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Position Development Paper

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

Executive Summary of the 2010 Position Development Conference on Interpretation and Use of FRAX® in Clinical Practice

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Abstract

The International Society for Clinical Densitometry (ISCD) and the International Osteoporosis Foundation (IOF) convened the FRAX® Position Development Conference (PDC) in Bucharest, Romania, on November 14, 2010,

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following a two-day joint meeting of the ISCD and IOF on the ''Interpretation and Use of FRAX® in Clinical Practice.'' These three days of critical discussion and debate, led by a panel of international experts from the ISCD, IOF and dedicated task forces, have clarified a number of important issues pertaining to the interpretation and implementation of FRAX® in clinical practice. The Official Positions resulting from the PDC are intended to enhance the quality and clinical utility of fracture risk assessment worldwide. Since the field of skeletal assessment is still evolving rapidly, some clinically important issues addressed at the PDCs are not associated with robust medical evidence. Accordingly, some Official Positions are based largely on expert opinion. Despite limitations inherent in such a process, the ISCD and IOF believe it is important to provide clinicians and technologists with the best distillation of current knowledge in the discipline of bone densitometry and provide an important focus for the scientific community to consider. This report describes the methodology and results of the ISCD-IOF PDC dedicated to FRAX®.

Key Words: Osteoporosis - clinical risk factors; fracture probability; risk assessment; clinical risk factors; bone mineral density; official positions; standards; world-wide.

Introduction

The International Society for Clinical Densitometry (ISCD) is an international non-profit professional society linking multiple disciplines with an interest in bone mass measurement and assessment of skeletal integrity. The ISCD's mission is to advance excellence in skeletal health assessment by: promoting education and a broader understanding of the clinical applications of bone mass measurement and other skeletal health assessment technologies; assuring proficiency and quality in the assessment of skeletal health through certification and accreditation; supporting clinical and scientific advances in the diagnosis and treatment of osteoporosis; and promoting appropriate patient access to bone mass measurement and other skeletal health assessment technologies. As skeletal health assessment evolves, differences develop in technologies, acquisition techniques, reference databases, reporting methods, terminology and osteoporotic fracture prediction. These differences may result in adverse effects on patient care and the exchange of scientific information. To address these issues, the ISCD periodically holds Position Development Conferences (PDCs), a process whereby an international panel of experts makes recommendations based on reviews of the scientific literature by ISCD Task Forces. Recommendations that are approved by the ISCD Board of Directors become Official Positions of the ISCD. Official Positions resulting from prior PDCs held biannually from 2001−2007 have previously been reported *(1−29)*.

The International Osteoporosis Foundation (IOF) is a non-profit, non-governmental umbrella organization dedicated to the worldwide fight against osteoporosis, the disease known as ''the silent epidemic''. The IOF's members − committees of scientific researchers, patients, medical and research societies and industry representatives from around the world − share a common vision of a world without osteoporotic fractures. The IOF now represents 195 societies in 93 locations.

The ultimate aim of the clinician in the management of osteoporosis should be to reduce the risk of fractures. Treatment decisions should be made through good clinical judgment and improved identification of patients at high risk. FRAX® (http://www.shef.ac.uk/FRAX) is a simple computer-based tool that integrates clinical information and femoral neck BMD as an option to predict the 10-year probability of major osteoporotic fracture and hip fracture *(30,31)*. It can be customized for use in both women and men over the age of 40 years and for different countries based upon local epidemiology of fracture and death. Developed at the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK, in collaboration with other scientific societies, the tool assists primary health care providers to better target patients for pharmacological intervention, ultimately improving the allocation of scarce healthcare resources for patients most likely to benefit from treatment.

FRAX is being used by an increasing number of clinicians around the world. However, the widespread application of FRAX in clinical practice has raised numerous questions regarding the information selected for input and the possible underestimation or overestimation of fracture risk in specific instances. In order to assist clinicians in deriving the greatest possible clinical value from using FRAX, the ISCD, in collaboration with the IOF, convened the FRAX PDC in Bucharest, Romania, on November 14, 2010, following a two-day collaborative meeting of the ISCD and IOF - ''Interpretation and Use of FRAX in Clinical Practice.'' These three days of critical discussion and debate, led by a panel of international experts from the ISCD, IOF and dedicated task forces, clarified a number of important issues pertaining to the interpretation and use of FRAX in clinical practice.

This report describes the methodology and results of the 2010 Bucharest, Romania ISCD-IOF PDC that was dedicated to FRAX.

The ISCD Official Positions resulting from a PDC are established in order to enhance the quality and clinical utility of skeletal assessment worldwide. However because the skeletal assessment field is still evolving rapidly, some clinically important issues addressed at the PDCs are not associated with robust medical evidence. Accordingly, some Official Positions are based largely on expert opinion. Despite limitations inherent in such a process, the ISCD and IOF believe it is appropriate to provide clinicians and technologists with the best distillation of current knowledge in the discipline of bone densitometry and provide an important focus for the scientific community to consider further research to resolve areas of ambiguity and/or ongoing controversy.

The ISCD and IOF wish to acknowledge the extraordinary efforts of the PDC Task Force Chairpersons and members, who represented a distinguished group of international experts. The dedication of these individuals for the past two years is exemplary.

Methodology

Topic Selection

Topics addressed at the 2010 PDC were selected by the ISCD Board of Directors (BOD), Scientific Advisory Committee (SAC) and the PDC Steering Committee according to criteria used for prior PDCs *(1,2,14)*. The topics selected were reviewed by and had the full scientific participation of the executive committee of the IOF. Each topic selected had been judged to be clinically relevant with a perceived need for an Official Position due to lack of overwhelming medical evidence or due to its controversial nature, and to have a reasonable likelihood of achieving a consensus by the Expert Panel. The PDC program committee divided the FRAX topics into three main categories of questions. The three topic areas and associated questions follow:

1. FRAX Clinical

a. In patients with rheumatoid arthritis (RA), how does disease activity, duration or non-glucocorticoid treatment affect fracture probability as estimated by FRAX?
   i. How does severity of disease interact with fracture risk?
   ii. Does increased falls risk in RA contribute to fracture risk?
   iii. Does an increased prevalence of morphometric or radiological vertebral fractures contribute to increased fracture risk in RA?
   iv. Do non-glucocorticoid medications in RA impact on fracture risk?
b. What guidance can be given to clinicians for how and when to include glucocorticoids as a risk in the FRAX calculations and, if included as a risk, should dose and duration of use be quantified? Should such modification be within the FRAX tool, or serve as guidance for the clinician to adjust 10 year fracture risk independent of FRAX?
   i. Should short term use of glucocorticoids be captured in FRAX? How is short term use defined?
   ii. Should low dose use of glucocorticoids be captured in FRAX? How is low dose defined?
   iii. Should intermittent use be captured in FRAX? How is intermittent use defined?
   iv. Should present and/or past use be captured in FRAX?
   v. Should inhaled, intranasal, topical, enteral or intravenous pulse dosing be captured in FRAX?
   vi. Should adrenal hormone replacement be captured in FRAX?
c. Is there sufficient evidence from recent studies to estimate how dose, type, duration and time from exposure for alcohol would impact on fracture probability as estimated by FRAX?
   i. Is there a dose relationship between alcohol intake and the risk of fracture?
d. Is there sufficient evidence from recent studies to estimate how dose, type, duration and time from exposure for tobacco would impact on fracture probability as estimated by FRAX?
   i. Is there a dose and type relationship between smoking and the risk of fracture?
   ii. Is there a dose relationship between the duration of smoking and the risk of fracture?
e. How does prior fracture affect fracture probability as estimated by FRAX?
   i. Does the number of past fractures affect future fracture risk?
   ii. Does the severity of past vertebral fractures affect future fracture risk?
   iii. Does the site of past fracture affect future fracture risk?
   iv. Is the relationship between past fracture and future fracture equivalent in women and men?
   v. Should the family history of fracture be expanded to include additional sites, additional family members, or account for age at fracture?
f. How does history of falls and frailty affect fracture probability as estimated by FRAX?
   i. Should a falls history be incorporated into FRAX?
g. How do bone turnover markers as measured by currently available biochemical markers affect fracture probability as estimated by FRAX?
   i. Are bone turnover markers of utility in predicting fracture outcomes?
   ii. Is their predictive ability independent of BMD?

2. FRAX BMD

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?

c. Can QUS of the calcaneus be used to assess fracture risk with FRAX?
i. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess vertebral, hip and any clinical fracture risk?
ii. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess major and any osteoporotic fracture risk?
iii. Should QUS of the calcaneus T-score be used to assess fracture risk with current FRAX?
iv. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess fracture risk with current FRAX?
v. Can QUS-measured parameters (SOS, BUA, SI) of the calcaneus be used to assess fracture risk within a FRAX-like model?

d. How useful is FRAX without BMD?
i. What are the circumstances when it is appropriate to use FRAX without BMD?
ii. What are the circumstances when it is not appropriate to use FRAX without BMD

e. Could a clinically useful simplified FRAX model be developed?
i. Which of the FRAX risk factors are the strongest predictors of fracture risk?
ii. Which of the FRAX risk factors are the weakest predictors of fracture risk?
iii. What is the effect of excluding the weaker FRAX risk factors on assessment of fracture risk?
iv. 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?

f. Could the rate of bone loss measured by DXA be used as risk factor for inclusion in FRAX?
i. Is bone loss an independent risk factor for fracture?
ii. Should rate of bone loss be included as a FRAX risk factor?

3. FRAX International

a. Are the US FRAX calculators for Blacks, Asians and Hispanics accurate enough for clinical use?
i. What is known about fracture rates in North American ethnic groups compared to whites?
ii. Are the assumptions used in the FRAX ethnic calculators reasonable given the data available in these populations?
a. Are the ethnic-specific adjustments in fracture risk used in FRAX (0.43 for women and 0.53 for men) under- or over-estimating fracture risk for Blacks?
b. Are the ethnic-specific adjustments in fracture risk used in FRAX (0.53 for women and 0.58 for men) under- or over-estimating fracture risk for Hispanics?
c. Are the ethnic-specific adjustments in fracture risk used in FRAX (0.50 for women and 0.64 for men) under- or over-estimating fracture risk for Asians?
d. Which FRAX calculator should be used for other ethnic groups not included in current FRAX models?
e. Does the association between BMD and mortality differ across ethnic group?
f. Is the assumption in FRAX that the association between BMD and other risk factors and fracture is similar across ethnic groups correct?

b. What should I do if my country does not have a FRAX calculator?
i. What is known about fracture rates throughout the world?
ii. What is the minimum requirement for the construction of a country-specific FRAX model?
iii. Which FRAX calculator should be used for countries without a FRAX model?

Overall more than 55 questions were considered.

PDC Planning

The PDC Steering Committee oversaw the planning and conduct of the 2010 PDC. The Steering Committee consisted of the ISCD President and IOF Committee of Scientific Advisors (CSA) Chair, who served as Chair and co-Chair respectively. Other members of the Steering Committee consisted of the President of the IOF and Past-president of the ISCD and members of both societies' Board of Directors and/or Executive Committees. The Steering Committee identified ISCD and IOF members to serve as Task Force Chair and co-Chair for each topic area. Task Force members were international experts in bone densitometry and other skeletal health disciplines appropriate to each topic area. The Steering Committee asked each Task Force to consider a series of clinical or technical questions pertaining to their assigned topic. Task Force members performed a medical literature search relevant to these questions using a method modified from that utilized by the Cochrane reviews *(32)*. The literature searches were conducted using electronic databases that included PubMed, EMBASE and MEDLINE. Appropriate articles were selected for further review and when necessary included publications in progress. Task Force chairs and members had the option of further refining the initially posed questions. Each Task Force submitted a draft of their Official Positions that was reviewed by the Expert Panel prior to the PDC conference.

PDC Expert Panel

Concurrent with Task Force work, international experts in the field of bone densitometry and other societies concerned with skeletal health were contacted by the PDC Steering Committee to serve as expert panelists. Of the 18 experts

who agreed to participate on the PDC Expert Panel, 16 were able to attend the PDC conference in Bucharest, Romania. The role of the Expert Panel was to discuss and evaluate the Task Force presentations, review the proposed Official Positions and supportive documents provided by the Task Forces and make final recommendations to the relevant committees of the ISCD and IOF.

PDC Moderators

PDC panel Moderators with experience in the RAND/UCLA (RAND Corporation/University of California Los Angeles-UCLA) Appropriateness Method (RAM) *(33)* process and FRAX topics were selected by the Steering Committee. Two Moderators assisted the Steering Committee of the PDC in the development and refinement of statements derived from the initial Task Forces questions, and with the Chair of the PDC, led the discussion and the rating by the Expert Panel during the PDC in Bucharest, Romania, November 12-14, 2010.

PDC Procedures

The procedures of the 2010 PDC (formulation of statements from initial questions, rating process and Expert Panel decisions) followed a modified RAM process *(33)*. The RAM has been applied as a mechanism to determine whether procedures or indications are expected to provide a specific health benefit, designated as ''appropriate'', that exceeds the potential negative consequences by such a wide margin that the procedure or indication is worth doing, irrespective of cost. The rationale for use of the RAM for the PDC is its ability to combine the best available scientific evidence with the collective judgment of experts in the bone field.

During the first two days, a representative of each Task Force group or sub-group presented their proposed Official Positions with supportive evidence to the Expert Panel at a meeting open to the public and attended by ISCD / IOF members, industry representatives, and other individuals with an interest in bone disease and densitometry. All participants were encouraged to provide comments and suggestions to the Expert Panelists. Following discussion, each member of the Expert Panel graded the proposed Position according to the criteria below. In making their recommendations, they considered the level of the medical evidence, expert opinion and the clinical need for a recommendation. In some instances, regulatory issues received consideration. Statements rated as ''appropriate'' with a sufficient level of ''agreement'' among the panelists were accepted as Preliminary Official Positions. Those that were considered ''uncertain'' or for which there was ''disagreement'' were then discussed further by the Expert Panelists and the Task Force chairs in closed session on the last day of the conference. Finally, Task Force chairs re-presented reports on their topics supporting the ''uncertain'' statements to the Expert Panel. Re-rating of ''uncertain'' statements occurred when the PDC Moderators felt there was a significant likelihood of change in the opinions of the Expert Panel.

After all statements rated as ''appropriate without disagreement'' had been selected and all supporting evidence presented, the Expert Panel performed a final rating for necessity, quality of the evidence, strength of the recommendation, and application of the recommendation. Lastly, the Expert Panelists determined the final wording of the proposed Official Positions.

Grading of the Official Positions

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) *(24,33)*:

1. ***Appropriateness*** *(graded from 1 = inappropriate to 9 = appropriate)* ***and Agreement:***

   A statement was defined as ''appropriate'' when the expected health benefits exceeded the expected negative consequences by such a significant margin that it was worthy of inclusion. Statements with a median score of 1−3 were not further considered. Statements with a median score between 4 and 6 were designated as ''uncertain.'' Agreement among the Expert Panelists was also required before a statement was considered for inclusion as a preliminary Official Position. ''Disagreement'' or lack of consensus was defined as four or more Expert Panelists' ratings in the upper or lower tertiles (e.g. 1−3 and 7−9). The statements rated as ''appropriate'' with a median score of 7 or higher without ''disagreement'' by the Expert Panel were designated as preliminary Official Positions. The statements rated as ''uncertain'' or any with ''disagreement'' were further discussed at the PDC. Preliminary official positions that were approved by the ISCD Board of Directors were designated as the Official Positions of the Society.

2. *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.

3. *Strength of recommendations*

   A: Strong recommendation supported by the evidence

   B: Recommendation supported by the evidence

   C: Recommendation supported primarily by expert opinion

4. *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.

Selection of the 2010 Joint ISCD-IOF Official Positions

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 Society. 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. The accompanying papers from each Task Force provide background, detailed rationale, and published references, which led to these Official Positions and can be found in this issue of *Journal of Clinical Densitometry.*

In addition, a resource document summarizing the discussions and conclusions of the PDC can be found in *Osteoporosis International*. The present summary informs clinicians about the use of FRAX in clinical practice and specifically the qualitative adjustments that can be made for many of the clinical risk factors resulting in improved refinements in the interpretation of FRAX-derived fracture probabilities *(34)*. Although the list of proposed enhancements to FRAX is large, in many instances these cannot presently be implemented due to insufficient data. However, an explanation and understanding of the reasons may be helpful in translating the information provided by FRAX into clinical practice.

Participants

The FRAX Initiative was comprised of the Organizers, Task Force liaisons, the three Task Forces, Moderators and the Expert Panel. Details of the participants can be found in Appendix.

Financial Support

Financial support for the 2010 PDC was received in the form of unrestricted grants from (in decreasing level of sponsorship) Amgen Pharmaceuticals, Servier, Hologic Inc, GE Healthcare/Medist, Daiichi-Sankyo, Terapia Ranbaxy, MSD, GlaxoSmithKline, Ascendys, Novartis, Teva, Eli Lilly & Company, CHUV (Lausanne University Hospital), Nycomed Switzerland , Besins Healthcare / Sodimed, Roche Switzerland, Chimimport-Plurimex, Romgermed Medical Group, Bioclinica, Synarc, Medimaps, Scanco Medical, Hyllan, Medilink, BeamMed. Funders and their representatives had no role in the selection of PDC topics, participants, or development and rating of the joint ISCD-IOF Official Positions.

Cumulative ISCD Official Positions

According to the model established by previous PDCs, a summary of the ISCD Official Positions would include combining the previous 2001, 2003, 2005 and 2007 PDCs with the 2010 PDC held in Bucharest, Romania. However, it was felt the joint ISCD-IOF PDC had such a unique focus on FRAX that it would be more appropriate as a stand-alone addendum to all previous PDCs.

New Joint ISCD-IOF Official Positions

The new joint ISCD-IOF Official Positions resulting from the 2010 PDC are summarized below. It should be noted that for a number of Task Force topic questions the Expert Panel could not reach a median score sufficient to rate the associated recommendations as appropriate. This does not imply the questions were unimportant but rather that the existing supportive scientific information at the time of the PDC was insufficient for the Expert Panel to rate them as ''appropriate without disagreement.''

Introductory Statements

1. FRAX® is a computer-based algorithm which uses easily obtained clinical risk factors to estimate an individual's 10-year fracture probability. It may be utilized by clinicians to assist in the identification of patients at high risk for fractures.

FRAX Clinical Statements *(35–45)*

2. Impaired functional status in patients with rheumatoid arthritis may be a risk factor for clinical fractures. FRAX may underestimate fracture probability in such patients.
   Grade: Good, A, W

3. There is no consistent evidence that non-glucocorticoid medications for rheumatoid arthritis alter fracture risk.
Grade: Fair, B, W

4. While there is evidence that duration and dose of tobacco smoking may impact on fracture risk, quantification of this risk is not possible.
Grade: Fair, B, W

5. Falls are a risk factor for fractures but are not accommodated as an entry variable in the current FRAX model. Fracture probability may be underestimated in individuals with a history of frequent falls, but quantification of this risk is not currently possible.
Grade: Good, A, W

6. There is a relationship between number of prior fractures and subsequent fracture risk. FRAX underestimates fracture probability in persons with a history of multiple fractures.
Grade: Good, A, W

7. There is a relationship between severity of prior vertebral fractures and subsequent fracture risk. FRAX may underestimate fracture probability in individuals with severe vertebral fractures.
Grade: Good, A, W

8. While there is evidence that hip, vertebral, and humeral fractures appear to confer greater risk of subsequent fracture than fractures at other sites, quantification of this incremental risk in FRAX is not possible.
Grade: Fair, B, W

9. A parental history of non-hip fragility fracture may be a risk factor for fracture. FRAX may underestimate fracture probability in individuals with a parental history of non-hip fragility fracture.
Grade: Fair, B, W

10. Evidence that bone turnover markers predict fracture risk independent of BMD is inconclusive. Therefore, bone turnover markers are not included as risk factors in FRAX.
Grade: Good, C, W

11. There is a dose relationship between glucocorticoid use of greater than 3 months and fracture risk. The average dose exposure captured within FRAX is likely to be a prednisone dose of 2.5-7.5 mg/day or its equivalent. Fracture probability is under-estimated when prednisone dose is greater than 7.5 mg/day and is over-estimated when prednisone dose is less than 2.5 mg/day.
Grade: Good, A, W

12. Frequent intermittent use of higher doses of glucocorticoids increases fracture risk. Because of variability in the dose and dosing schedule, quantification of this risk is not possible with use of the FRAX tool.
Grade: Good, B, W

13. High dose inhaled glucocorticoids may be a risk factor for fracture. FRAX may underestimate fracture probability in users of high dose inhaled glucocorticoids.
Grade: Fair, B, W

14. Appropriate glucocorticoid replacement in individuals with adrenal insufficiency has not been shown to increase fracture risk. In such patients, use of glucocorticoids should not be included in FRAX calculations.
Grade: Fair, B, W

FRAX BMD Statements *(35)*

15. Measurements other than BMD or T-score at the femoral neck by DXA are not recommended for use in FRAX.
Grade: Good, A, W

16. 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

17. 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

18. The ISCD 2007 PDC Statements *(20,24)* 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

19. Currently validated heel QUS devices, using criteria defined in the 2007 ISCD PDC *(20,24)*, predict fracture risk similarly.
Grade: Good, A, W

20. 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 a BMD measurement.
Grade: Good, A, W

21. It is not appropriate to use FRAX to monitor treatment response.
Grade: Good, C, W

22. Evidence that 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

FRAX International Statements *(35–45)*

23. Separate FRAX models are available for US Asians, Blacks and Hispanics because hip and major osteoporotic fracture rates are lower in these ethnic groups than in US Whites. Until additional data are available, the US Caucasian FRAX calculator should be used to assess fracture risk in US Native American women.
Grade: Fair, B, W

24. Changing fracture and mortality rates and improved quality of data are expected. Therefore, periodic review of country-specific fracture rates used in the FRAX model is recommended.
Grade: Good, B, W

25. There is significant variability in hip fracture rates throughout the world. The minimum requirement for construction of a country-specific FRAX model is hip fracture incidence data that are of high quality and representative of that country.
Grade: Good, A, W

26. The accuracy of FRAX models is improved by the inclusion of country-, age- and sex-specific rates of other major osteoporotic fractures (clinical vertebral, humerus, distal forearm).
Grade: Good, B, W

27. In the absence of high quality, national hip fracture data, a country-specific FRAX model can be built using hip fracture incidence rates from a surrogate country, but with incorporation of country-specific mortality rates.
Grade: Fair, C, W

28. In the absence of any hip fracture data, development of FRAX models based on broad categories of fracture risk (e.g. low, medium, high), adjusted for country-specific mortality rates is recommended.
Grade: Fair, C, W

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Appendix. Position Development Conference Members

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FRAX® Clinical: Eugene V. McCloskey (Chair), Neil Binkley (Co-chair), Jonathan D. Adachi, Sanford Baim (Program committee liaison), Robert D. Blank, Steven Boonen, Susan B. Broy, Olivier Bruyere, Manju Chandran, Cyrus Cooper, Bess Dawson-Hughes (Co-program committee liaison), Richard Eastell, Kris Ensrud, Hans P. Dimai, Joseph Foldes, Patrick Garnero, Piet P. Geusen, Andrea Griesmacher, Marian T. Hannan, John A. Kanis, Michael Kleerekoper, Marc-Antoine Krieg, Bente Langdahl, Andrew Laster, Edward S. Leib, Tahir Masud, Mike McClung, Howard Morris, Sergio Ortolani, Kenneth G. Saag, Ethel Siris, Stuart Silverman, S. Bobo Tanner, Tommaso Trenti, Samuel Vasikaran, Peter Vestergaard, Denys A. Wahl.

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Expert Panel: John P. Bilezekian (Moderator), Socrates E. Papapoulos (Co-moderator), Jonathan D. Adachi, Robert D. Blank, Roland Chapurlat, Wu (Paulo) Chih-Hsing, Edward Czerwinski, Aldolfo Diez Perez, Hans P. Dimai, Ghada El-Hajj Fuleihan, Saeko Fujiwara, Ruxandra M. Ionescu, John A. Kanis, Mike McClung, Sergio Ragi-Eis, Jan Stepan, Kenneth G. Saag, John T. Schousboe, Wei Yu, Cristiano Zerbini.

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