Absolute fracture risk

What does it mean for your patient?

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Fracture prevention is the main goal of treatment for osteoporosis. Absolute fracture risk calculators have been developed that aim to better quantify fracture risk and may help to guide treatment decisions in certain situations.

Key points

- **Absolute fracture risk calculators aim to better quantify fracture risk by incorporating clinical risk factors as well as bone mineral density (BMD) into risk estimations.**
- **Fracture risk calculators most commonly used in Australia are the WHO Fracture Risk Assessment Tool (FRAX) and the Garvan Fracture Risk Calculator (GFRC).**
- **Absolute fracture risk calculators may have clinical application for identifying patients at higher risk of fracture and potentially for better targeting therapy.**

ENDOCRINOLOGY TODAY 2015; 4(5): 31-34

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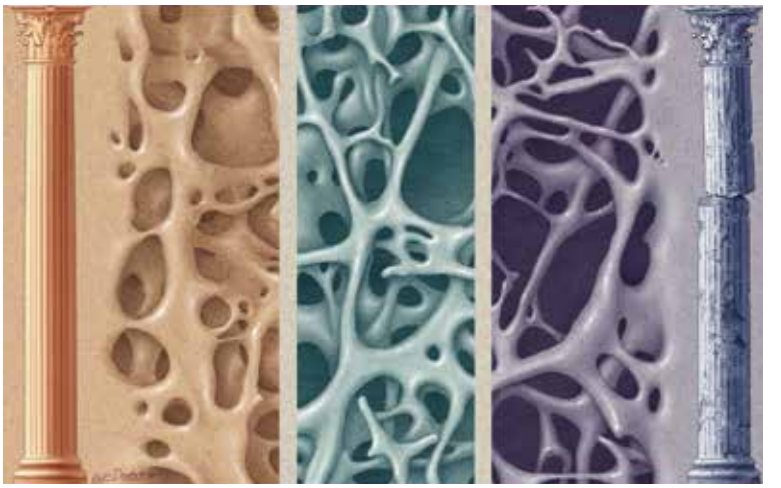

Bone mineral density (BMD), which is most commonly measured by dual energy x-ray absorptiometry (DXA), is one of the major determinants of fracture risk. BMD is categorised into normal, osteopenic or osteoporotic using T-score thresholds recommended by the WHO.[1,2] For every one unit of T-score decrease in BMD, an individual's relative fracture risk, compared with age-matched controls, increases about twofold.[3] The risk of low trauma (fragility) fractures is higher in the osteoporotic population than in the osteopenic population, but most fragility fractures seen in clinical practice occur within the osteopenic range of BMD because there are many more people with osteopenia than with osteoporosis.[4]

Several other (non-BMD) clinical risk factors are associated with fracture risk. Consequently, two individuals who have the same BMD measurement but different clinical profiles may have very different risks of fracture. Advancing age, a prior history of a fragility fracture and falls are the clinical risk factors most strongly associated with increased fracture risk.[5]

Relative risk and absolute risk

Risk may be described as either relative risk or absolute risk.

Relative risk is an individual's risk of an event (such as a fracture) compared with the risk of that event in a reference group or compared with background risk. Thus, the risk for an individual depends on the risk to which it is compared – for example, if the background risk of a fracture is low then even a doubling of that risk will still be low.

Absolute risk is the actual risk of the event for an individual over a specified period of time. Absolute osteoporotic fracture risk is usually expressed as an individual's percentage chance of an osteoporotic fracture over a given period of time, generally five or 10 years.

Absolute fracture risk calculators

Several absolute fracture risk calculators have been developed that aim to better quantify an individual's fracture risk by incorporating clinical risk factors as well as BMD into their risk calculations. These calculators may be useful for identifying patients at higher risk and potentially for better targeting therapy. The absolute fracture risk calculators that are most commonly used in Australia are:

- WHO Fracture Risk Assessment Tool (FRAX), available at https://www.shef.ac.uk/FRAX/tool.jsp – this calculator uses data from nine epidemiological studies and results of placebo-controlled arms of clinical studies to estimate fracture risk.[6,7]
- Garvan Fracture Risk Calculator (GFRC), available at http://www.garvan.org.au/promotions/bone-fracture-risk/calculator – this calculator was developed in Australia using data from the Dubbo Osteoporosis Epidemiology Study.[8,9]

Table. Risk factors included in absolute fracture risk calculators

WHO Fracture Risk Assessment Tool (FRAX)	Garvan Fracture Risk Calculator (GFRC)
Age	Sex
Sex	Age
Weight (kg)	Number of fractures since the age of 50 years
Height (cm)	Number of falls in past 12 months
Previous fracture	Weight OR femoral neck BMD
Parental history of fractured hip	
Current smoking	
Use of glucocorticoids	
Rheumatoid arthritis	
Secondary osteoporosis	
Alcohol intake	
Femoral neck BMD (g/cm^2)	
Trabecular bone score (TBS)*	

* TBS is a recent addition to FRAX. An adjusted 10-year probability of fracture can be calculated in FRAX if a TBS value is available.

The FRAX and GFRC differ in the algorithms used to estimate absolute fracture risk. The FRAX algorithm includes 13 risk factors whereas GFRC includes five (Table). Interestingly, fracture risk tools with five or fewer variables have been shown to perform as well as tools that have more variables.[10] Both FRAX and GRFC can be used to calculate absolute fracture risk when BMD measurement is not available because BMD is largely determined by age and weight.

FRAX calculates the absolute risk for both hip fracture and 'major osteoporotic fracture' (defined as clinical spine, hip, forearm and shoulder fracture). It was developed with multinational epidemiological data, so FRAX offers a country-specific correction to account for different baseline fracture and mortality rates of many countries, including Australia. (If a particular patient's country is not available in the list, use of the one that is most similar to the patient's background is recommended.)

There are other differences between FRAX and GFRC. The two calculators are predictive of a different spectrum of fracture risk: FRAX predicts spine, hip, forearm or shoulder fracture whereas GFRC predicts any osteoporotic fracture. In addition, the FRAX algorithm determines an individual's fracture risk over a 10-year period whereas the GFRC algorithm provides both five- and 10-year fracture predictions.

The FRAX and GFRC calculators each have their limitations.

- Falls-related fracture risk is excluded from the FRAX calculator. However, falls risk is a recognised independent risk of fracture.
- The FRAX questionnaire concerning previous fracture is a binary variable (yes/no) and does not account for multiple prior fractures. Fracture risk is increased with greater number of prior fractures.
- FRAX calculates a 10-year fracture risk for hip fracture and for the combined group of 'major osteoporotic' fractures. Many other fractures, including rib, other femur, tibia and fibular fractures, are excluded.
- GFRC does not include variables such as corticosteroid use or family history of fracture in its algorithm. These variables have independent predictive effects.
- GFRC is based on an Australian population and may be less reliable in immigrants who have spent a significant period of their lives overseas. However, it has been validated in several international populations, including Canada, The Netherlands and Poland.[11,12]

Trabecular bone score

Recently, FRAX has incorporated the trabecular bone score (TBS) into its algorithm. Although BMD is one of the risk factors for fracture, a number of patients fracture at higher than expected BMD. Bone microarchitecture is also known to contribute to overall fracture risk, but direct measurement of microarchitecture remains difficult to obtain without performing a bone biopsy. TBS provides an indirect index of trabecular microarchitecture by evaluating the pixel grey-scale variations in the lumbar spine DXA image (so patients do not require additional scanning) and has been shown to be an independent predictor of fracture.[13]

The addition of TBS into FRAX has been shown to improve fracture prediction in a prospective study cohort in Manitoba, Canada,[14] and in a meta-analysis of 14 multinational cohorts of 17,809 patients.[15] However, there are limitations of TBS, including decreased reliability in obese patients and in men. Although it is now included in FRAX, it is unclear by how much TBS improves fracture prediction over and above the other factors currently included in the calculators.

Predictive accuracy

Several studies have compared the ability of FRAX and GFRC to estimate fracture risk. Most validation studies agree that FRAX tends to underestimate the risk of fracture in both men and women; GFRC appears to perform at least as well as FRAX in postmenopausal women and possibly better in men.[16] The GFRC may overestimate fracture risk for patients in the highest quintile of risk, but osteoporosis treatment would generally be recommended in this group in any case.[17] Some studies have suggested that neither calculator provides a better estimate of fracture risk than using age and BMD alone.[18,19]

Barriers

There are two major factors limiting widespread uptake of absolute fracture risk calculators by clinicians. First, there is a general lack of awareness about how and when to use fracture risk calculators. This situation could be changing, however, as there is increased interest in the clinical application of these tools. Work is being undertaken to trial the integration of fracture risk calculators into GP software (this is

similar to the integration of cardiovascular risk calculators into the software). Second, the PBS does not recognise absolute fracture risk as an indication for access to subsidised therapies to treat osteoporosis.

Fracture risk threshold for intervention

An important clinical application for a fracture risk calculator is better selection of individuals for whom to recommend treatment. For individuals who are without fracture but are in the osteoporotic range (T score <-2.5 in the spine or hip) and for middle-aged to elderly individuals with prior fragility fracture, the calculated absolute fracture risk is generally high and confirms the need for treatment. A recent analysis has suggested that women aged over 70 years with prior fractures may have a sufficiently high risk of fracture to obviate the need for bone density testing, but in general this is not our clinical practice.[20]

Absolute fracture risk algorithms may, however, be particularly useful for individuals with BMD within the osteopenic range but with no prior history of fracture. Economic modelling using populations in the UK[21] and USA[22,23] has demonstrated that treatment is cost-effective when using FRAX to select at-risk patients. The US National Osteoporosis Foundation guidelines recommend treatment when the 10-year risk of hip fracture is at least 3% and the 10-year risk of major osteoporotic fracture is at least 20% based on FRAX scores.[24] This was based on a drug cost of $US600/year for five years (with 35% fracture reduction) and an average cost per quality-adjusted life year (QALY) gained of $US60,000.[23] However, there are no prospective studies validating the clinical benefit and cost-effectiveness of this recommendation. Post-hoc analyses of denosumab[25] and bazedoxifene (a third-generation selective oestrogen-receptor modulator)[26] suggest that reduction in relative risk of fracture is dependent on the initial absolute fracture risk; participants who had moderate to high risk of fracture as assessed by FRAX had the greatest benefit. Teriparatide, however, resulted in similar relative risk reduction regardless of baseline absolute fracture risk.[27,28]

Conclusion

Fracture prevention is the main goal of treatment for osteoporosis. Assessment of an individual's fracture risk can help to guide treatment, especially in situations where the need for treatment is unclear. It may also help to clarify situations of low absolute fracture risk where treatment is not indicated. Discussion of absolute fracture risk with patients may facilitate the uptake of treatment and potentially help them to better understand their own fracture risk, and thus make a more informed decision whether or not treatment would be warranted. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

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