FRAX updates 2012

Eugene McCloskey[a,b] *and John A. Kanis*[b]

Purpose of review
There is an increasing recognition that the management of osteoporosis requires the characterization of fracture risk to be based on absolute risk rather than single measures such as bone mineral density (BMD). FRAX, the most widely used tool that incorporates clinical risk factors with or without BMD, was launched in 2008. This brief review addresses the development of FRAX since then and describes some of the issues that continue to be discussed as FRAX plays an increasing role in clinical practice.

Recent findings
FRAX is a platform technology that will continue to develop. High-quality updated epidemiology of fracture and mortality can lead to recalibration of models. The addition of new risk factors is complex as the process requires validation in an international setting as well as a comprehensive assessment of how such new factors interact with the existing FRAX variables. Nonetheless, clinical interpretation can be enhanced by taking into account the potential adjustments of FRAX probabilities and several of these are described.

Summary
FRAX is being incorporated in an increasing number of clinical guidelines, and assessment and intervention thresholds have been provided to instruct clinical decision-making. There is an increasing body of evidence that patients deemed at highest risk of fracture by FRAX, with or without the use of BMD, will overlap significantly with those identified by previous guidelines and will respond to appropriate osteoporosis therapy.

Keywords
epidemiology, fracture risk, FRAX, guidelines, treatment

INTRODUCTION

The ultimate aim of osteoporosis clinical management is to reduce the incidence of fractures in those identified to be at highest risk. The important role of bone mineral density (BMD) in defining osteoporosis and assessing fracture risk tool was recognized by the WHO in 1994 [1]. Since then, treatment decisions have largely been driven by a combination of clinical judgment and the BMD value, expressed as the T-score. In the context of fracture risk assessment, prospective studies [2,3] with BMD, usually measured by dual-energy X-ray absorptiometry (DXA), indicate that the risk of fracture approximately doubles for each standard deviation (SD) reduction in BMD. However, the measurement of BMD, like any prognostic risk factor in a multifactorial disease, only captures a component of the likelihood of the outcome. Thus, in osteoporosis, BMD captures a minority of the fracture risk, for example, the increase in hip fracture risk with age is approximately seven times greater than expected on the basis of age-related BMD loss alone. Thus, intervention thresholds based on BMD alone lack sensitivity over most reasonable assumptions – that is, the detection rate is low [4]. The use of clinical risk factors (CRFs) that add information on fracture risk independently of BMD improves the sensitivity of the assessment for any specificity [4]. Over the past decade, several groups have developed tools that make use of this approach [5–7], most notably the FRAX tool (www.shef.ac.uk/FRAX) (Fig. 1). FRAX is a computer-based tool that integrates clinical information in men and women, with or without femoral neck BMD, to calculate the 10-year probability of a major osteoporotic fracture (distal forearm, proximal humerus, clinical spine and hip) and hip fracture alone [5]. Uniquely, it is calibrated to the local epidemiology of fracture and mortality within countries and, in some cases, within ethnicities.

[a]Academic Unit of Bone Metabolism and [b]WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK

Correspondence to Eugene McCloskey, Professor of Adult Bone Diseases, Academic Unit of Bone Metabolism, Metabolic Bone Centre, Northern General Hospital, Herries Road, Sheffield, S5 7AU, UK. Tel: +44 114 2714705; e-mail: e.v.mccloskey@shef.ac.uk

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KEY POINTS

- Osteoporosis management should be directed by absolute fracture risk rather than BMD alone.
- FRAX, the most widely used prediction algorithm, is able to incorporate the updated epidemiology of fracture and mortality.
- There is increasing awareness of the ways in which FRAX probabilities may be adjusted to aid in clinical decision-making.
- Patients identified by high FRAX probabilities, with or without BMD, overlap significantly with those identified under current guidelines and are responsive to treatment.

Currently, it is available in 50 models for 45 countries and the website has been translated into 19 languages (FRAX version 3.6). Approximately 2.8 milllion calculations are processed by the website each year. FRAX has also been incorporated into DXA scanners to provide FRAX probabilities at the time of BMD measurement. For those without internet access, desktop versions of FRAX can be downloaded (www.who-frax.org) and an application for the iPhone or iPad has been developed by the International Osteoporosis Foundation (IOF) (http://itunes.apple.com/us/app/frax/id370146412?mt=8). A FRAX pad is also available in several languages from the IOF (www.iofbonehealth.org) to capture patients' risk variables prior to medical consultation. The purpose of this short review is to provide an update on the developments of the FRAX tool since its launch in April 2008 and to discuss some of the issues around its clinical interpretation.

EPIDEMIOLOGY AND UPDATING FRAX

The core algorithms within FRAX have been derived from meta-analyses of primary data on CRFs from prospective population-based studies of fracture risk [5,8–14]. These analyses permitted the interdependence of each of the risk factors for outcomes

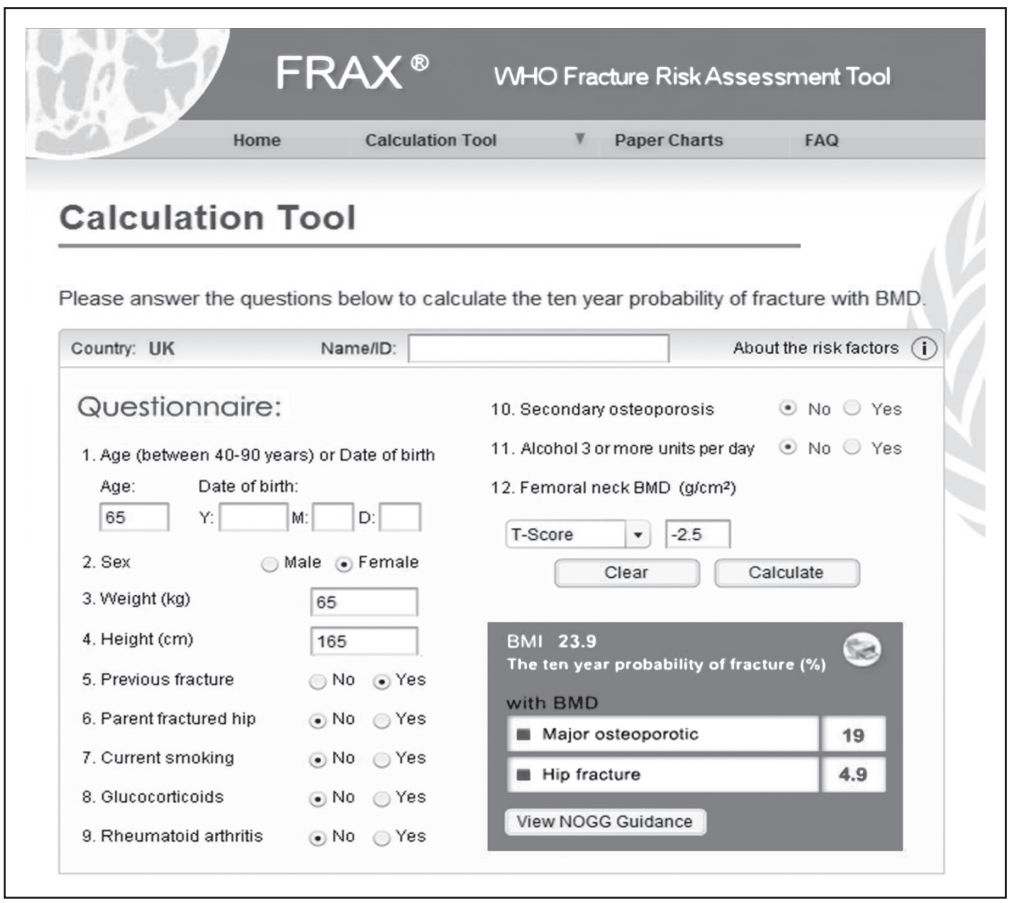

FIGURE 1. Screenshot for input of data and output of results in the UK version of the FRAX tool (FRAX, version 3.6. http://www.shef.ac.uk/FRAX). With permission of the WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK.

of fracture and mortality to be examined and combined for clinical use.

The need for calibration of any fracture algorithm is driven by the significant variability in hip fracture and mortality rates throughout the world [15▪,16]. The minimum requirement to construct a country-specific FRAX model is the availability of high-quality, representative hip fracture incidence data. Where possible, the ideal is to also have country-specific, age-specific and sex-specific rates of other major osteoporotic fractures (clinical vertebral, humerus and distal forearm). Frequently such data are not available, so that the FRAX model is constructed using age-specific and sex-specific ratios of hip to these other fractures. 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. Changing fracture and mortality rates and improved quality of data are expected over time, so that periodic review of country-specific fracture rates is recommended. Since the launch of FRAX in 2008, updated epidemiology has been incorporated into a number of models, for example, the USA [17].

CONSIDERATIONS AROUND RISK FACTORS IN FRAX

FRAX should not be considered as a gold standard in patient assessment, but rather as a reference platform that can be developed. FRAX risk factors, well recognized independent contributors to fracture risk, were purposefully selected to be limited in number and easily captured, but this simplicity has engendered some criticism, for example, FRAX only accommodates a yes or no response to the question of glucocorticoid exposure and does not take account of the extent of exposure. Similar examples of 'dose–response' include the number of prior fractures, the consumption of alcohol and ranges of severity of disease, particularly rheumatoid arthritis. These apparent limitations and their implications have recently been addressed in a joint exercise between the International Society of Clinical Densitometry (ISCD) and the IOF [18▪,19▪▪,20▪▪,21▪]. This exercise recognized that adjustment of FRAX would require information not only on fracture risk associated with these exposures but also their inter-dependence on the other FRAX risk variables and their independent effect on mortality. Such information will be derived from future population cohorts, but in the meantime available research can temper clinical judgement [20▪▪] and interpretation and examples related to rheumatology are discussed briefly below.

Long-term use of oral glucocorticoids

An example of a potential adjustment to FRAX probabilities has recently been published for oral glucocorticoids [22▪▪]. This made the assumption that ever glucocorticoid use captured in FRAX is comparable to an average dose and duration of exposure to glucocorticoids as found in the studies of the UK General Practice Research Database (GPRD) [23–25]. The recent analysis explored the possible impact of different doses of glucocorticoids to that of the medium daily dose (2.5–7.5 mg prednisolone or equivalent) on fracture probability using the UK FRAX model and the fracture risks reported in GPRD. By the design of the analysis, the unadjusted FRAX value can be used at medium doses. For low-dose exposure (<2.5 mg daily), the probability of a major fracture was decreased by about 20% depending on age, whereas for high doses (>7.5 mg daily), probabilities can be upward revised by about 15% [22▪▪]. Conversion factors were also determined for the adjustment of hip fracture probability. It is important to note the limitations of this early approach to adjusting FRAX and caution should be exercised until the adjustment factors are independently validated. Other considerations need to be borne in mind, including the potential impact of the underlying disease on fracture risk independently of glucocorticoid therapy. There is reasonable evidence, for example, that chronic obstructive pulmonary disease (COPD) itself is a risk factor for fracture, so that the association with low-dose glucocorticoids may not be causal [26]. Currently, the best evidence of an independent effect on fracture risk for an underlying disease is that for rheumatoid arthritis, but the interplay between disease severity and fracture is less well established.

Severity of rheumatoid arthritis

Although functional disability has been associated with increased fracture risk in patients with rheumatoid arthritis, evidence is limited that more severe or active disease is associated with a greater fracture risk [27▪]. Apart from glucocorticoids, there is little evidence that therapies for rheumatoid arthritis adversely affect fracture risk. Indeed, anti-TNF therapies have consistently maintained or improved BMD and may decrease fracture risk [28▪,29]. Interestingly, the risk associated with rheumatoid arthritis from the FRAX cohorts is likely to be diluted by patients over-reporting the condition, but this

underestimation may be partly offset by improving the efficacy of therapies for rheumatoid arthritis.

POTENTIAL ADJUSTMENTS TO FRAX PROBABILITIES

Many clinicians have a wish list of risk factors not considered in FRAX, including increasing the number of causes of secondary osteoporosis, the inclusion of falls risk, bone turnover markers and lumbar spine BMD. Given the proviso recognized in the ISCD/IOF review that new, high-quality data are required to modify the algorithms, consideration can be given to potential methods of adjusting the probability outcomes rather than the FRAX models themselves.

More than 80 causes of secondary osteoporosis were noted in the U.S. Surgeon General's report on osteoporosis, of which only a minority are described in FRAX [30]. As stated earlier, with the exception of rheumatoid arthritis, FRAX assumes that their effects on fracture risk can usually be explained by the effect of the disease to decrease BMD. This may change as the evidence base improves. For example, recent studies [26,31▪] suggest that type-2 diabetes mellitus may influence fracture risk independently of FRAX probabilities and COPD may have BMD-independent effects on fracture risk.

The lack of prior falls as a distinct risk variable in FRAX is a frequent criticism [32▪]. Several problems need to be overcome, primarily related to the inconsistent capture of falls risk within the FRAX and other cohorts, but also to lack of international data on falls risk and its interaction with FRAX variables and mortality. For example, the construct of questions on prior falls is very heterogeneous with a marked impact on the apparent prevalence of falls (Fig. 2). It is important to note that falls risk is partially, if indirectly, taken into account in the algorithm, given the association between some of the FRAX variables and falls (e.g. age, prior fracture and excess alcohol intake). Until better data are available, it is reasonable to assume that individuals who fall more frequently than the average are likely to have a higher fracture probability than that provided by FRAX [19▪▪]. The obverse is, of course, also true.

There are a number of limitations to the incorporation of bone turnover markers into risk prediction models, including biological variability and multiple methodologies used for the same analyte [33▪▪]. The associations between markers and fracture outcomes have been heterogeneous, and there are little or no data examining the interactions between the markers and other FRAX variables in an international perspective [33▪▪].

The femoral neck is the only skeletal region of interest currently validated for use with FRAX. For any given age and BMD, the fracture risk is approximately the same in men and women so that the T-score used in FRAX is derived from a single reference standard (the NHANES III database for female Caucasians aged 20–29 years) [3,34,35]. Although the lumbar spine BMD or T-score cannot be substituted for those at the femoral neck, there are situations where consideration of a large discordance between the two sites in individuals might enhance the accuracy of risk assessment. In a recent exploration of the potential adjustment, there was an approximately 10% change in fracture risk for each unit of T-score discordance [36▪]. On this basis, the authors proposed that the clinician may

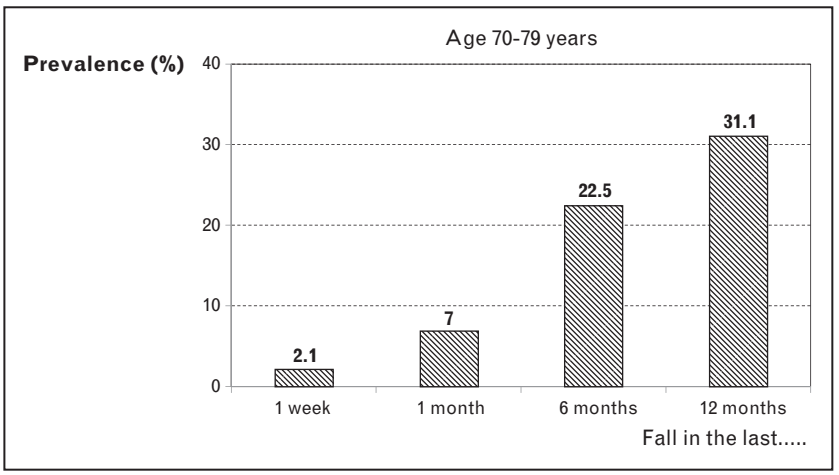

FIGURE 2. Prevalence of prior falls in 70–79-year-old women from a variety of cohorts demonstrating the heterogeneity in the interval over which falls history is captured and the impact on prevalence (unpublished data; with permission of the WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK).

'Increase/decrease FRAX estimate for a major fracture by one-tenth for each rounded T-score difference between the lumbar spine and femoral neck'. This rule may provide some guidance for physicians, particularly for those reporting on patients with probabilities lying close to an intervention threshold, but requires external validation in independent cohorts.

FRAX, TREATMENT RESPONSIVENESS AND GUIDELINES

An important consideration in the design of FRAX was to identify a fracture risk that is amenable to therapeutic intervention. Despite wide acceptance of the tool, there has been controversy surrounding the use of FRAX in targeting therapies without ensuring that BMD is low. This reflects the fact that the entry criteria for most, but not all, clinical trials of fracture prevention have been based upon the presence of a reduced BMD. Differences in interpretation of these data have largely been accommodated by differences in international guideline recommendations around treatment directed by FRAX in the absence of a BMD test [37–39]. It is important to note that the CRFs in FRAX are not totally independent of BMD. Indeed, there is a weak but significant correlation between the CRF score for hip fracture (assessed without BMD) and BMD at the femoral neck ($r = -0.25$) [40]. This indicates that the selection of individuals with the use of FRAX, without knowledge of BMD, will preferentially select those with low BMD and that the higher the fracture probability, the lower will be the BMD (Fig. 3) [41,42▪▪]. A large body of data on a wide variety of interventions indicates that treatment effects, with the possible exception of alendronate, are not dependent on baseline BMD. These data strongly suggest that FRAX identifies high-risk patients who respond to pharmaceutical interventions, a finding that has been confirmed in an increasing number of post hoc analyses of fracture trials [43▪,44▪,45–47].

CONCLUSION

As ever, clinical judgement cannot be replaced by any algorithm. Much discussion continues around the development of guidelines incorporating FRAX. Some have stated, perhaps perversely, that the use of probability is ageist and prevents fracture prevention therapy in the very elderly; they argue that a higher risk, calculated without accounting for mortality, would prompt treatment. The flaw in this interpretation is that it assumes that clinical judgement can only be applied in the case of fracture incidence (i.e. deciding not to treat a high-risk elderly person because of concomitant morbidities and poor life-expectancy), whereas exactly the same clinical judgement cannot be used to decide to treat an older person with a slightly lower probability but better life-expectancy.

Of the various fracture risk tools available, FRAX has a number of advantages. With regard to clinical utility, it has been incorporated in an increasing number of clinical guidelines so that assessment and intervention thresholds have been provided to instruct clinical decision-making (e.g. www.shef.ac.uk/NOGG). Furthermore, in contrast to many other algorithms, there is an increasing body of evidence that patients deemed at highest risk of fracture by FRAX, with or without the use of BMD,

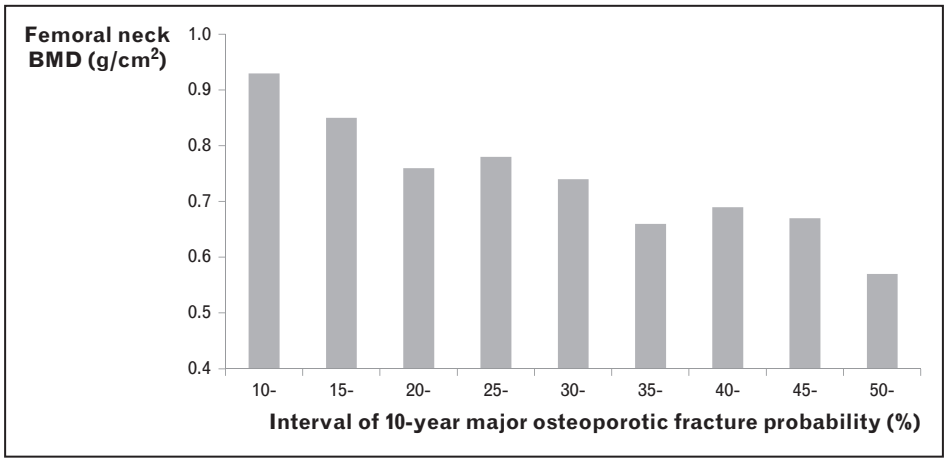

FIGURE 3. Mean bone mineral density (BMD) at the femoral neck (with 95% confidence intervals) in randomly selected women aged 75 years or more according to their 10-year probability of a major fracture calculated without BMD (data from [41]).

will overlap significantly with those identified by previous guidelines and will respond to appropriate osteoporosis therapy.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 592).

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12. Kanis JA, Johansson H, Oden A, *et al.* A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004; 19:893–899.
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The country-specific risk of hip fracture and the 10-year probability of a major osteoporotic fracture were determined on a worldwide basis from a systematic review of literature. There was a greater than 10-fold variation in hip fracture risk and fracture probability between countries.

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17. Ettinger B, Black DM, Dawson-Hughes B, *et al.* Updated fracture incidence rates for the US version of FRAX. Osteoporos Int 2010; 21:25–33.
18. ■ Cauley JA, El-Hajj Fuleihan G, Arabi A, *et al.* Official Positions for FRAX(R) clinical regarding international differences from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). J Clin Densitom 2011; 14:240–262.

A review of issues around epidemiological inputs into FRAX and their implications. These include the use of surrogate countries when no model exists and assumptions around ethnic specific calculators.

19. ■■ Hans DB, Kanis JA, Baim S, *et al.* Joint Official Positions of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX((R)). Executive Summary of the 2010 Position Development Conference on Interpretation and use of FRAX(R) in clinical practice. J Clin Densitom 2011; 14:171–180.

A summary of the joint initiative between the two societies to examine and clarify a number of important issues pertaining to the interpretation and implementation of FRAX() in clinical practice. The resulting Official Positions are intended to enhance the quality and clinical utility of fracture risk assessment worldwide.

20. ■■ Kanis JA, Hans D, Cooper C, *et al.* Interpretation and use of FRAX in clinical practice. Osteoporos Int 2011; 22:2395–2411.

A study reviewing the resource documents and joint position statements of ISCD and IOF. Details on the clinical risk factors currently used in FRAX, and the reasons for the exclusion of others, are provided. A helpful explanation to aid translation of the information provided by FRAX into clinical practice.

21. ■ Lewiecki EM, Compston JE, Miller PD, *et al.* Official Positions for FRAX(R) Bone Mineral Density and FRAX(R) simplification from Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). J Clin Densitom 2011; 14:226–236.

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.

22. ■■ Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 2011; 22:809–816.

The aim of this work was to estimate the adjustment for FRAX probability based upon the dose of glucocorticoids. Dose responses for fracture risk during glucocorticoid exposure were taken from the General Practice Research Database and used to adjust the relative risks in FRAX. An adjustment for the death hazard was estimated and both variables were used to populate the FRAX model for the UK. For low-dose exposure (<2.5 mg daily of prednisolone or equivalent), the probability of a major fracture was decreased by about 20%, whereas that for high doses (>7.5 mg daily) was increased by about 15%. A relatively simple adjustment of conventional FRAX estimates of probabilities of hip fracture and a major osteoporotic fracture can be applied to modulate the risk assessment with knowledge of the dose of glucocorticoids.

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This review examined whether disease severity or activity in rheumatoid arthritis is associated with a greater risk for fracture. Although many studies document a correlation between various parameters of disease activity or severity and decreased bone density, few have associated these variables with fracture risk. There was little evidence to correlate measures of disease, such as DAS or acute phase reactants, and increased fracture risk. FRAX may underestimate the fracture probability in patients with impaired functional status from rheumatoid arthritis but that this could not be quantified at this time.

28. ■ Roux C. Anti-TNFα therapy and prevention of bone loss in rheumatoid arthritis. IBMS BoneKEy 2011; 8:154–158.

The increase in bone resorption related to chronic inflammation is increasingly recognized. Anti-TNFα therapy is an effective therapy for RA and appears to have a positive effect on bone loss through its potent anti-inflammatory effect.

29. Coulson KA, Reed G, Gilliam BE, *et al.* Factors influencing fracture risk, T score, and management of osteoporosis in patients with rheumatoid arthritis in the Consortium of Rheumatology Researchers of North America (CORRONA) registry. J Clin Rheumatol 2009; 15:155–160.
30. Office of the Surgeon General (US). Bone health and osteoporosis: a report of the surgeon general. Office of the Surgeon General (US) Rockville; 2004.

31. Giangregorio LM, Leslie WD, Lix LM, *et al.* FRAX underestimates fracture risk ■ in patients with diabetes. J Bone Miner Res 2012; 27:301–308.

This study, conducted in a large clinical database from Manitoba, Canada, examined whether diabetes is a risk factor for incident hip or major osteoporotic fractures independent of FRAX. Diabetes was a significant predictor of subsequent major osteoporotic fracture [hazard ratio = 1.61, 95% confidence interval (CI) 1.42–1.83] after controlling for age, sex, medication use and FRAX risk factors including BMD. Similar results were seen after adjusting for FRAX probability directly (hazard ratio = 1.59, 95% CI 1.40–1.79). Diabetes was also associated with significantly higher risk for hip fractures ($P < 0.001$). This study suggests that diabetes might be considered for inclusion as an independent risk factor in future iterations of FRAX.

32. Masud T, Binkley N, Boonen S, Hannan MT. Official Positions for FRAX(R) ■ clinical regarding falls and frailty: can falls and frailty be used in FRAX(R)? From Joint Official Positions Development Conference of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX(R). J Clin Densitom 2011; 14:194–204.

The remit of this study was to review the evidence and consider whether falls should be incorporated into the FRAX model or, alternatively, to provide guidance to assist clinicians in clinical decision-making for patients with a falls history. Clinicians should recognize that patients with frequent falls may be at higher fracture risk than currently estimated by FRAX and include this in decision-making. In the long term, incorporation of falls as a risk factor in the FRAX model would be ideal.

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This review evaluated the clinical potential of bone turnover markers (BTMs) in the prediction of fracture risk and for monitoring treatment. It concluded that there is still a need for stronger evidence on which to base practice in both situations. Importantly, the review recommends one bone formation marker (serum PINP) and one bone resorption marker (serum CTX) to be used as reference markers and measured by standardized assays in observational and intervention studies in order to enlarge the international experience of the application of markers to clinical medicine and to help resolve uncertainties over their clinical use.

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35. Kanis JA, McCloskey EV, Johansson H, *et al.* A reference standard for the description of osteoporosis. Bone 2008; 42:467–475.

36. Leslie WD, Lix LM, Johansson H, *et al.* Spine-hip discordance and fracture risk ■ assessment: a physician-friendly FRAX enhancement. Osteoporos Int 2011; 22:839–847.

Discordance between lumbar spine and femoral neck T-scores is relatively common. The purpose of this study was to develop a procedure for adjusting FRAX probability based upon the T-score difference between the lumbar spine and femoral neck (termed offset). The following rule was formulated: 'Increase/decrease FRAX estimate for a major fracture by one tenth for each rounded T-score difference between lumbar spine and femoral neck'. The authors concluded that a simple procedure that incorporates the offset between the lumbar spine and femoral neck T-scores can enhance the fracture risk prediction under the FRAX system. The offset is currently being examined in other cohorts.

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42. Leslie WD, Morin S, Lix LM, *et al.* Fracture risk assessment without bone ■■ density measurement in routine clinical practice. Osteoporos Int 2012; 23:75–85.

This study examined clinical decision-making using FRAX probability assessed without BMD and compared it to current NOF guidelines. When 10-year probability for major osteoporotic fracture estimated without BMD was high (≥20%), the vast majority (93%) qualified for intervention under NOF guidelines, whereas among those at low risk (<10%), the vast majority (80.5%) did not satisfy any NOF intervention criteria. The benefit of including BMD in the risk assessment was greatest among those initially at moderate risk (10–19%). The authors concluded that FRAX without BMD is able to risk stratify women in terms of future fracture risk and could potentially be sufficient for clinical decision-making in many of those designated at low or high fracture risk.

43. McCloskey EV, Johansson H, Oden A, *et al.* Denosumab reduces the risk of ■ osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX(R). J Bone Miner Res 2012.

The aim of this study was to determine whether the antifracture efficacy of denosumab in the phase 3 FREEDOM study was dependent on baseline fracture probability assessed by FRAX. Denosumab reduced the fracture risk to a greater extent in those at moderate to high risk. For example, at 10% probability, denosumab decreased the fracture risk by 11% ($P = 0.629$), whereas at 30% probability (90th percentile of study population) the reduction was 50% ($P = 0.001$). The reduction in fracture was independent of prior fracture, parental history of hip fracture or secondary causes of osteoporosis.

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This study determined the efficacy of strontium ranelate in the SOTI and TROPOS studies as a function of baseline fracture risk assessed by FRAX. Treatment with strontium ranelate was associated with a significant 31% decrease in all clinical osteoporotic fractures (vertebral fractures included). Hazard ratios for the effect of strontium ranelate on the fracture outcome did not change significantly with increasing fracture probability.

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