRAX is the only tool that provides absolute fracture risks; it can be used for both men and women; and it has been extensively validated. The large sample on which the construct is based permits the examination of the general relationship of each risk factor by age, sex, duration of follow-up, and, for continuous variables [BMD and BMI], the relationship of risk with the variable itself in a manner hitherto not possible. The use of primary data

also eliminates the risk of publication bias.

In addition, because fracture probability varies markedly in different regions of the world, the FRAX model has been calibrated by level of risk to countries where the epidemiology of fracture and death is known. At present, models are available for China, France, Japan, Spain, Sweden, Turkey, the United Kingdom, and the United States, and others are being developed. In the absence of a model for a particular country, a model for a surrogate country that is likely representative of the index country model should be chosen.

RN: How easily can FRAX be incorporated into clinical practice?

Dr. Kanis: The calculation of fracture probability is straightforward from the Web site. If online access is limited, paper charts can be downloaded, which give ranges of fracture probabilities according to the number of clinical risk factors. Ultimately, the tool will become available on thumb drives and other devices, and plans to incorporate it into BMD machines are being discussed.

RN: How can FRAX be used to guide management decisions?

Dr. Kanis: Doctors will require guidance on how to translate fracture probabilities into management decisions. Such guidance is unlikely to be provided by NICE, at least in the short term. The National Osteoporosis Guideline Group (NOGG) has prepared guidance for the United Kingdom which is currently being circulated for wider consultation. Finalized guidelines should be available in the next few months. In brief, NOGG recommends that FRAX assessments be made in men and women with one or more of the not-

ed clinical risk factors. Guidance, based on the fracture probability, is then given on the need to undertake a BMD test and/or whether to recommend treatment. Physicians using FRAX in the United Kingdom will be able to input fracture probabilities directly to a NOGG Web site for the translation of probabilities to management decisions. Guidelines to accommodate FRAX have also been developed for the United States, Europe, and Japan. In the United States specifically, the National Osteoporosis Foundation recently released the Clinician's Guide to Prevention and Treatment of Osteoporosis, which instructs clinicians on how to incorporate FRAX into their practices.

RN: What are the limitations of FRAX?

Dr. Kanis: There are several caveats and limitations that should be mentioned. Several of the clinical risk factors identified take no account of dose-response, but instead give risk ratios for an average dose or exposure. However, there is good evidence that the risk associated with the excess alcohol consumption and the use of glucocorticoids, for example, is dose-responsive. In addition, the risk of fractures increases progressively with the number of prior fractures. These limitations should be recognized when interpreting the FRAX results in the clinic, as should the need for cautious interpretation of the results in patients taking treatments for osteoporosis.

For these reasons, FRAX should not be considered the preferred method that replaces clinical judgment. Rather, it should be considered a platform technology that aids clinical judgment. ■

By Diana Mahoney, New England Bureau



JOHN A. KANIS, M.D.

Teriparatide Lowers Hip Bone Density but Also Fracture Risk

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Women with osteoporosis treated with teriparatide often gain lumbar spine bone mineral density and lower their risk of vertebral fracture, even if they lose hip bone mineral density, Dr. Nelson B. Watts reported in a poster presentation at the annual meeting of the International Society for Clinical Densitometry.

Previous studies have shown that increased areal lumbar spine bone mineral density (BMD) accounts for 30%-41% of the reduction in vertebral fracture risk from teriparatide treatment. In clinical practice, loss of BMD in other areas, such as the femoral neck, has been viewed by some as a lack of response to therapy.

The current post hoc analysis of data on 1,216 women found vertebral fracture risk was indepen-

dent of gains or losses in femoral neck BMD in women taking teriparatide, compared with women on placebo, reported Dr. Watts, program director of the bone health and osteoporosis center at the University of Cincinnati.

The investigators analyzed data on women with a history of vertebral fractures randomized to take 20 or 40 mcg/day of teriparatide or placebo in the double-blind Fracture Prevention Trial. The women self-administered the treatments subcutaneously and also received daily supplements of 1,000 mg of calcium and 400-1,200 IU of vitamin D.

The current analysis focused on a subset of 1,216 women who had femoral neck BMD measured both at baseline and after 12 months of therapy by dual-energy x-ray absorptiometry (DXA) and who had lateral thoracic and lumbar spine radiographs taken both at baseline and at the study

end point, a median of 19 months from baseline.

The risk of vertebral fracture was calculated for women on placebo and for women in four subgroups of teriparatide therapy based on changes in femoral neck BMD 1 year from baseline. The women on teriparatide were divided as follows: those who lost more than 4% of femoral neck BMD, those who lost up to 4% in density, those who gained up to 4% in density, and those who gained more than 4% in femoral neck BMD.

In the combined teriparatide groups, a significantly greater proportion (35%) gained more than 4% in femoral neck BMD, compared with those on placebo (17%).

Women also showed significant reductions in vertebral fracture

risk on teriparatide therapy, compared with placebo, regardless of changes in femoral neck BMD at 1 year, Dr. Watts reported.

Among women with greater



In the combined teriparatide groups, 35% gained more than 4% in neck BMD versus 17% of those on placebo.

DR. WATTS

than a 4% loss in femoral neck density, 2 (2%) of 82 women on teriparatide developed vertebral fractures, compared with 14 (23%) of 61 women on placebo. Among women with up to a 4% loss in femoral neck density, 5 (3%) of 182 women on teriparatide and 15 (10%) of 149 women on placebo developed vertebral fractures.

Among women with up to a 4% gain in femoral neck BMD, vertebral fractures were seen in 5 (3%) of 182 women on teriparatide and 19 (15%) of 124 women on placebo. Among women with greater than a 4% gain in femoral neck density, 14 (5%) of 282 on teriparatide and 9 (14%) of 66 on placebo developed vertebral fractures.

Lumbar spine BMD increased significantly more in women on teriparatide, compared with placebo, regardless of changes in femoral neck density. Lumbar spine density increased by 3% or greater in 78%-92% of women on teriparatide in the four femoral neck subgroups.

The study was funded by the maker of teriparatide, Eli Lilly & Co., which also provided the layout for the poster. Dr. Watts is a consultant for the company. His report was rated one of the top posters at the meeting. ■