The FRAX®: critical appraisal

The threshold for pharmacological intervention in osteoporosis remains controversial. Tools predicting the future risk of new fractures are increasingly used to establish a convenient individual risk:benefit ratio for a long-term treatment. The Fracture Risk Assessment Tool (FRAX®) is likely to become the most widely used tool for assessing fracture risk and is also likely to receive a WHO endorsement. The inevitable limitations will not hamper its value. As for any tool like this, a continuous process of validation and further development is highly warranted. The use of FRAX should be extended to other ethnicities for which a permutation factor was not established, and to those with additional specific frequent risk factors. For this process of validation and further development, the FRAX algorithms should be disclosed and challenged against new databases that are already available or that will be collected in the future. It should also be well understood that no substantial benefits are expected from a pharmacological intervention when the fracture risk is increased for reasons that are not treatable with bone-acting drugs.

KEYWORDS: fracture risk ▪ fragility fractures ▪ FRAX® ▪ osteoporosis ▪ osteoporosis treatment threshold

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The number of fragility fractures has been continuously increasing in Western countries and a further increase in numbers over the next years is anticipated as a result of the aging population [1].

Population interventions are only recommended to tackle extremely frequent risk factors, such as vitamin D deficiency in the elderly [2], or when the recommendations are of general health benefit, such as giving up smoking, moderate physical activity and a calcium-rich diet. A case-finding approach appears to be obligatory for a pharmacological treatment. This problem has been approached by the health authorities of some countries, such as Italy and France, by only granting drug reimbursement for patients at a higher risk of fractures. Patients were deemed to be at adequately high risk if they suffered prevalent vertebral and hip fracture and/or very low levels of bone mineral density (BMD). In the countries where drug reimbursability is not regulated and all registered drugs are automatically reimbursed, the threshold for pharmacological intervention is often recommended by scientific societies on the basis of low BMD values. Thus, for example, the North America Osteoporosis Foundation (NOF) recommended initiating therapy in patients with a T-score of -2.5 or lower in the lumbar vertebrae, hip or distal one-third radius [101].

However, it was soon realized that low BMD was only modulating the effect of other relevant risk factors such as age, previous fracture and corticosteroid therapy. By analyzing data from large epidemiological studies or their meta-analysis, it was found that the combination of several risk factors could substantially enhance fracture predictivity, allowing the development of tools to predict the future risk of fracture in postmenopausal women.

Most of the earlier tools were based on the analysis of a single database such as the Study of Osteoporotic Fractures (SOF) [3], the Rotterdam [4], the Dubbo [5], the Women's Health Initiative (WHI) studies [6] or those from a Canadian cohort [7]. It was also found to be more convenient to express the risk over a given lag time (typically 5 or 10 years), rather than in terms of relative risk.

On 21 February 2008, the WHO unveiled the Fracture Risk Assessment Tool (FRAX®) to calculate the percentage 10-year probability of a patient sustaining a fracture (10YFR) of the hip or other bones [102,8–10]. The databases used included 59,232 subjects, 249,898 person years, 957 hip fractures and 3495 osteoporotic fractures. For the extent of the study population and also for the WHO endorsement, FRAX is likely to become the reference tool for assessing fracture risk in most countries. The first national organization endorsing FRAX was the NOF [11], which revised its guidelines for the management of patients with osteopenia in the USA, and recommended initiating therapy in patients with osteopenia if the 10-year probability of sustaining a

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hip or other major osteoporotic fracture equaled or exceeded 3 and 20%, respectively [12]. The NOF recommendations for initiating therapy in patients with osteoporosis (i.e., in patients demonstrating evidence of a fragility fracture or a T-score of -2.5 or lower in the lumbar vertebrae, hips or distal one-third radius) remained unchanged, even for the patients in whom the estimated 10YFR was lower than 3 and 20% for hip and multiple fractures, respectively.

Risk factors included in the FRAX® model

At present, the FRAX permutation is specific for a number of countries and is achieved by simply multiplying the risk of the reference population by a fixed factor [102]. Thus, for example, by simulating 15 cases with a broad range of fracture risk, we found that the permutation of the risk for the Italian population is 35% lower than that of the Swedish women for any level of risk. In this regard, nothing is said for subjects who have been born and spent some of their life in one country and are now residing in a different country, or for those who live in an ancient multiethnic country (e.g., the USA or Brazil) and have mixed ethnic backgrounds. In these cases, adopting the mean genetic component of the risk appears to be more evidence based.

When calculating the 10YFR for both sexes, the FRAX tool takes into consideration three continuous variables and seven categorical risk factors. The continuous variables are:

- Age: the age range extends from 40–90 years;
- BMI (body weight divided by square height);
- BMD: only hip measurements are considered, but the 10YFR can be calculated without including the BMD in the permutation.

These three variables are strongly intercorrelated and give rise to an algorithm that is not disclosed in the FRAX website but can be roughly derived from the tables published in the WHO technical report [102] and in several other publications [8–10]. The value of this algorithm with the three continuous variables (age, BMD and BMI) cannot be compared with data published in the literature and it requires a prospective validation.

The FRAX also includes seven clinical dichotomous risk factors:

- History of fragility fractures (yes/no answer): a fragility fracture is a fracture sustained after falling from a height, not exceeding the body height or occurring after minimal or no trauma. The answer should be yes if the patient has sustained any fragility fractures;
- Parental history of hip fractures (yes/no answer): the answer should be yes if a biological parent has sustained a hip fracture;
- Current corticosteroid therapy (yes/no answer): the intake of corticosteroids is ranked as yes if the patient has been on prednisone or equivalent of at least 5 mg daily for at least 3 months;
- Rheumatoid arthritis;
- Current cigarette smoking (yes/no answer);
- Current alcohol abuse: 3 or more units of alcohol per day (yes/no answer);
- Conditions leading to bone demineralization (yes/no answer): the following are included in the FRAX model – insulin-dependent diabetes mellitus, menopause before the age of 45 years, hypogonadism, chronic malnutrition, malabsorption, chronic liver disease and untreated long-standing hyperthyroidism.

The FRAX is correcting the risk esteemed with the algorithm by fixed gradients that are specific for each clinical risk factor (CRF), see above. At variance to what is often implicitly suggested in the WHO report [102], these gradients appears to be fixed without cross-interactions. We simulated 155 cases with one, two and three CRFs and with a broad range of fracture risk. For these cases, the 10YFR was estimated by FRAX and the gradients for each CRF were then roughly estimated. The results of these simulations are listed in Table 1.

Major advantages of the FRAX tool

Until the FRAX tool became available, the only guidelines existing to determine whether or not a patient should be treated relied heavily on the patient's T-score for BMD. However, this meant over-treating many relatively young women with a low BMD but who were at low risk of fracture. When the decision to start treatment is taken, in most cases the treatment should be life-long, and it can be predicted that the long-term medication could potentially outweigh the possible benefits of the therapy if the risk is not adequately estimated. In many countries, owing to economic restraints, the drug reimbursement policy is based on a stringent pharmacoeconomic analysis (for example, NICE in the UK [103]) that might be appropriately calculated by making use of tools like FRAX.

Table 1. Approximate gradients associated with each clinical risk factor in FRAX®.

Risk factors	FRAX risk gradients (with BMD)		FRAX risk gradients (without BMD)	
	Hip fracture	*Multiple fractures*	*Hip fracture*	*Multiple fractures*
Previous fractures	1.55	1.50	2.1	2
Family history	2.12	1.64	2.1	1.7
Smoking	1.63	1.15	1.4	1.15
Glucocorticoid therapy	1.80	1.58	2.1	1.7
Rheumatoid arthritis	1.42	1.28	1.7	1.4
Secondary osteoporosis	1	1	1.7	1.4
Alcohol >3 units/day	1.50	1.25	1.4	1.2

The 10-year fracture risk derived from the computation of the three continuous variables is multiplied by the specific gradient whenever the clinical risk factor is occurring. The gradient apparently does not change when multiple clinical risk factors are present.
BMD: Bone mineral density; FRAX: Fracture Risk Assessment Tool.

Treatment compliance to osteoporosis treatment is typically low, and this is often due to a lack of motivation. In order to convince patients to take medications (with potential adverse effects) on a long-term basis, many clinicians describe the condition in a general, often colorful way, and these descriptions are highly variable among different experts. This is often perceived by other specialists as a sign of poor clinical and scientific evidence. From this point of view, the main advantage of the FRAX tool is that it provides objective and reproducible documentation of the severity and potential impact of the disease. In addition, by using the FRAX tool, only those at a substantially increased risk of fracture will be further investigated and treated. The patients and their treating clinicians are more likely to appreciate the impact of the disease if they know the probability of sustaining, for instance, a hip fracture, as opposed to a relative risk.

In conclusion, the broad diffusion of FRAX or similar tools might be of great help in improving the way osteoporosis management is perceived by the patients, care givers and healthcare providers.

Limitations of the FRAX tool

Although the FRAX tool represents a major step forward in the management of osteoporosis, it has significant limitations that may undermine its usefulness.

The 10YFR can be calculated without including the BMD evaluation, even though the predictivity of risk factors for low BMD is rather poor and mostly driven by body weight [13]. For establishing a treatment threshold, the FRAX without BMD evaluation might be considered acceptable in countries where dual x-ray absorptiometry (DXA) scans are not readily available. However, in such countries, even the treatment of patients with established or severe osteoporosis is often a remarkable achievement. Furthermore, the Hip Intervention Program study on risedronate has eloquently demonstrated that the fracture risk is not significantly reduced when patients are treated solely based on the presence of risk factors [14]. Thus, in countries where DXA scans are available, the FRAX without BMD should only be used for more conveniently selecting patients in whom a DXA evaluation is warranted, while its use for selecting patients for treatment should not be recommended [15].

The spine BMD or quantitative ultrasound (US) assessments are not included in the FRAX permutation, since the algorithm was only established on the hip BMD values. However, in some conditions, hip BMD cannot be obtained or only US devices are available. In these cases, permutation algorithms also allowing the use of spine BMD or US values would be warranted.

Parental history of hip fractures appears to be intuitively associated with the life-spans of the relatives since the risk of hip fracture rises exponentially with ageing. This limitation is tapered by the theoretical longer, genetically determined, longer life expectancy, which, paradoxically is a risk factor for hip fracture.

The risk associated with previous fractures raises a number of problems. With FRAX, the answer should be either yes or no, but it is not clear whether silent, mild morphometric vertebral compression fracture, detected by chance by DXA Vertebral Fracture Assessment or by an x-ray, should be included [16]. At present, the program does not differentiate whether the patient has sustained several fragility fractures or a single asymptomatic morphometric vertebral fracture. It is well known that the risk of fractures increases with the number and type of previous fractures sustained [17].

Some major risk factors for fractures are not taken into account, such as the risk of falling [18] and the use of medication that is likely

to interfere with the state of alertness, equilibrium or cognitive functions. These risk factors are only partially taken up by age.

Rheumatoid arthritis is considered by FRAX as an important risk factor. Other similar conditions are not considered, not because they are not harmful to bone, but rather because they are not sufficiently frequent to be detected as a risk factor in epidemiological studies. Thus, the lack of permutation with other similar diseases (psoriatric arthritis) or less common rheumatic diseases (spondiloarthritis, lupus and systemic sclerosis) is an objective limitation of the tool that might be missed by an approximation based on common sense, for example, by attributing the same risk gradient to these conditions.

Corticosteroid therapy is possibly one of the most prominent fracture risks. FRAX does not differentiate the risk according to the dose and the duration of treatment. Larger doses and longer duration should have more weight than a smaller dose for a shorter duration. Similarly, it is not taken into account if the patient has been on one or more courses of corticosteroids in the past. The attributed gradient risk by FRAX is considerably lower (at least 50% lower) than that found in the few available studies or in the placebo arm of randomized clinical trials [19].

The database used for FRAX development is comprehensive, but inevitably, a number of risk factors are overlooked, not because they are unimportant, but simply because they are rare. In addition to some rheumatic diseases, other risk factors that are definitely associated with osteoporosis and increased fracture risk include the use of a number of drugs (heparin and antiretroviral agents) and history of some diseases associated with even transient immobilization or poor nutrition. In addition, it seems logical to think that the nature or strength of risk factors for fracture may vary according to the women's age and/or the type of fracture. For example, parity and previous hormone replacement therapy is more likely to affect the risk of fracture early after menopause, but not at a more advanced age [20]. The risk of falling is not included in FRAX, possibly because this was found to be largely explained by aging. However, for the same age, the risk of falling is dependent on a variety of factors such as muscle strength, use of bezodiazepins, environmental risk, cognitive conditions and so on. For the future development of FRAX, it would be useful to include the number of falls that have occurred in the past year.

The FRAX tool is potentially a process in evolution, but it is not clear who is committed to that. The disclosure of the algorithm would allow the large-scale planning of a process of validation and further development, even with the inclusion of new risk factors.

FRAX is only suitable for use in a limited number of countries or ethnicities for which epidemiological data are available or were provided. Therefore, the tool will continually require updating.

FRAX & treatment threshold

Until now, decisions regarding osteoporosis therapy were made based on the presence or absence of fractures and of a T-score of -2.5 standard deviations or less, which remains the cornerstone for the definition of osteoporosis. Although these criteria are used by regulatory agencies, they fail to reflect the broad variety of situations encountered in clinical practice. FRAX is intended to take into account all these factors, but awareness of its limitations is crucial to ensure that this tool is used optimally.

FRAX should not be used for identifying a fixed threshold for pharmacological treatment for two important reasons. First, any decision regarding the commencement of a life-long therapy has to be taken on an individual (perception of the risk) and economic (willingness to pay) basis. Second, many CRFs used for estimating the 10YFR cannot be modified by a pharmacological approach, even though cost–effectiveness is likely to increase with the absolute risk.

Despite that, FRAX, with the additional value associated with the WHO endorsement, is likely to change the way of identifying candidates for pharmacological treatment for osteoporosis in many countries. Indeed, for the first time, one may obtain a value – the 10YFR – that can also be used by health authorities to work out the cost–benefits of pharmacological treatments. This use raises some practical problems. Since the 10YFR rapidly rises with aging, a fixed threshold might be considered inappropriate. Intuitively, a 10YFR of 10% is likely to be perceived differently in a woman aged 55 and otherwise in perfect health than in an 80-year-old patient with a number of other severe clinical problems.

This problem can be faced in two different ways. The most common approach has been to assess the cost–effectiveness of osteoporosis treatment based on the so-called quality-adjusted life years (QALYs) gained with a given pharmacological treatment. In this context, for prevention of osteoporotic fractures,

NICE in the UK used a GB£20,000/QALY threshold that rose in an USA evaluation to US$60,000/QUALY [7].

This approach might be perceived as unacceptable in many countries where the ratio between benefits and risks associated with any pharmacological therapy appears to be politically easier to explain and to be accepted.

An alternative approach, yielding basically the same results, but considerably easier to explain to individual patients, is to plot the value of the 10YFR obtained by using FRAX versus approximate normative values. This would provide a visual indication of how far the patient's risk is from the mean risk of the general population.

Conclusion & future perspective

■ FRAX validation & future development

The validation process is critically important for any tool of this nature and the validation should be both universal and country (or ethnicity) specific.

The lack of flexibility remains a critical limitation of FRAX. A flexible tool should allow the adjustment of risk gradients or even the inclusion of new risk factors agreed with the local health authorities. The disclosure of the algorithm remains the preliminary step to encourage individuals to start the process of validation and further development of FRAX. Alternatively, all major research centers will continue to elaborate their own algorithm with an inevitable huge loss of resources and opportunities.

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Executive summary

- The treatment threshold for osteoporosis is still controversial but of crucial importance for both individual patients and healthcare providers.
- Tools predicting the future risk of new fractures might be used to establish a convenient individual risk:benefit ratio and cost–effectiveness.
- The Fracture Risk Assessment Tool (FRAX®) is likely to become the most widely used tool for assessing fracture risk.
- FRAX, as for any tool of this kind, should undergo a process of validation and further development with the inclusions of other ethnicities and cohort-specific risk factors. This requires the disclosure of the underlying algorithms.
- The availability of this kind of tool is likely to substantially modify the general perception of osteoporosis.
- While establishing the threshold for a pharmacological intervention, it should be understood that many clinical risk factors used for estimating the fracture risk cannot be modified by bone-acting drugs.

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▪ **Details the potential uses of FRAX®, and pharmacological treatments of osteoporosis are also analyzed.**

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▪▪ **The analysis of epidemiological studies that allowed the development of FRAX are reported in detail.**

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