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Position Development Paper

Official Positions for FRAX® Bone Mineral Density and FRAX® Simplification

From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX®

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Abstract

Tools to predict fracture risk are useful for selecting patients for pharmacological therapy in order to reduce fracture risk and redirect limited healthcare resources to those who are most likely to benefit. FRAX® is a World Health Organization fracture risk assessment algorithm for estimating the 10-year probability of hip fracture and major osteoporotic fracture. Effective application of FRAX® in clinical practice requires a thorough understanding of its limitations as well as its utility. For some patients, FRAX® may underestimate or overestimate fracture risk. In order to address some of the common issues encountered with the use of FRAX® for individual patients, the International Society for Clinical Densitometry (ISCD) and International Osteoporosis Foundation (IOF) assigned task forces to review the medical evidence and make recommendations for optimal use of FRAX® in clinical

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practice. Among the issues addressed were the use of bone mineral density (BMD) measurements at skeletal sites other than the femoral neck, the use of technologies other than dual-energy X-ray absorptiometry, the use of FRAX® without BMD input, the use of FRAX® to monitor treatment, and the addition of the rate of bone loss as a clinical risk factor for FRAX®. The evidence and recommendations were presented to a panel of experts at the Joint ISCD-IOF FRAX® Position Development Conference, resulting in the development of Joint ISCD-IOF Official Positions addressing FRAX®-related issues.

Key Words: Osteoporosis; fracture risk; ISCD; official positions; FRAX; QUS.

Introduction

FRAX® is a fracture risk assessment algorithm developed by the World Health Organization (WHO) to estimate the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical vertebral, proximal humerus, distal forearm) in untreated men and women from the age of 40 to 90 years. The input for FRAX is demographic patient information (age, sex, height, weight, and in the US only, one of 4 ethnicities) and femoral neck bone mineral density (BMD), when available. The output of FRAX can be used with clinical guidelines to aid in the selection of patients for starting pharmacological therapy to reduce fracture risk. The use of FRAX in clinical practice has raised concern that FRAX may underestimate or overestimate fracture risk in some patients, and raises the question of whether adjustments to the FRAX algorithm might improve the accuracy of fracture prediction or simplify the ease of use. To address such issues, the International Society for Clinical Densitometry (ISCD), in cooperation with the International Osteoporosis Foundation (IOF), convened the FRAX Position Development Conference (PDC) in Bucharest, Romania, on November 14, 2010. The topics considered at the PDC included the use of lumbar spine or distal 1/3 (33%) radius BMD for FRAX input as an alternative to femoral neck BMD, the use of quantitative ultrasound (QUS) of the heel instead of femoral neck BMD, and methods for simplifying the use of FRAX in clinical practice.

FRAX currently allows for the input of BMD for only the femoral neck measured by dual-energy X-ray absorptiometry (DXA), whereas the ISCD recommends that the diagnosis of osteoporosis in clinical practice be made according to the lowest DXA-measured T-score of the lumbar spine, total hip, femoral neck, or distal 1/3 (33%) radius, if measured. In some patients, the femoral neck BMD value may not be valid (e.g., structural abnormalities, surgical hardware) or measurable (e.g., the patient's weight exceeds the weight limit of the table, the patient is unable to be placed on the table due to disability), and in others the BMD at other skeletal sites, particularly the lumbar spine, may be much lower than at the femoral neck, suggesting that FRAX may underestimate fracture risk in such individuals. ISCD Official Positions were developed to address the use of lumbar spine and distal 1/3 radius BMD to predict fracture risk and whether these skeletal sites should be included in the FRAX algorithm.

FRAX is a validated tool to predict fracture risk using an input of clinical risk factors without femoral neck BMD. This is particularly useful when DXA is not available, accessible, or affordable. However, fracture risk prediction is improved when clinical risk factors are combined with BMD. In world regions where DXA measurements cannot be easily obtained, QUS is a potential alternative. QUS devices are less expensive than DXA, use no radiation, and are portable. Limitations of QUS include inability to diagnose osteoporosis with the WHO criteria, which are based on DXA-derived T-scores, and poor utility for monitoring patients treated for osteoporosis. The potential use of QUS-measured parameters of the heel for assessment of fracture risk and inclusion with FRAX was addressed at the PDC.

For the busy clinician, a simplified version of FRAX might make it more likely to be used when time and resources are limited. The utility of FRAX without BMD was evaluated, and the circumstances under which it might be appropriate to use FRAX without BMD were assessed. The evidence regarding the robustness of each of the FRAX risk factors in predicting fracture risk was evaluated, and the possibility of using fewer clinical risk factors was considered. The potential use of adding an additional risk factor, the rate of bone loss, was discussed.

All Official Positions were rated by the Expert Panel in three categories: quality of the evidence, strength of the evidence, and applicability.

Methodology & Data sources

Each task force subgroup performed a comprehensive review of the medical literature following PubMed searches using appropriate keywords for each topic question. Based on the findings of the reviews, preliminary Official Positions were developed and presented to the Expert Panel for consideration. All Official Positions for the 2010 PDC were rated by the Expert Panel in the following categories according to predefined criteria derived from the RAND/UCLA Appropriateness Method (RAM). Preliminary Official Positions were either accepted, rejected, or modified by the Expert Panel. Grading was conducted according to the quality of evidence (Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations; Fair: Evidence is sufficient to determine effects on outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; Poor: Evidence is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information), strength of recommendations (A: Strong recommendation supported by the evidence;

B: Recommendation supported by the evidence; C: Recommendation supported primarily by expert opinion), and application of recommendations (W: Worldwide recommendation; L: Application of recommendation may vary according to local requirements). Ratings of each Official Position from the 2010 PDC are expressed in the form of three characters representing quality of the evidence, strength of the recommendation, and application of the recommendation. For example, a rating ''Good-A-W'' indicates that the evidence includes consistent results from well-designed, well-conducted studies in representative populations, a strong recommendation supported by the evidence and applicable worldwide. Since PDC topics are often selected because strong medical evidence is unavailable, it is the nature of the process that Official Positions are not always supported by the highest possible level of evidence. Nevertheless, the ISCD Official Positions encourage consistent approaches in the clinical practice of skeletal assessment, and focus attention on issues that require further study. Following completion of the PDC, the Steering Committee finalized wording of the recommendations without changing content. The preliminary Official Positions were then presented to the ISCD BOD for review and approved as the Official Positions of the ISCD. The BOD did not alter the content or wording of the proposed Official Positions. Recommendations approved by a majority vote of the ISCD BOD became ISCD Official Positions. A parallel process occurred at the IOF that included their executive committee as well as a full review and voting by the IOF Committee of Scientific Advisors. Recommendations approved by a majority vote of the IOF and ISCD became Joint ISCD IOF Official Positions and are summarized below.

BMD at Skeletal Sites other than Femoral Neck for FRAX Input

Questions:

a. Can lumbar spine BMD and/or T-score be used to assess fracture risk with FRAX?
   i. Can lumbar spine BMD be used to assess vertebral, hip, major or any osteoporotic and any clinical fracture risk?
   ii. Should lumbar spine T-score be used to assess fracture risk with FRAX?
   iii. Should lumbar spine BMD be used to assess fracture risk with FRAX when the lumbar spine T-score is lower than the femoral neck T-score?
   iv. Can lumbar spine BMD be used to assess fracture risk with FRAX when femoral neck BMD cannot be measured or is invalid?

b. Can distal 1/3 radius BMD and/or T-score measured by DXA be used to assess fracture risk with FRAX?
   i. Can distal 1/3 radius BMD measured by DXA be used to assess vertebral, hip, major or any osteoporotic and any clinical fracture risk?
   ii. Should distal 1/3 radius T-score measured by DXA be used to assess fracture risk with FRAX?
   iii. Should distal 1/3 radius BMD measured by DXA be used to assess fracture risk with FRAX when the distal 1/3 radius T-score is lower than the femoral neck T-score?
   iv. Can distal 1/3 radius BMD measured by DXA be used to assess fracture risk with FRAX?
   v. Can distal 1/3 radius BMD measured by DXA be used to assess major osteoporotic fracture risk with FRAX?
   vi. Can distal 1/3 radius BMD measured by DXA be used to assess hip fracture risk with FRAX?

Official Position: Measurements other than BMD or T-score at the femoral neck by DXA are not recommended for use in FRAX.

Grade: Good, A, W

Rationale: FRAX estimates the 10-year probability of major osteoporotic fracture and hip fracture using clinical risk factors and an optional femoral neck BMD measurement *(1)*. The FRAX algorithm was calibrated for use with femoral neck BMD based upon the strength of the association with subsequent fractures (particularly hip fractures) in the FRAX derivation cohorts and the availability of a standardized young-adult reference database (NHANES III white female) for calculation of T-scores *(2–5)*. Lumbar spine BMD is also strongly associated with future fracture risk, especially spine fractures *(5)*, but is not incorporated in the FRAX algorithm. Limitations in the use of lumbar spine BMD include commonly occurring age-related degenerative artifacts *(6–8)* and lack of a consistent approach for excluding vertebral levels with artifact in the FRAX derivation cohorts *(9–11)*.

Lumbar spine T-score cannot be substituted for the femoral neck T-score in the FRAX calculation for several reasons. Age-related decreases in T-scores differ by skeletal site *(12)* and, unlike hip BMD, there is no standardized young-adult reference database for calculation of lumbar spine T-scores. Prediction of hip fracture risk with lumbar spine measurements is not as robust as with the femoral neck, although prediction of all osteoporotic fractures is similar for the two measurements *(5)*. In addition, there are differences in standard deviation (SD) values used to compute the gradient of risk in the Marshall meta-analysis versus those used for T-score calculation. The SD used in the former was based upon the SD for BMD in the study populations *(5)*, which is greater for the lumbar spine than the SD of the young-adult reference population used in T-score calculations with DXA. One large study found that the population SD for the lumbar spine was 54% greater than the manufacturer young-adult reference SD, although the equivalent femoral neck SD values were virtually identical *(13)*. Substitution of lumbar spine T-score for femoral neck T-score in the FRAX calculator may therefore lead to erroneous results with overestimation of major osteoporotic fracture probability.

Distal radius BMD has been shown to predict the risk of fracture in postmenopausal women *(5,14)*. In the Marshall meta-analysis *(5)*, there was a relative risk (RR) increase of 1.7 (95% confidence interval [CI] 1.4–2.1) for vertebral fracture, 1.8 (95% CI 1.4–2.2) for hip fracture, 1.7 (95% CI

1.4−2.0) for forearm fracture, and 1.4 (95% CI 1.3−1.6) for all fractures with each age-adjusted SD decrease in distal radius BMD. No data are available for men. The distal 1/3 radius BMD or T-score were not included in the original FRAX algorithm due to insufficient data in the FRAX derivation cohorts, lack of an international standard for forearm regions of interest, and absence of a standardized young-adult reference database for calculation of T-scores.

Discussion: At the time of construction of FRAX, the available data correlating lumbar spine and forearm BMD with fracture risk were much less than for femoral neck BMD. Since FRAX was launched, other population-based data sets have become available, several of which contain information on BMD measured at the lumbar spine and other skeletal sites. The fracture prediction provided by measuring the forearm varies among studies, but where comparisons have been made, the results suggest that site-specific measurements are more robust *(5)*.

Additional Questions for Future Research: Future studies should include meta-analyses of the predictive value in men and women of measurements made at different skeletal sites for different fracture outcomes. A decision can then be made as to whether the information base is sufficiently robust to be incorporated into FRAX or to design a FRAX model using BMD measured at the lumbar spine or other skeletal sites. Since different manufacturers may use different regions of interest (ROIs) of the forearm and different reference databases for calculating T-scores, any clinical applications must take these variables into account.

Official Position: FRAX may underestimate or overestimate major osteoporotic fracture risk when lumbar spine T-score is much lower or higher (>1 SD discrepancy) than femoral neck T-score.

Grade: Fair, B, W

Rationale: It is not uncommon to find situations where T-scores in the lumbar spine and femoral neck show ''discordance'', given the modest correlation in BMD between these two sites (typically R = 0.6−0.7) *(15,16)*. Although the definition of discordance is not well standardized, it is often applied when the absolute difference in T-scores is greater than 1 or 2 SD. One report found that approximately one in eight women had discordance exceeding 2 SD based upon lumbar spine, femoral neck, total hip and trochanter *(17)*. It may seem intuitively obvious to practicing clinicians that when two individuals differ in their spine measurements (e.g., Patient 1 with lumbar spine T-score = −1.5 versus Patient 2 with lumbar spine T-score = −3.5) but who are identical in all other respects (Patient 1 and Patient 2 both have femoral neck T-score = −1.5), the individual with the lower lumbar spine measurement (Patient 2) would be at higher fracture risk. As noted above, since femoral neck BMD or T-score measured by DXA is the only skeletal measure currently recommended as an input variable to FRAX, these two individuals would generate identical fracture probabilities under FRAX.

Available data suggest that Patient 2 in the scenario above does indeed have higher fracture risk than Patient 1. A report from the Study of Osteoporotic Fractures found that discordant spine and hip BMD values predicted different fracture patterns, and that women who were osteoporotic only at the spine had elevated fracture risk compared with women that were not osteoporotic at the spine or hip *(18)*. However, the latter used categorical criteria to define between-site BMD discordance and did not analyze data according to the magnitude of the T-score difference. A large clinical cohort study found that there was incremental information in fracture risk prediction in women when lumbar spine BMD was included in a model that already included femoral neck BMD *(17)*. The lumbar spine was the most useful skeletal site for prediction of spine fractures alone, but not when non-vertebral fractures were also considered. There was no improvement over a model using femoral neck BMD alone when the analysis was limited to those with discordant osteoporosis categorization (one T-score below −2.5 with another above −2.5) or with large differences in T-scores (more than 2 SD). A subsequent report found that a large T-score difference between the lumbar spine and femoral neck significantly altered the estimation of major osteoporotic fracture risk compared with using femoral neck BMD alone *(19)*. Observed fracture rates exceeded those predicted by FRAX when the lumbar spine T-score was much lower than the femoral neck T-score (>1 SD discrepancy), and conversely, fracture rates were lower than predicted when the lumbar spine T-score was much higher than the femoral neck T-score.

Discussion: On a theoretical basis, combining BMD measurement sites is associated with limited incremental improvement in fracture prediction according to simulation studies performed by Blake et al. *(20)*. In this work, two skeletal sites with varying RR (values of 1.5, 2.0, and 2.5) and degrees of correlation (r = 0, 0.5, and 0.7) were assessed to determine their individual and joint contribution to fracture prediction. Slightly better fracture discrimination was obtained using the weighted mean Z-score approach, although the differences were small. It was concluded that there is unlikely to be any benefit from combining information from different types of bone density measurements unless they are completely unrelated. In the situation where RRs from the two sites are unequal (such as femoral neck T-score and lumbar spine T-score) then there will be even less benefit in using the combination, and the risk prediction will be dominated by the stronger predictor variable. This may explain why the effects of spine-hip discordance (ratio 1.12 per SD lumbar spine lower than femoral neck) are relatively small *(19)*.

Additional Questions for Future Research: Additional cohort studies are needed to determine the importance of lumbar spine and femoral neck T-score ''discordance'' as an independent risk factor for fracture. Whether this applies to other BMD measurement sites, such as the forearm, is unknown.

Official Position: A procedure based upon the difference (offset) between the LS and FN T-scores can enhance fracture prediction in the current version of FRAX.

Grade: Fair, B, W

Rationale: A simple procedure for adjusting the FRAX estimation of major osteoporotic fracture probability based upon

the T-score difference (offset) between the lumbar spine and femoral neck was recently reported *(19)*. For every offset SD difference there was an approximately 10% change in fracture risk that was higher when the lumbar spine T-score was less than the femoral neck T-score and lower when the lumbar spine T-score was greater than the femoral neck T-score. Using a split cohort derivation/validation technique, the offset adjustment was found to reclassify fracture probability in a relatively small proportion overall (less than 10%) but a larger number of individuals with moderate risk and offset greater than 1 SD (one in four). The rule that was developed was, ''Increase/decrease FRAX estimate for a major fracture by one-tenth for each rounded T-score difference between the lumbar spine and femoral neck.'' An example of the rule application follows: ''Consider an individual with femoral neck T-score −1.7 and major osteoporotic FRAX probability 18%. If the lumbar spine T-score is −3.5 then this indicates an offset of −1.8 (3.5 minus −1.7). This is rounded to the nearest whole number (−2). One tenth of the FRAX estimate based upon the femoral neck is 1.8%, which is multiplied by the rounded offset value (giving 3.6%). This is then added (because lumbar spine T-score is lower than femoral neck T-score) to the original FRAX estimate (18%) giving a final (rounded) probability of 22% (18% + 3.6%).

Discussion and Additional Questions for Future Research: Whether the simple T-score offset approach outlined above can be used with FRAX requires external validation in additional cohorts and other populations before widespread adoption. Since vertebral exclusions were applied for computing the lumbar spine T-score (approximately 1 in 3 spine scans had vertebral exclusions), it is unclear whether similar results would be achieved without vertebral exclusions or with a more conservative approach. Some of these limitations were recently addressed in an independent validation study from the Canadian Multicentre Osteoporosis Study (CaMos), a population-based cohort of 4,575 women and 1,813 men aged 50 and older *(21)*. The T-score offset between the lumbar spine and femoral neck was confirmed to be a FRAX-independent risk factor for major osteoporotic fractures. Sex- and age-dependent offsets (equivalent to an offset based upon Z-scores) showed improved risk classification among individuals designated to be at moderate risk with the conventional FRAX probability measurement, and may help to account for site-specific differences in T-score declines with aging and age-related degenerative artifact. Analyses to date have been underpowered to identify specific subgroups where the offset contributes more or less information, and whether there are significant interactions with sex, age or ethnicity. Detailed subgroup analyses would be better assessed in a meta-analysis using the multiple FRAX cohorts.

QUS of the Heel FRAX Input

Questions:

a. Can QUS of the calcaneus be used to assess fracture risk with FRAX?
vii. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess vertebral, hip and any clinical fracture risk?
viii. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess major and any osteoporotic fracture risk?
ix. Should QUS of the calcaneus T-score be used to assess fracture risk with current FRAX?
x. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess fracture risk with current FRAX?
xi. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess fracture risk within a FRAX-like model?

Official Position: The ISCD 2007 PDC Statements *(20,25)* on fracture risk prediction and application of heel QUS are supported by a higher level of evidence in men and women than was available in 2007.

Grade: Good, B, W

Rationale: The ISCD 2007 PDC addressed clinical applications of QUS for fracture risk assessment, diagnosis of osteoporosis, treatment initiation, monitoring of treatment, and quality assurance/quality control *(22)*. For fracture risk assessment, the ISCD advised that validated heel QUS devices predict fragility fracture in postmenopausal women (hip, vertebral and global fracture risk) and men over the age of 65 years (hip and all non-vertebral fractures), independently of central DXA BMD. The highest level of evidence at that time came from a meta-analysis by Marin et al. in 2006 *(23)*, which summarized 14 prospective population-based studies with heel QUS measurements and fracture outcomes.

We used similar criteria to find new prospective QUS studies published recently (up to July 2010) and conducted a random-effects meta-analysis of the studies for different available outcomes and different QUS parameters. In total, 55,164 women and 13,742 men from 21 studies were included in our meta-analysis. The details of methodology and results are described in an ancillary paper *(24)*. The new meta-analysis provided convincing evidence that QUS of the heel predicts fracture risk. The gradient of risk (relative risk per standard deviation) attributed to broadband ultrasound attenuation (BUA) was estimated to be 1.40 (95% CI 1.25−1.57) for any clinical fracture (based on 9 studies), 1.69 (95% CI 1.43−2.00) for hip fracture (11 studies), and 1.80 (95% CI 1.42−2.28) for vertebral fracture (3 studies). The gradient of risk for speed of sound (SOS) for any clinical fracture was 1.46 (95% CI 1.33−1.60), for hip fracture 1.96 (95% CI 1.64−2.34), and for vertebral fracture 2.60 (95% CI 1.81−3.73). There was considerable heterogeneity among studies for the association of BUA and SOS measures and risk of fracture, especially for hip fracture outcome. However, this may be partly due to heterogeneity of results in men and women in studies that included both sexes. Moreover, funnel plots reject the potential for publication bias since most of high-weight studies show relative risks that are higher than

average *(24)*. Whilst cross-sectional and case-control studies suggest that QUS measures can differentiate between fracture cases and controls in young adults, large-scale prospective studies have generally been performed in older age-groups. All women in the studies included in the meta-analysis were postmenopausal and over the age 45 years *(14,25−32)*. Men included in prospective studies of fracture risk assessment were over the age of 65 or 70 years *(30,33−35)*. Therefore, it is suggested that use of QUS for fracture risk assessment is reserved for women and men in these age ranges until results of studies in younger populations become available.

Several studies have compared the performance of QUS with DXA in predicting fracture risk. In The Study of Osteoporotic Fractures (SOF), the strength of the association between BUA and fracture risk among older women was similar to that observed with BMD *(31)*. The MrOS study showed that QUS measurements predict the risk of hip and non-vertebral fracture in older men similarly to hip BMD, but the combined measurements of QUS and BMD were not superior to either measurement alone *(33)*. The APOSS study even suggested that BUA may be a better fracture predictor than DXA, because the relative risk was highest for BUA, and independent of BMD *(36)*. A sub-study of EPIC-Norfolk used estimates of 10-year absolute risk of fracture for comparison between QUS and DXA and found that fracture probabilities estimated by QUS were comparable to those estimated by DXA *(35)*. Furthermore, adding QUS measures to models based on clinical risk factors and BMD has been shown to improve the predictive power of the models *(37)*. Five of the studies included in our meta-analysis reported relative risks for QUS parameters adjusted for BMD values *(33,35,36,38,39)*. The overall gradient of risk for BUA and fracture risk was 1.34 (95% CI 1.22−1.49). There was a significant association (BMD-adjusted RRs 1.39; 95% CI 1.08−1.79) for BUA and hip fracture. The associations observed were homogeneous between studies and there was no sign of publication bias in this analysis.

Discussion: Evidence synthesis based on 21 population-based prospective studies confirms that QUS of the heel using validated devices predicts risk of different fracture outcomes in elderly men and women. The weight of evidence is highest among Caucasian postmenopausal women and Caucasian men over the age of 65, and QUS seems to perform similarly in men and women. Fracture risk estimates using QUS are similar to, and independent of, DXA BMD estimates. This summary of evidence supports the previous ISCD Official Position regarding fracture risk assessment using QUS.

Despite these advantages, there are several problems that preclude use of QUS measures in the current FRAX model. Most importantly, there are no studies that provide a standardized QUS measurement similar to the standardization of DXA measurements between manufacturers *(40−42)*. So far, all the large-scale studies have used their population-specific standard deviations to calculate Z-scores and smaller studies used different reference populations provided by manufacturers, which have not been validated or standardized with other devices. Therefore, to use QUS measures in FRAX, it would be necessary to take data from each device and derive the standardized QUS measures. Many of the commercially available QUS devices have not been used in large prospective studies and some of the devices used (e.g. Walker Sonix UBA 575) are no longer commercially available. Another problem is the duration of published prospective QUS studies, which typically have follow-up periods of around 2 to 5 years only. This means that, while QUS is a good clinical predictor of short- and medium-term fracture risk, its performance for long-term risk assessment of fracture (as in FRAX) has not been tested adequately.

For these reasons, the predictive ability of FRAX using QUS is likely to be less robust because the calculation will be based on fewer studies, fewer patients, and fewer fractures on a more diverse selection of devices.

Additional Questions for Future Research: What is the performance of QUS for fracture risk prediction in younger age groups? How is it possible to reinforce the strength of evidence for the clinical use of QUS in non-Caucasian women and men? How can QUS be used to optimize a case-finding strategy? Can QUS play a role in monitoring treatment for osteoporosis?

Official Position: Currently validated heel QUS devices, using criteria defined in the 2007 ISCD PDC, predict fracture risk similarly.

Grade: Good, A, W

Rationale: The performance of different QUS devices for prediction of fracture risk may vary. Several cross-sectional studies have attempted to overcome this potential problem by inclusion of different QUS devices in the same study, all subjects being measured on all machines. As summarized in the previous ISCD Official Positions *(22)*, the performance of heel QUS devices in 11 relevant studies was relatively similar. Two prospective studies, SEMOF *(26)* and the Basel Osteoporosis Study *(43)*, have assessed two QUS devices (Achilles+ and Sahara) in the same elderly populations. Both studies showed significant associations between measured parameters and fracture risk and a similar performance for GE-Lunar and Hologic devices. The potential effect of device performance on the associations between different parameters and risk of fracture were examined using stratified meta-analysis. The association between BUA, as measured by QUS devices from 4 different manufacturers (Walker Sonix UBA 575/1001, McCue CUBA, GE-Lunar Achilles/Achilles+, and Hologic Sahara devices), and 'any clinical' or hip fracture was estimated. All QUS devices showed a similar performance for prediction of hip or any clinical fracture *(21)*. Meta-regression analysis also showed a non-significant difference between these devices for prediction of 'any clinical' (p value = 0.8) and hip fracture (p value = 0.7).

The association between different parameters of QUS and risk of fracture was also assessed. BUA, in dB/MHz, and SOS, in m/s, are the recommended ultrasound attenuation and velocity parameters, respectively. Some QUS devices report composite parameters combining BUA and SOS in order to simplify the interpretation of QUS results. The two most frequently used composite parameters are Stiffness Index (SI)

for GE-Lunar Achilles+ and Quantitative Ultrasound Index (QUI) for Hologic Sahara devices. Meta-analysis of 9 studies reporting SI for 23,521 participants showed a gradient of risk of 1.79 (95% CI 1.58−2.04). Similarly, a meta-analysis of 4 studies reporting QUI for 18,903 participants showed a gradient of risk of 1.79 (95% CI 1.35−2.36) for all fractures and 1.99 (95% CI 1.49−2.67) for hip fracture. Overall, the performance of SI and QUI measures in fracture prediction seems to be similar to, or higher than, that of BUA and SOS.

Discussion: The new evidence confirms that all four approved QUS-measured parameters (BUA, SOS, SI, and QUI) can be used for fracture risk assessment and that validated devices from different manufacturers can predict fracture risk with a similar performance. However, care should be taken in extrapolating results from one QUS device to another technologically different one. The technical diversity of QUS devices and parameters is much greater than for DXA. Indeed, QUS instruments from different manufacturers have significant differences, particularly in their calibration methods, skeletal sites of measurement and analysis, acquisition technique, analysis software and scanner designs. These increase the difficulties in comparing measurements from different QUS devices and may lead to misinterpretation of results.

Additional questions for future research: What is the optimal approach to standardization and cross-calibration of QUS parameters from different QUS manufacturers?

Simplification of FRAX

Questions:

a. How useful is FRAX without BMD?
   - xii. What are the circumstances when it is appropriate to use FRAX without BMD?
   - xiii. What are the circumstances when it is not appropriate to use FRAX without BMD
b. Could a clinically useful simplified FRAX model be developed?
   - xiv. Which of the FRAX risk factors are the strongest predictors of fracture risk?
   - xv. Which of the FRAX risk factors are the weakest predictors of fracture risk?
   - xvi. What is the effect of excluding the weaker FRAX risk factors on assessment of fracture risk?
   - xvii. Is there a combination of a few risk factors that provides an assessment of fracture risk with FRAX that is close to the current FRAX model using all risk factors?
c. Could the rate of bone loss measured by DXA be used as risk factor for inclusion in FRAX?
   - xviii. Is bone loss an independent risk factor for fracture?
   - xix. Should rate of bone loss be included as a FRAX risk factor?

Official Position: FRAX with BMD predicts fracture risk better than clinical risk factors or BMD alone. Use of FRAX without BMD is appropriate when BMD is not readily available or to identify individuals who may benefit from BMD measurement.

Grade: Good, A, W

Rationale: Kanis et al. evaluated 9 population based studies in which BMD and clinical risk factors were documented and found that combining BMD and clinical risk factors provided a higher specificity and sensitivity than either alone *(44)*. The higher sensitivity in those at a high risk of fracture who are not identified by BMD alone is explained by the addition of the FRAX risk factors.

Johansson et al. examined the effects of the use of clinical risk factors alone, BMD alone or the combination using the FRAX tool for the detection of women at risk of hip fracture *(45)*. BMD tests alone selected women at higher risk of hip fracture than the use of clinical risk factors alone. BMD tests alone also identified a greater number of hip fracture cases compared to clinical risk factors alone. The combined use of clinical risk factors and BMD identified fewer women above a threshold risk than BMD alone (fewer false positives), but with a higher hip fracture risk, and consequently a lower number needed to treat. In sensitivity analyses, the positive predictive value and number needed to treat were always better for the combination than either BMD or clinical risk factors alone across all ages studied.

Two separate Canadian studies have demonstrated the ability of FRAX, with or without BMD, to predict hip fractures and major osteoporotic fractures. Fraser et al. observed that estimates of 10-year fracture risk made by FRAX with and without BMD are close to the number of fractures observed in men and women *(46)*; in most cases, FRAX underestimated the observed fracture rate by only 1−2%, leading the authors to conclude that FRAX accurately predicts fracture risk *(46)*. In a separate study, Leslie et al. assessed a large clinical cohort from the Manitoba Bone Density Program database and compared calculated FRAX scores with actual fracture outcomes *(47)*. Once again, FRAX performed well, generally underestimating the observed fracture rate by 1−2%.

Based on these studies, FRAX with BMD gives a reliable estimate of fracture risk and FRAX without BMD provides a reasonable measure of fracture risk in areas where resources for BMD measurement are absent or limited. Johansson et al. and others have suggested that FRAX without BMD could be used to determine those who might benefit from BMD testing and more definitive fracture risk assessment *(46,48)*. This strategy has been proposed by the US Preventive Services Task Force as a method for identifying which women under age 65 might benefit from having a BMD test *(49)*. Curtis et al. evaluated 324 high-risk patients and concluded that although FRAX without BMD is sensitive for fracture risk prediction, adding BMD enhances specificity *(50,51)*. However, fracture prediction by FRAX without BMD is reasonable good and yields similar sensitivity and specificity to FRAX with BMD, especially for hip fractures.

Discussion: FRAX with or without BMD is a useful tool for predicting fracture risk. In those countries where BMD is not readily available, FRAX without BMD may be useful

in determining who may benefit from additional BMD measurement for more definitive fracture risk assessment. BMD is not always necessary to determine whether or not a patient needs treatment, although a BMD measurement prior to starting treatment may be clinically useful to confirm the presence of low BMD and establish a baseline for monitoring treatment effect. A woman with a previous fragility fracture of the spine or hip could be treated for osteoporosis without measuring BMD. FRAX without BMD will generally confirm that an elderly woman or man with a previous fragility fracture of the spine or hip needs treatment regardless of BMD. This, however, is very dependent upon country-specific treatment thresholds. If FRAX indicates that a patient is above a treatment threshold, BMD is not necessary to determine whether treatment is needed; thus, the cost of BMD testing could be avoided altogether. For this economic benefit to be realized in developing countries with inadequate BMD testing facilities, data specific to these countries must be incorporated into FRAX.

Additional Questions for Future Research: Given the differences in country-specific hip fracture and mortality rates, country-specific FRAX tools should be developed, when possible, and used to set thresholds for cost-effective intervention with pharmacological agents to reduce fracture risk.

Official Position: It is not appropriate to use FRAX to monitor treatment response.

Grade: Good, C, W

Rationale: There are circumstances when FRAX, with or without BMD, may not be appropriate. FRAX, with or without BMD, was not developed to monitor treatment response, but to evaluate fracture risk in those who are not on treatment. Until further studies have been done, FRAX should not be used to monitor treatment.

Discussion: At present, many clinicians use BMD measurements and/or biochemical markers to determine the response to treatment. Having a tool that quantifies the risk for fracture following treatment would be useful for clinicians and patients alike.

Additional Questions for Future Research: Research should be conducted to define treatment response and to determine if changes in FRAX scores reflect treatment response. Ultimately it is important to determine whether changes in FRAX scores reflect changes in the risk for fracture and actual fracture incidence in treated patients.

Official Position: Evidence that the rate of bone loss may be an independent risk factor for fracture is conflicting. Therefore, rate of bone loss is not included as a FRAX risk factor.

Grade: Poor, C, W

Rationale: There are several studies that have examined bone loss as a predictor of fracture. Two studies measuring hip BMD showed that decreases in BMD are associated with an increase in fracture risk *(52,53)*. Separate studies, one measuring total hip BMD and the other forearm BMD, did not confirm these findings *(54,55)*.

Nguyen et al studied 966 postmenopausal women, who had been followed for an average of 10.7 years *(53)*. Low trauma fractures of the hip, clinical vertebral fractures, and major fragility fractures were confirmed by radiographs. In the multivariable Cox's proportional hazards analysis, femoral neck bone loss, baseline femoral neck BMD, and advancing age were significant predictors of fracture risk. The proportion of fractures attributable to the three factors was 45%. For hip fracture, the attributable risk fraction was approximately 90%.

In contrast, Hillier et al measured total hip BMD in 4124 older women with a mean age of 72 years at baseline and again 8 years later *(54)*. Over a mean of 5 years after the second BMD measurement, 877 women experienced an incident low trauma non-vertebral fracture including 275 hip fractures and 340 women developed a vertebral fracture. After adjustment for age and weight change, initial and repeat BMD measurements were similarly associated with fracture risk for non-vertebral, vertebral, and hip fractures ($p < 0.001$ for all models). No significant differences were found to enable discrimination of non-vertebral, vertebral, or hip fractures between models with initial BMD, repeat BMD, or initial BMD plus change in BMD.

Berger et al studied 3635 women and 1417 men aged 50−85 years who had at least two BMD measurements of the lumbar spine and hip within the first 5 years of the study and fragility fractures within the first 7 years *(52)*. Among nonusers of antiresorptives, independent of baseline BMD, a decrease of 0.01 g/cm^2/yr in total hip BMD was associated with an increased risk of fragility fracture in women and in men. In addition they found that BMD change better predicted the risk of fragility fractures in subgroups such as fast losers and those with osteopenia than models that included baseline BMD but excluded BMD change. Their results suggest that addition of BMD change to other variables may enhance fracture risk prediction.

Ahmed et al studied 1,208 postmenopausal women aged 50 to 74 years, and 1,336 men aged 55 to 74 years from the Tromso Study, who had repeated distal and ultra-distal forearm BMD measurements *(55)*. Independent of baseline BMD, the relative risk associated with distal site bone loss of 1 SD % per year was 1.23 (95% CI 1.01−1.50) for low trauma fractures and 1.32 (95% CI 1.07−1.62) for osteoporotic fractures (hip, wrist and shoulder). However, bone loss did not predict fracture after adjusting for follow-up BMD. The BMD level at follow-up became the significant predictor of fracture risk and not the rate of bone loss.

Rate of bone loss could potentially be an important independent risk factor for fracture in the FRAX algorithm; however, few studies have examined the effect on fracture risk prediction of incorporating rate of bone loss as a risk factor in FRAX *(52)*. On the other hand, BMD levels at follow-up rather than the rate of bone loss may be more important in determining fracture risk.

Discussion: The evidence supporting the contention that a high rate of bone loss is associated with an increased risk of fracture is conflicting and not sufficiently robust to draw a definitive conclusion at this time. The correlation between rate of bone loss and fracture risk may be dependent, at least

in part, on the baseline BMD. The value of the most recent BMD measurement appears to be more relevant in estimating fracture risk than the rate of change since the previous BMD measurement.

Additional Questions for Future Research: Unless compelling and consistent data emerge of a relationship between rate of bone loss and fracture risk that is independent of final BMD, efforts to incorporate rate of bone loss in the FRAX algorithm should not be pursued.

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