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NEWS

When to Treat Bone Fragility, 2010: FRAX® and Beyond

Third IBMS BoneKEy Online Forum examined the current and future use of FRAX® in assessing fracture probabilities and determining intervention thresholds

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Introduced in 2008, FRAX®, the World Health Organization Fracture Risk Assessment Tool available online at http://www.shef.ac.uk/FRAX/, has already become a popular instrument to calculate an individual's risk of sustaining an osteoporotic fracture. Indeed, the FRAX® website, where physicians can enter information about a patient's risk factors for fracture into a calculation tool that provides for each patient a ten-year probability of fracture, now receives between 50 to 60 thousand hits each day, totaling approximately 20 million hits each year. However, despite the rising usage of FRAX®, the fracture probability estimate that it provides can be viewed not only as a kind of end-result, but also as the starting point for a number of complicated questions still being addressed by fracture experts. For instance, what is the best way to determine the FRAX® fracture probability at which a therapeutic intervention should be recommended? Is the FRAX® fracture probability estimate more accurate than one provided by a simpler risk assessment tool, and can it be refined further? Should patients with low bone mineral density (BMD) alone, *i.e.*, in the absence of a high fracture probability according to FRAX®, still be treated, as suggested by guidelines from the National Osteoporosis Foundation (NOF)?

Recently, these important questions were the focus of When to Treat Bone Fragility, 2010: FRAX® and Beyond, the third IBMS BoneKEy Online Forum; the Forum, a webinar that took place on February 16th, 2010, can be heard in its entirety on BoneKEy here. Participants in the Forum included presenter John Kanis (WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield), and panelists Steven Cummings (University of California, San Francisco), Adolfo Diez-Perez (Autonomous University of Barcelona), Eugene McCloskey (University of Sheffield), and Michael McClung (Oregon Osteoporosis Center). Participants agreed that FRAX® will play an increasingly large role in the osteoporosis arena, both as a key clinical tool for physicians, as well a vital educational tool for both doctors and patients, even as the bone field continues to address the thornier questions the advent of FRAX® has raised.

FRAX® Identifies Reversible Risk, but Many Questions Remain

For a risk assessment tool to be truly useful, it must not simply identify patients at risk; it must identify risk that is reversible through therapeutic intervention. Dr. Kanis first noted that for some of the risk factors included in FRAX®, including low BMD, prior fractures, and glucocorticoid use, clinical trials have already demonstrated that treatment does in fact lower the risk of fractures in patients having those risk factors. Second, other risk factors in FRAX®, such as smoking and alcohol use, have been shown to be neutral with regard to treatment efficacy. “We managed to go systematically through nearly all the phase 3 studies to address this, and for the remaining risk factors – age, BMI, family history, smoking, and alcohol – the risk factor doesn't affect either beneficially or adversely the efficacy of the intervention," Dr. Kanis said. Third, Dr. Kanis cited evidence demonstrating an interaction between the FRAX® fracture probability estimate, based on integrated risk factors, and responsiveness to an intervention. For instance, a published study examining the effect of clodronate found an

interaction between treatment with this bisphosphonate and the FRAX® fracture probability that was calculated without information about BMD; the efficacy of the drug increased with increasing fracture probability. “Patients identified to be at high risk respond to clodronate even in the absence of doing a bone density measurement,” according to Dr. Kanis, who along with colleagues is performing similar analyses with other agents that have been investigated in phase 3 trials.

Dr. Kanis then reviewed additional evidence to support the claim that FRAX® identifies reversible risk. This evidence comes from studies of agents like risedronate, strontium ranelate, raloxifene and clodronate showing that patients with normal BMD do respond to treatment; from population-based intervention studies such as those examining hormone replacement therapy, vitamin D, and clodronate; and from studies showing that a FRAX® calculation made without the inclusion of BMD does indeed identify patients with low BMD. Regarding the latter, Dr. Kanis cited published evidence from a 2007 study of clodronate by Helena Johansson and colleagues showing that as 10-year fracture probability as calculated by FRAX® without information about BMD increased, average femoral neck BMD progressively decreased, as did the T-score. “I think the concerns about whether or not you are identifying individuals at high risk even in the absence of BMD can be largely allayed with this kind of evidence,” Dr. Kanis said. Ultimately, in considering all of the above evidence, Dr. Kanis concluded that FRAX® accomplishes what any good risk assessment tool should. “In the absence of prospective randomized controlled trials of FRAX®, we have very good evidence that patients at high risk are amenable to therapeutic interventions that are available,” he said.

Is It Better To Keep Things Simple?

While FRAX® identifies patients able to respond to treatment, the generation of a FRAX® fracture probability estimate raises a number of questions. One of the more obvious ones is whether the many risk factors included in FRAX® are necessary. “Could we do as well as FRAX® in establishing fracture probability using a more simplified approach?”, Serge Ferrari, Editor-in-Chief of BoneKEy and moderator of the Forum, asked the panelists.

Addressing this question, panelist Steven Cummings described studies he has performed with colleagues showing that a simpler model using just age, body mass index and past history of fracture as risk factors allows for the prediction of fractures just as well as FRAX® does. However, he noted that these findings come from population-based studies, while unpublished work suggests the story is different for individual patients. “For clinical practice, about 25-30% of patients whose risk of fractures would be based just on those 3 simple components have their treatment decisions changed if you use a FRAX® score instead. So, from that point of view, although on a population basis simpler algorithms may work almost as well, for application to individual patients, the use of additional risk factors such as rheumatoid arthritis, or smoking, or family history, does make a difference to a substantial fraction of patients when you come to making decisions about therapies,” he stressed. The ability of FRAX® to classify individual patients is not the only thing to recommend it; its already widespread dissemination also means it will be the risk assessment tool of choice. “The FRAX® tool is widely available, and so I think just from a practical point of view, FRAX® remains and will be the standard for assessing risk and making decisions for individual patients,” Dr. Cummings noted.

When To Intervene With Treatment?

Certainly, then, FRAX®, is here to stay. Yet, a fracture probability estimate from FRAX® only identifies people at risk; it doesn't in and of itself provide information about when to intervene with treatment. This issue of how intervention thresholds for treatment should be set occupied the second half of Dr. Kanis' main presentation, and much of the ensuing panel discussion. One approach for determining intervention thresholds uses primarily health economic considerations and thus aims to determine the FRAX®

fracture probability at which intervention with therapy becomes cost-effective. One problem with this approach is that it is drug-dependent, since the cost-effectiveness of any particular drug depends both on the drug's efficacy and its price. Yet, choosing when to treat on the basis of the particular drug, rather than on the basis of the patient, conflicts with how physicians like to function in clinical reality, according to Dr Kanis. “It is counterintuitive to clinical practice. You don't say ‘which drug am I going to use?’ and then ‘I should treat this patient.’ The first decision is ‘should I treat this patient?’ and then ‘which drug would be most suitable,’” he said. A second limitation of a health economics approach, according to panelist Eugene McCloskey, is that it assumes a static healthcare system where costs stay fixed for a sufficient length of time, when in reality the price of treatment can change quickly. “The health economics analysis can be out-of-date relatively soon,” noted Dr. McCloskey.

A second option for setting an intervention threshold is to choose a particular fracture probability estimate derived from FRAX®, say 15 or 20%, and then to use that fracture probability as a fixed threshold to treat. Great care must be taken here, though, since even a small change in the fracture probability chosen as the basis to intervene with treatment can have a huge impact on how many patients will be treated. For instance, Dr. Kanis estimated the number of women to be treated in the UK based on three FRAX® thresholds – greater than 10%, greater than 15%, or greater than 20% fracture probability – only to find huge differences in the number of women who would be treated. “Although these probability thresholds don't vary by all that much, plus or minus 5%, the impact on the number of individuals treated is enormous, varying from 50% of postmenopausal women down to 17% – 1 in 2, or 1 in 5 – so it does mean that these thresholds have to be set with enormous care,” Dr. Kanis stressed.

However, a third approach has been taken both in the UK and in the US. Indeed, both countries have pursued a “translational” route where existing guidelines are translated into FRAX® fracture probabilities. These translational approaches, however, have been quite different. As Dr. Kanis explained, in the UK, the National Osteoporosis Guideline Group (NOGG) worked to translate existing guidelines from the Royal College of Physicians (RCP) into FRAX® probability-based assessment. RCP guidelines had stated that women with a prior fracture could be considered for treatment in the absence of a BMD measurement. Consequently, for the new guidance, the probability of fracture in a woman who had experienced a prior fracture was calculated and used as the intervention threshold. NOGG, in addition to this intervention threshold for treatment, also provided thresholds for BMD assessment; individuals who fall within these assessment thresholds are recommended to have a BMD test, and then the FRAX® fracture probability can be recalculated with this additional information.

Meanwhile, in the US, a different kind of translational approach has been taken to incorporate FRAX® into existing guidelines from the NOF. It differs from the UK/NOGG approach because it is driven mainly, rather than just supported, by cost-effectiveness analyses. According to NOF guidelines from before the advent of FRAX®, treatment was recommended for individuals over 50 years of age with a hip or spine fracture, and for those with a T-score less than or equal to -2.5 at the spine or proximal femur, and those recommendations remain in force. However, for those with T-scores between -1 and -2.5, that is, for patients in the osteopenic range, the NOF, using health economic considerations, determined that treatment should be considered for those individuals whose 10-year risk of major osteoporotic fracture was 20% or more according to FRAX®, and in those whose 10-year risk of hip fracture was 3% or more according to FRAX®. (**Note:** For a recent discussion about applying UK vs. US guidelines, see Bolland *et al.* Disparate outcomes from applying U.K. and U.S. osteoporosis treatment guidelines. *J Clin Endocrinol Metab*. 2010 Feb 10. [Epub ahead of print]. For a recent discussion of NOF guidelines and the proposal of a FRAX® filter, see Watts NB, Siris ES,

Cummings SR, Bauer DC. Filtering FRAX. *Osteoporos Int*. 2010 Apr;21(4):537-41).

Country-Specific Differences?

Because of these differences in the ways that the UK and US guidelines were assembled, an individual with particular characteristics could be recommended for treatment according to the guidelines of one country but not according to the guidelines of another. To illustrate this potential disparity, Dr. Ferrari posed the example of a 55-year-old woman with a T-score of -2.7 at the spine but osteopenia at the hip, and no other risk factors. “This woman would qualify for treatment according to NOF guidelines because of her low T-score at the spine, but her probability of fracture by FRAX® would be low because of her better femoral neck BMD and the absence of other risk factors. Therefore, she would qualify for treatment by one rule, but not by FRAX® alone,” Dr. Ferrari said.

Dr. McClung acknowledged that such a disparity would arise because of how each country's guidelines were constructed, but stressed that important clinical considerations dictated the different approach adopted by the NOF. “In the US the decision was made that it would be an awkward clinical circumstance to make the diagnosis of osteoporosis based upon BMD testing and then not to recommend treatment. While some of us might understand why that might be legitimate, that is a difficult discussion to have with patients and primary care physicians,” Dr. McClung explained.

Regarding NOF guidelines, another related question Forum participants debated was whether these recommendations are too permissive and would substantially increase the number of women recommended for treatment. Dr. McClung explained that, overall, under the new NOF guidelines, similar numbers of women would be treated compared to the old guidelines. “While it's true that incorporating FRAX® and treating patients with a fracture probability of 20% or higher will increase the proportion of older patients that are treated, it will simultaneously substantially decrease the number of younger postmenopausal women who are recommended to treatment, and overall the total number of women recommended for treatment isn't actually different from our previous guidelines.” To Dr. McClung, then, one of the important outcomes of the incorporation of FRAX® into NOF guidelines it that it focuses the spotlight on older, higher-risk patients rather than on younger, lower-risk patients.

As the differences between the new US and UK guidelines illustrate, the question of how to use FRAX® is destined to have many different answers; the FRAX® world is going to be a diverse one with no single guideline that is universally applicable to all countries. This outcome is unavoidable since the key factors that go into devising new guidelines – fracture probabilities, existing guidelines, and the ability to pay for treatment – will differ between countries.

What is the Role of Clinical Judgment in the FRAX® Universe?

Despite the variety of approaches to setting intervention thresholds taken by different countries, physicians across the globe, regardless of the particular healthcare system in which they function, will continue to share one thing in common as they use FRAX®: the use of clinical acumen. Indeed, all Forum participants agreed that clinical judgment must remain a crucial part of the equation determining which patients should receive treatment. Several instances of this necessity for continued keen clinical insight were the focus of much of the panel discussion.

One example the panel considered was whether fracture probability generated by a FRAX® calculation should override the T-score. Panelists agreed that both provide important information, and so there is no need to choose one over the other. However, the physician's clinical judgment can help decide if one should receive more weight than the other in specific situations. “If FRAX® provides a very high risk, for sure this is a compelling reason for treating the patient even if BMD is not terribly low, although we know the correlation between FRAX® scoring and BMD is very high,”

according to panelist Adolfo Diez-Perez. “On the other hand, if FRAX® gives a low risk of hip fracture in the next ten years, it's very difficult, even if BMD is quite low, to treat the patient, so after using both tools, clinical judgment is the real final step in deciding whether to treat or not,” Dr. Diez-Perez explained.

Another example highlighting the importance of clinical insight in a world dominated by FRAX® concerns patients who have already received an osteoporosis drug. Dr. Kanis stressed that FRAX® can certainly be used in such patients, but in this circumstance the fracture probability generated from a FRAX® calculation must be interpreted in the light of the physician's clinical judgment, just as it would in regard to patients who smoke cigarettes. Indeed, Dr. Kanis explained that smoking, as a FRAX® variable, assumes an average exposure to cigarettes, but while some people may smoke only 1 or 2 cigarettes per day, others might smoke several packs per day; how the physician uses the FRAX® fracture probability estimate will differ between the former and the latter. “In the same way, if somebody is on prior treatment, depending on the treatment, then you must temper the FRAX® number by your clinical judgment,” Dr. Kanis said.

A third instance where clinical judgment must come to the forefront is during specific situations where bone loss is likely to occur rapidly because of drugs patients might be taking. “There are patients who we identify who are about to lose bone quickly for a variety of reasons,” Dr. McClung explained, such as those taking high doses of glucocorticoids, or men starting GnRH therapy for prostate cancer. “In these circumstances the purpose of treatment isn't necessarily to reduce fracture risk in the long run, but to protect patients from the immediate bone loss that's happening.” Here, too, physicians must continue to rely on their clinical experience to provide the best possible care to patients.

Of course, one of the most important decisions a physician will make – opting for one particular drug instead of another to treat the patient – will continue to be based on clinical judgment. “Expecting FRAX® to help us choose which treatment to use is beyond where FRAX® was planned and beyond where FRAX® is at the moment,” Dr. McClung said.

How Can FRAX® Be Improved?

One final example where clinical judgment must supplement FRAX® is when the FRAX® fracture probability estimate says a patient is at low risk for fracture, but that patient has another strong risk factor for fracture that is not yet included in FRAX®, in particular, a risk of falling. The issue of falls, though, became part of a broader discussion of how FRAX® can be improved. Including additional risk factors like falls is one potential way. Thus far, falls have been excluded from FRAX® as a risk factor for several reasons. First, Dr. Kanis noted that information about falls risk is available only for a small number of the cohorts used to develop FRAX®. Second, he stressed that the field still lacks a standardized way to assess falls risk. “There is no well-established falls risk factor question that has been validated. Everybody has their own question construct,” Dr. Kanis said. Dr. McCloskey noted a third reason: there have been some concerns in the literature that the risk of falling might be a risk factor that is not amenable to treatment. However, with the accumulation of evidence, this is a concern that has lessened over time. “I'm feeling more and more secure that these drugs [skeletally-targeted therapies] do work in patients who are at increased risk of falls,” Dr. McCloskey said.

Along with adding a new risk factor such as falls, another area of improvement of FRAX® could be to refine even further risk factors that are already in FRAX®. This is true for risk factors like smoking, alcohol intake, and glucocorticoid use. Indeed, as mentioned above for smoking but true for the latter two risk factors as well, FRAX® assumes an average exposure to each, when in reality individuals will be exposed to greater or lesser amounts depending upon their particular circumstances.

Finally, Dr. McClung noted that because, with the exception of falls, FRAX® already

includes the major skeletal risk factors for fractures, what is most important to him is not improving FRAX® itself but rather studying how clinical outcomes may differ according to which particular guideline is followed. Results from such studies can then be used to refine how FRAX® is incorporated into each guideline.

An Educational Tool

Ultimately, the panelists agreed that the impact of FRAX® will go far beyond risk assessment into the realm of education. “I tend to regard FRAX® not just as a clinical tool but as an educational tool because in many countries we're starting off from a very low threshold in terms of actively managing osteoporosis,” Dr. McCloskey underscored. Indeed, for countries where osteoporosis is under-recognized and under-treated, FRAX® can increase knowledge, amongst physicians, of osteoporosis and the factors that affect fracture risk. FRAX® will also educate patients. “The principal thing for me is estimating the benefit for individual patients and then having a discussion with them about the potential benefit,” Dr. Cummings said. With the use of FRAX® and absolute probabilities of fracture, patients can now be educated on what their absolute risk of fracture is, and how likely they will be to benefit from treatment, and to what degree. “Moving to FRAX® and absolute probabilities of fracture helps you counsel the patient about whether treatment would be worthwhile independent of the label of osteoporosis or osteopenia,” Dr. Cummings stressed.

In the end, eschewing these labels based upon BMD is where FRAX's true educational value resides, as Dr. Kanis emphasized. “What FRAX® is doing is actually educating us slowly that solely or principally targeting on the basis of BMD is inappropriate.”