

REVIEW

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Recent developments towards closing the gap in osteoporosis management

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Abstract

Background: A fracture that occurs in people with low bone mass in the setting of minimal trauma—such as a fall from standing height—meets the criteria for the clinical diagnosis of osteoporosis and qualifies this particular individual for being at high risk of further fractures, particularly in the first 2 years after the index fracture. Therefore, it is vital to identify those individuals at very high and high fracture risk with the potential of instantly starting osteoporosis therapy.

Main body: Currently, there are unmet needs in the management of bone fragility and fracture prevention. Therefore, re-stratification of the people according to their risk of fracture, and, also, identify what is and is not achievable using different osteoporosis therapies, represent a major step forward. In 2020, the dichotomisation of high risk into high and very high-risk categories, which represent a new concept in osteoporosis assessment, was published by the IOF and the ESCEO. This coincided with proliferation of the available therapies with different modes of action and new therapeutic targets for treating osteoporosis. Fear of complications, even though rare, associated with long-term bisphosphonates and the positive impact of osteoanabolic agents on fracture reduction and bone quality, have changed the prescribing patterns and paved the way for sequential and combined therapy.

Conclusion: The incorporation of recent concepts in osteoporosis and the development of new interventional thresholds have positive implication on strategies for osteoporotic patients' diagnosis and management.

Keywords: Osteoporosis, FRAX, BMD, Bisphosphonates, Anabolic therapy, Sequential, Combination therapy, Anabolic window

Background

As the main target of osteoporosis treatment is to reduce the risk of sustaining fragility fractures, there has been a significant shift in the paradigm of osteoporosis assessment and management [1, 2]. Historically, the cornerstone of the fragility fracture risk assessment has been based on measurement of bone mineral density (BMD). In the absence of a true gold standard, the WHO has defined osteoporosis as a BMD that lies 2.5 standard deviations or more below the average value for young healthy women (a T -score of ≤ -2.5 SD) [3, 4]. Although the osteoporosis diagnostic criteria set by the WHO were primarily meant for descriptive epidemiology, later, it was adopted in clinical and medications trials as

the inclusion criteria critical for identifying patients who are eligible for intervention; subsequently, it was also suggested as intervention thresholds for patients' management [5].

However, the use of a T -score has been criticised in recent years as a universal intervention threshold for patients' identification and management. These results of the National Osteoporosis Risk Assessment (NORA) study [6], a longitudinal observational study that included over 200,000 postmenopausal women who range in age from 50 to 104 years revealed that more than half (52%) of the women included in that work, who experienced an incident osteoporotic fracture, had a BMD T -score of -1.0 to -2.5 . In another work, the Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study [7], the entire population age 65–80 years were randomised to either receive a

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care algorithm including FRAX and drug targeting or usual primary care for osteoporosis based on opportunistic case finding. Results revealed that the treatment strategy based on BMD (lowest *T*-score of two site assessment) weakens the power of FRAX by excluding some high-risk individuals [8]. On another front, analyses of four phase 3 studies of raloxifene [9], strontium ranelate [10], and teriparatide [11, 12] have elaborated several important implications. First, they alleviate the concern that patients identified based on FRAX clinical risk factors would not respond to medical interventions. In fact, high-fracture probabilities estimated by FRAX were correlated to therapeutic efficacy, even when BMD was not implemented to identify the risk. Second, they endorse the concept that medical management should be targeted favourably to men and women at high risk of sustaining fragility fracture(s). Third, as treatments directed to patients with the high-fracture risk probability, has positive impact on the budget; approaching the higher-risk groups can be considered as a cost-effective intervention [13]. Lastly, other studies that assessed the relation between *T*-score and fracture risk revealed that any given *T*-score threshold has a different significance at different ages [14–18].

In view of this, it has been suggested that interventions based on BMD thresholds alone, do not optimally identify subjects at high risk of sustaining fragility fractures, and support the rationale for implementing/developing risk assessment tools able to influence osteoporotic patients' management [19–21]. The scope of this article is to discuss the incorporation of recent concepts in osteoporosis, the development of new interventional thresholds and its implication on strategies for osteoporotic patients' diagnosis and management.

Main text

Case finding strategy

In 2018, the guidelines for the diagnosis and management of postmenopausal osteoporosis were updated by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO) [22]. However, to be applicable for use in standard day to day practice and to facilitate the identification and management of individuals at high-fracture risk, these guidelines had to be transformed into practical algorithms. According to IOF and ESCEO recommendations, the fracture risk should be expressed as an "absolute risk". This means the fracture probability over an interval of 10 years [22]. The absolute fracture risk relies on age, life expectancy, and the current risk of fracture. The 10-year period was selected to cover the likely duration of medical management and the time period over which benefits may last or risks occur if osteoporosis therapy was stopped [23].

In concordance with most of the published guidelines, subjects who sustained a prior fragility fracture can be considered for osteoporosis management without the need for further risk assessment, though BMD assessment may be advised particularly in younger people or to monitor medical therapy. Earlier studies revealed that immediately after an index fracture, the risk of a subsequent osteoporotic fracture is particularly acute; and the risk wanes progressively over time [24–29]. This very high risk of fracture and the subsequent further loss of utility occurring instantly after a consequent fracture (termed "imminent risk" attributed to the temporal association), endorse the concept that preventive medical management given as soon as possible after a fragility fracture would help to minimize the risk of a higher number of new fractures and decrease the possible associated morbidity; compared to therapy given later. This new concept of imminent fracture risk supports the rationale for very early intervention immediately after a sentinel fracture and mandates management with therapies that have the most rapid impact on fracture reduction. A further development is the recent demonstration of an extra rapid and greater fracture risk reduction induced by anabolic agents in contrast to that reported with anti-resorptive therapies [30–34]. This represents a potential to revolutionise osteoporosis management strategies, particularly in subjects at very high-fracture risk [35, 36]. Therefore, in addition to the standard clinical risk factors, it became vital for the case finding process to identify those individuals at very high and high risk of fragility fracture(s).

The concept of very high-fracture risk

In 2020, the dichotomisation of high risk into high- and very high-risk categories was published by the IOF and the ESCEO [37]. Basically, this was based on the assessment of the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm, or humerus). Women with fracture probabilities below the lower assessment threshold can be considered at low risk. Women with probabilities above the upper assessment threshold can be considered for treatment. Women with probabilities between the upper and lower assessment threshold should be referred for BMD measurements and their fracture probability reassessed. The subgroup eligible for treatment was then stratified into high- and very high-fracture risk categories as will be shown below.

This new concept of high-fracture risk was driven by the data emerging from drug trials of the recently approved romosozumab, abaloparatide, and the established medications such as teriparatide. In contrast to anti-resorptive therapies, anabolic agents demonstrated a more rapid and greater fracture risk reductions [31, 38, 39]. Such strategy of tailoring the medical management to the

patient’s needs represents a revolution in the management of osteoporosis, particularly for those subjects at very high-fracture risk. So, whilst the current guidelines for management of post-menopausal women at high-fracture risk advise to start with anti-resorptive therapy (mostly oral bisphosphonates) [22, 40, 41], according to the recent recommendations, it would be more suitable for post-menopausal women at very high-fracture risk to start treatment with anabolic therapy followed by an anti-resorptive agent [31, 42–44].

Assessment and interventional thresholds

Two approaches have been published describing how to identify the high- and very high-fracture risk categories; these are the following:

National Osteoporosis Guideline Group (NOGG)

NOGG developed age-dependent assessment thresholds for the UK. The intervention threshold is set at a risk equivalent to that associated with a prior fracture. Two bounds around the intervention threshold have been identified where the assessment of BMD will help to determine whether the individual close to the threshold either exceed that bound or lie below the intervention threshold. These are called assessment threshold for bones. The lower assessment threshold was set to rule out the requirement for BMD testing among women without any clinical risk factors [45, 46]. The upper assessment threshold was set at 1.2 times the intervention threshold [47]. Very high risk is identified as the risk lying above the upper assessment threshold, whereas high risk lies between the intervention threshold and the upper assessment threshold. On the other hand, low risk is reported when the risk lies below the intervention

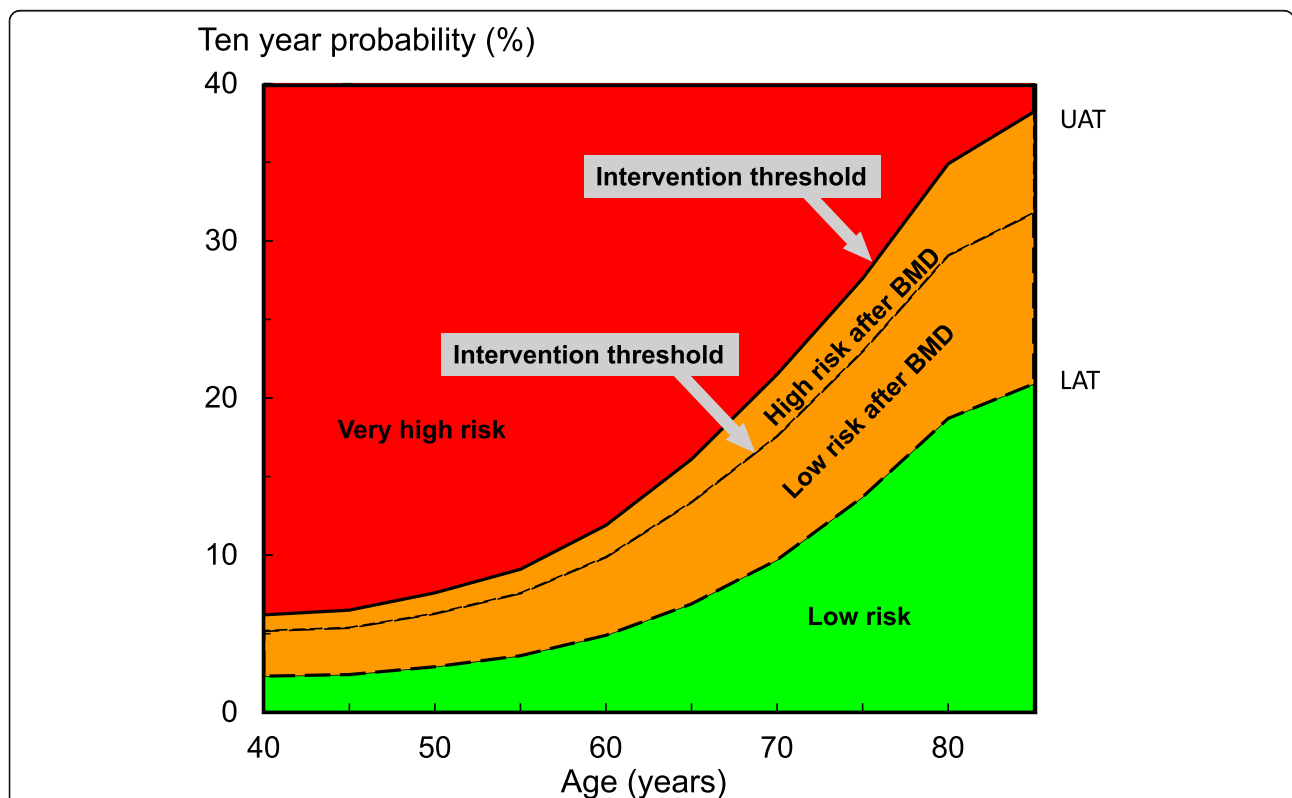


Fig. 1 Infographic outlining the four osteoporosis risk categories. Initial risk assessment relies on using FRAX with clinical risk factors alone. Two intervention thresholds are identified. FRAX probability in the red zone, above intervention threshold (2) indicates very high risk. For this group of people, an initial course of anabolic therapy followed by anti-resorptive treatment may be appropriate. FRAX probability in the green zone suggests low risk, with advice to be given regarding lifestyle, calcium, and vitamin D supplementation. FRAX probability in the intermediate (yellow) zone should be followed by BMD assessment and recalculation of FRAX probability including femoral neck BMD. After recalculation, if the risk got in the red zone above intervention threshold 2, this indicates very high-fracture risk, whereas if the risk got in between intervention threshold 1 and below intervention threshold 2, this would indicate high risk, which suggests initial anti-resorptive therapy. If the risk lies below the intervention threshold 1, this would indicate low risk (management would be similar to green zone). Patients with a prior fragility fracture are designated either at high risk or possibly at very high risk dependent on the FRAX probability (amended from Fig. 1 published in Kanis, J.A., Harvey, N.C., McCloskey, E. et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporos Int* 2020; 31: 1–12 (quoted under open access scheme)

threshold. The assessment thresholds are illustrated in Fig. 1.

European Society of Endocrinology

In 2019, the European Society of Endocrinology published its algorithm for the management of postmenopausal osteoporosis [48]. The algorithm was based on the proposal that a determination of fracture risk would include measurement of lumbar spine and hip BMD and inserting the total hip or femoral neck BMD value into the FRAX tool. Using that FRAX algorithm, four risk categories were identified: “low risk” includes no prior hip or spine fractures, a BMD *T*-score at the hip and spine both above -1.0 , and 10-year hip fracture risk $< 3\%$ and 10-year risk of major osteoporotic fractures $< 20\%$; “moderate risk” includes no prior hip or spine fractures, a BMD *T*-score at the hip and spine both above -2.5 , or 10-year hip fracture risk $< 3\%$ or risk of major osteoporotic fractures $< 20\%$; “high risk” includes a prior spine or hip fracture, or a BMD *T*-score at the hip or spine of -2.5 or below, or 10-year hip fracture risk $\geq 3\%$, or risk of major osteoporotic fracture risk $\geq 20\%$; and “very high risk” includes multiple spine fractures and a BMD *T*-score at the hip or spine of -2.5 or below (Table 1).

Impact on patients’ treatment

Most of the current clinical guidelines endorse the standard osteoporosis management protocols advising the use of an anti-resorptive agent, mostly a bisphosphonate as an initial course of therapy with denosumab given to those who are intolerant to or who have failed bisphosphonate therapy. Anabolic agents are often reserved for severe cases with high fractures risk or those who have failed other initial therapies. Data revealed from recent clinical trials [31, 49] revealed significant anti-fracture benefits with recently approved romosozumab. Studies using abaloparatide build on our long-standing experience with teriparatide in inducing a positive remodelling balance state [44, 50]. The importance of consolidating the bone mineral density gains achieved from an anabolic agent by following it with an anti-resorptive was also observed. Emerging data favours the use of osteoanabolic agents as a first line regimen for severe osteoporotic cases followed by an anti-resorptive agent. Consequently, several forms of

combination and sequential therapeutic modalities have been assessed with positive outcomes. The recently published re-classification of fracture risk categories and the potential of using osteoanabolic agents for subjects with very high risk of fracture as a first option, change the whole treatment paradigms. On the horizon is the potential for targeted osteoporosis therapy tailored to the patient needs. The goals are not only securing gains in bone mass or bone density measure but also improvements in bone quality and reduced fracture rates with minimal skeletal as well as non-skeletal adverse events. Considering the new re-classification of the fracture risk categories, and the potential of reversing the standard sequence of osteoporosis therapy, which is based on starting treatment with anti-resorptive therapy followed by anabolic therapy; there are some hopes that we can reach a state of cure of osteoporosis. These new models of management will be discussed in the following section.

Sequential therapy

The availability of different osteoporosis therapy options, with 2 main different mechanisms of action whether anabolic or potent anti-resorptive raised the question which treatment modality is the best for the patient and which medication to start treatment with. Clinical trial data show significant anti-fracture benefits with recently approved romosozumab. The extension of FRAME study investigated the efficacy of 1-year treatment with romosozumab followed by 2 years of denosumab [49]. Results revealed further increase in the BMD after switching romosozumab to denosumab. At the end of the 36-month period, the subjects who received romosozumab followed by denosumab achieved significantly higher BMD increases from baseline compared to the placebo-to-denosumab group (lumbar spine 10.6; total hip 5.2%; femoral neck 4.8%) [49]. Furthermore, patients who received romosozumab in the first year of the study exhibited significantly higher fracture risk reductions compared with those who received placebo (66%, 27%, and 21% for vertebral, clinical, and non-vertebral fractures, respectively). In concordance, in the extension of the ARCH study, postmenopausal women transitioning to alendronate after 1 year of romosozumab maintained

Table 1 Characteristics of the four osteoporosis risk categories identified according to the European Society of Endocrinology

	Low risk	Moderate risk	High risk	Very high risk
FRAX	Hip: $< 3\%$ Spine: $< 20\%$	Hip: $< 3\%$ Spine: $< 20\%$	Hip: $\geq 3\%$ Spine: $\geq 20\%$	Hip: $\geq 3\%$ Spine: $\geq 20\%$
BMD	Above -1.0	-1.0 to -2.5	≤ -2.5	≤ -2.5
Fracture	No prior hip or spine fractures	No prior hip or spine fractures	A prior hip or spine fractures	Multiple spine fractures

BMD bone mineral density

the BMD gains at lumbar spine, total hip, and femoral neck BMD, which were initially achieved with romosozumab without further increases [31]. However, over a total period of 24 months treatment with romosozumab followed by alendronate, resulted in a higher fracture risk reduction of 48% for vertebral fractures, 27% for clinical fractures, 19% for non-vertebral fractures, and 38% for hip fractures compared with alendronate alone [31].

In the DATA-Switch study, 2 years of teriparatide therapy followed by 2 years of denosumab resulted in further increases in the BMD [50]. Results of the study showed that when denosumab is given for 2 years after 2 years of teriparatide, there was additional increase in the spine BMD by 9.4% (18.3% total 4-year increase) and increased total hip BMD an additional 4.8% (6.6% total 4-year increase). In other publication of the abaloparatide, in the trial by Bone et al. [44], alendronate was administered after abaloparatide (given for 18 months), which maintained the fracture risk reduction relative to placebo.

In summary, results of these studies using anabolic agents as first treatment modality followed by an anti-resorptive agent consolidate the bone mineral density gains achieved from the anabolic agent and impact positively on the fracture risk reduction.

Combination therapy

Combination therapy refers to co-administration of an osteoanabolic agent (most studies referring to teriparatide) with a variety of anti-resorptive agents or HRT with other anti-resorptives [51]. Among all combination treatments published so far, studies of teriparatide and denosumab co-administration demonstrated the best and most promising results. In the DATA trial, which included a cohort of largely treatment-naïve postmenopausal women, the teriparatide/denosumab combination treatment induced greater increases in all the three sites: lumbar spine, total hip, and femoral neck as well as radius BMD compared to either agent alone after 12 [52] and 24 months of therapy [53]. BMD changes with the teriparatide/denosumab combination in this study were similar to those seen with the teriparatide/zoledronate combination in the first 6 months [54], although the magnitude does not refer to direct comparison. However, in contrast to the teriparatide/zoledronate combination, BMD levels continued to increase with the teriparatide/denosumab combination after the first 6 months, when the waning effect of zoledronate on bone resorption is seen. In the DATA-HD trial, the combination of denosumab with higher teriparatide dose (40 µg), increased lumbar spine as well as total hip BMD more than the standard teriparatide 20 µg/denosumab combination therapy [55, 56], further supporting

rationale of using this combination in severe osteoporosis such as those with very high-fracture risk.

Regarding the other two currently commercially available osteoanabolic agents, abaloparatide and romosozumab, there are no studies published so far on the co-administration of either drug with an anti-resorptive agent.

To accommodate such new classification of the fracture risk, an updated algorithm for management of postmenopausal osteoporosis has been published recently by the Endocrine Society [57] which involves an updated evidence-based approach to the management of osteoporosis developed to accommodate the high-fracture risk category and the new recently approved medications (e.g. romosozumab).

Conclusion

It is the dawn of a new era in osteoporosis care. The identification of the new concept of very high-fracture risk, highlight a subgroup of individuals who require special care and facilitates the opening of the anabolic window in osteoporosis management. Starting treatment with an anabolic agent, in individuals at very high-risk of fracture seems most appropriate to promptly reduce the fracture risk. Combination therapy with teriparatide and denosumab or zoledronate has achieved higher BMD gains compared to each agent alone; however, due to the high cost, combination therapy is rarely compensated.

Abbreviations

BMD: Bone mineral density; IOF: International Osteoporosis Foundation; ESCEO: European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis; FRAX: Fracture Risk Assessment

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