Osteoporosis: advances in risk assessment and management

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ABSTRACT

In the past three decades, there have been major advances in our understanding of bone biology and these have been accompanied by a significant improvement in the management of osteoporosis. Fracture risk prediction algorithms using clinical risk factors, with or without measurement of bone mineral density, have enabled more accurate targeting of treatment and a range of cost-effective pharmacological interventions is available to reduce fracture risk. Despite these advances, a number of challenges remain. In particular, treatment rates in high-risk individuals are low and adherence to treatment is poor. Addressing this treatment gap through measures such as fracture liaison services, which provide a coordinated and cost-effective strategy for secondary fracture prevention, is an important future priority.

KEYWORDS: Bisphosphonates, bone density, fracture, FRAX, osteoporosis, risk factors

Assessment of fracture risk

Fracture risk algorithms

For many years, measurement of bone mineral density (BMD) by dual energy X-ray absorptiometry provided the main approach to fracture risk assessment, based on the inverse association between BMD and fracture risk. However, while this approach has high specificity, it has relatively low sensitivity and the majority of fractures in postmenopausal women occur at a BMD T-score higher than –2.5 (the World Health Organization (WHO) defined threshold for osteoporosis).[1] One reason for this is that some clinical risk factors increase fracture risk by mechanisms that are at least partially independent of BMD, and this provides the rationale for fracture risk algorithms that combine clinical risk factors and BMD.[2] These clinical risk factors include increasing age, low body mass index, previous fracture, a parental history of hip fracture, oral glucocorticoid therapy, some forms of secondary osteoporosis, tobacco use, alcohol abuse and falls.

The most widely used fracture risk prediction tool in the UK is FRAX,[3] which has been incorporated into the UK National Osteoporosis Guideline Group (NOGG) guideline and a number of other international guidelines, including the US National Osteoporosis Foundation guideline. FRAX estimates the 10-year fracture probability of hip fracture and of major osteoporotic fracture (hip, spine, wrist or humerus) from clinical risk factors, with or without hip BMD. The UK version of FRAX contains a link to the NOGG intervention thresholds, which are age-dependent and based on the fracture risk in a woman with a previous fracture in whom BMD is unknown.[4,5] In clinical practice, a case-finding strategy is generally adopted, using FRAX without BMD in individuals with clinical risk factors and then repeating the FRAX assessment with inclusion of BMD in those with intermediate fracture risk. Intervention thresholds should be used only as a guide to making decisions about treatment and do not replace clinical judgment.

Current NICE guidance on fracture risk assessment

National Institute for Health and Care Excellence (NICE) guidance on the assessment of fracture risk was issued in August 2012.[6] It recommends that fracture risk assessment should be considered in women aged ≥65 years and men aged ≥75 years, and also in younger women and men with clinical risk factors. The guidance states that fracture risk may be estimated using either FRAX or Qfracture;[7] measurement of BMD should be considered if fracture probability is close to the intervention threshold, although intervention thresholds are not defined in this guidance. Other individuals in whom BMD measurement should be considered include premenopausal women and younger men with strong risk factors, for example previous low trauma fracture or high-dose oral glucocorticoid therapy, women starting aromatase inhibitor therapy for breast cancer and men treated with androgen deprivation therapy for prostate cancer.

FRAX and Qfracture: comparison and limitations

Some points of comparison between FRAX and Qfracture are shown in Table 1. It should be noted that the output of the two algorithms differs – FRAX generating a 10-year probability that takes into account the competing effect of mortality and Qfracture generating a 1–10-year cumulative fracture incidence. Although the two algorithms produce similar estimates for hip fracture probability, there is a substantial divergence in the estimated probability of major osteoporotic fracture with

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Table 1. Comparison of FRAX and QFracture

	FRAX	QFracture
Age range, years	40–90	30–99
Derivation	International cohort studies	General practice database (UK)
Output	10-year fracture probability	1–10-year cumulative fracture incidence
Fractures included	Hip, major osteoporotic fractures (hip, spine, humerus, wrist)	Hip, major osteoporotic fractures (hip, spine, humerus, wrist)
No of CRFs	7	21
Dose response for CRFs	No	Yes for smoking and alcohol
Inclusion of BMD	Yes	No
Inclusion of falls	No	Yes

BMD = bone mineral density; CRF = clinical risk factor

Table 2. Anti-fracture efficacy of drugs used in the treatment of osteoporosis in postmenopausal women

Intervention	Vertebral fracture (30–70% reduction)	Non-vertebral fracture (15–20% reduction)	Hip fracture (≤40% reduction)
Alendronate*	+	+	+
Ibandronate	+	+**	–
Risedronate*	+	+	+
Zoledronic acid*	+	+	+
Denosumab*	+	+	+
HRT	+	+	+
Raloxifene	+	ND	ND
Strontium ranelate*	+	+	+**
Teriparatide*	+	+	ND

*also approved in men, **post hoc analysis
HRT = hormone replacement therapy; ND = not determined

higher values being obtained by FRAX than by Qfracture.[8] BMD values cannot be included in fracture risk assessment when using Qfracture.

Both FRAX and Qfracture have some limitations. They do not take dose response into account for some important risk factors, such as previous fracture and glucocorticoid therapy, although an adjustment of FRAX-derived fracture probabilities for glucocorticoid dose has been published and is incorporated into the NOGG guideline.[9] Both algorithms are only applicable to treatment-naïve individuals and the output of both is limited to four fracture sites. Because the risk factor profile differs between individual fracture sites, the probability of any clinical fracture is underestimated. Finally, the response to pharmacological intervention in people selected for treatment on the basis of fracture probability (as opposed to low BMD ± fracture, as mostly tested in pivotal clinical trials) requires further study.

Pharmacological interventions to reduce fracture risk

Available options

A number of pharmacological options are approved for use in postmenopausal women at increased risk of fracture and some of these are also licensed for treatment in men (Table 2). Head-to-head studies of these agents with fracture as the primary outcome have not been conducted and thus direct comparison of their efficacy cannot be made. All have been shown to reduce vertebral fractures whereas evidence for reduction in hip fracture is lacking for ibandronate, raloxifene and teriparatide. Reduction in all non-vertebral fractures has been shown for most. In general, the largest reductions are seen for vertebral fractures (30–70%), with up to 40% reduction in hip fracture but only 15–20% reduction for all non-vertebral fractures. The lower efficacy against non-vertebral fractures may reflect, in part, the importance of falls in the pathogenesis of these fractures.

These drugs act on bone by a variety of mechanisms. The bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid), denosumab, raloxifene and hormone replacement therapy act by inhibiting bone resorption, whereas teriparatide has anabolic effects on bone, increasing bone formation. Strontium ranelate has only weak effects on bone remodeling and acts primarily though effects on bone material properties. [10] Approved dosing regimens for the drugs are shown in Table 3.

Current NICE guidance on treatment of osteoporosis dates back to 2008 for most interventions and 2010 for denosumab.[11–13] An update of guidance was suspended in July 2015. At present, there is no guidance from NICE on treatment of osteoporosis in men or treatment of glucocorticoid-induced osteoporosis, and none for the use of zoledronic acid. Furthermore, the cost-effectiveness analyses on which the intervention thresholds were based are outdated because of the availability of generic formulations of oral bisphosphonates.

Table 3. Dosing regimens for drugs used in the treatment of osteoporosis

Oral	Parenteral
Once daily	Once daily
> Raloxifene	> Teriparatide (sc)
> Strontium ranelate	
Once weekly	Once 3-monthly
> Alendronate	> Ibandronate (iv)
> Risedronate	
Once monthly	Once 6-monthly
> Ibandronate	> Denosumab (sc)
	Once yearly
	> Zoledronic acid (iv)

iv = intravenous; sc = subcutaneous

Challenges in the treatment of osteoporosis

Despite improvements in fracture risk assessment and the range of approved options to reduce fracture risk, there is evidence from many parts of the world, including the UK, that only a minority of high-risk individuals receives appropriate assessment and treatment. Even in older individuals who have suffered a hip fracture, treatment rates as low as 30% have been consistently reported.[14] Fracture liaison services, which may be based either in primary or secondary care, are designed to ensure that all individuals who suffer a fragility fracture receive appropriate assessment and treatment. These services have been quite widely implemented in the UK and have been shown to be cost effective.[15] Secondly, in common with many other chronic diseases, adherence to anti-osteoporosis medication is poor and at least 50% of people taking oral bisphosphonates discontinue their treatment during the first year.[16] Thirdly, there is a need for the development of more effective strategies to reduce non-hip non-vertebral fractures, which collectively constitute the majority of the fracture burden in older people.

Duration of treatment

The optimal duration of therapy for osteoporosis has not been clearly established. Relevant issues include whether anti-fracture efficacy is maintained with long-term treatment, whether fracture protection persists after therapy is stopped and whether adverse effects of long-term treatment may outweigh its benefits.

Although robust evidence for efficacy of most interventions is limited to 3 years, extension studies indicate that beneficial effects on fracture risk are maintained with continued treatment.[17–19] The rate of offset of these benefits after withdrawal of therapy varies according to the therapy. The prolonged half-life of bisphosphonates in bone results in some continuation of their effects following withdrawal; this is greatest for zoledronic acid, intermediate for alendronate and least for risedronate. Thus, withdrawal of zoledronic acid therapy after 3 years of treatment was associated with only very small decreases in BMD after 3 years off treatment, whereas significant reductions in BMD are seen 2 years after withdrawal of alendronate and 1 year after withdrawal of risedronate and ibandronate. Conversely, withdrawal of denosumab is followed by rapid bone loss and increased bone turnover.

Concerns about long-term adverse effects of bisphosphonates, particularly osteonecrosis of the jaw and atypical femoral fracture, have raised the issue of whether temporary discontinuation of treatment should be considered after 3 years of zoledronic acid or 5 years of oral bisphosphonate therapy. Evidence from post hoc analyses of clinical trials indicates that women with a prevalent vertebral fracture and/or low femoral neck BMD are at higher risk of incident vertebral fracture if treatment is discontinued.[20,21] In addition, older women, those with a previous hip fracture, those taking oral glucocorticoid therapy and those who sustain one or more fractures while on treatment are likely to be at higher risk and, in all such individuals, continuation of therapy is generally advisable. In other women, it may be reasonable to consider temporary cessation of treatment for 2–3 years, with reassessment of risk at the end of that time.[22,23] However, it should be emphasised that the evidence on which these recommendations are based is limited and clinical judgment should always be used in the assessment of individual patients.

Osteonecrosis of the jaw and atypical femoral fractures

Osteonecrosis of the jaw (ONJ) has been linked to treatment with bisphosphonates and denosumab, but is extremely rare in people receiving the doses used for treatment of osteoporosis; it has an estimated incidence of 1/10,000 to 1/100,000 person years of bisphosphonate exposure.[24] Dental disease and trauma are strong risk factors for the development of ONJ and the start of treatment with either zoledronic acid or denosumab should be delayed where possible in people with unhealed open soft tissue oral lesions. Dental examination and, where appropriate, preventive dentistry prior to starting treatment is recommended and all patients should be encouraged to maintain good oral hygiene and have regular dental checks. There is no evidence that interrupting treatment, once established, in those requiring invasive dental procedures reduces the risk of ONJ; however, close proximity of such procedures to the treatment administration should be avoided, if possible.

Atypical femoral fractures comprise approximately 1% of all femoral fractures and are related to the duration of bisphosphonate therapy. They have also been reported in patients receiving denosumab. They are bilateral in up to 50% of cases, occur after minimal or no trauma and are often associated with prodromal groin, hip or thigh pain. Therefore, patients receiving bisphosphonates or denosumab should be advised to consult their doctor if such pain occurs and bilateral imaging should be performed. Estimates of the incidence of these fractures vary, but for up to 5 years of bisphosphonate therapy in people at high risk of fracture, the benefits outweigh the risks.[25]

Emerging new treatments

New approaches to treatment on the horizon include romosozumab, an inhibitor of sclerostin, and abaloparatide, a parathyroid hormone-related protein analogue. Treatment of osteoporotic postmenopausal women with once monthly subcutaneous romosozumab for 1 year resulted in a 73% reduction in vertebral fractures and a 36% reduction in all clinical fractures.[26] Daily subcutaneous injections of abaloparatide for 18 months in postmenopausal women with severe osteoporosis was associated with a 86% reduction in vertebral fractures and 43% reduction in nonvertebral fractures.[27] ■

Conflicts of interest

The author has no conflicts of interest to declare.

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