POSITION PAPER

Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures

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Abstract

Summary Guidance is provided in an international setting on the assessment and specific treatment of postmenopausal women at low, high and very high risk of fragility fractures.

Introduction The International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis published guidance for the diagnosis and management of osteoporosis in 2019. This manuscript seeks to apply this in an international setting, taking additional account of further categorisation of increased risk of fracture, which may inform choice of therapeutic approach.

Methods Clinical perspective and updated literature search.

Results The following areas are reviewed: categorisation of fracture risk and general pharmacological management of osteoporosis.

Conclusions A platform is provided on which specific guidelines can be developed for national use to characterise fracture risk and direct interventions.

Keywords Anabolic agents · Fracture risk assessment · FRAX · Inhibitors of bone resorption · Treatment of osteoporosis

Introduction

In 2018, the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO) updated guidelines for the diagnosis and management of postmenopausal osteoporosis, subsequently published in full in 2019 [1] and as executive summaries [2, 3]. Translation of this guideline into easy to use, practical algorithms is needed to facilitate the recognition and

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treatment of women at increased risk of fracture. This translation could also enable the incorporation of several recent developments that significantly impact on strategies for the management of patients. The first is the widespread recognition that the risk of a subsequent osteoporotic fracture is particularly acute immediately after an index fracture and wanes progressively with time [4–9]. This very high fracture risk and the consequent further utility loss immediately after a subsequent fracture (often termed "imminent risk" because of the temporal association) suggests that preventive treatment given as soon as possible after fracture would avoid a higher number of new fractures and reduce the attendant morbidity, compared with treatment given later. This provides the rationale for very early intervention immediately after a sentinel fracture and necessitates treatment with agents that have the most rapid effect on fracture reduction. A further recent development is the demonstration of a more rapid and greater fracture risk reduction of anabolic compared with antiresorptive treatments [10–14], with the potential to revolutionise treatment strategies, particularly in individuals at very high fracture risk [15, 16].

The scope of the present report is to review and update the assessment of osteoporosis, in particular the categorisation of risk to better target therapeutic interventions for the prevention of fragility fracture in postmenopausal women. The guideline is intended for all healthcare professionals involved in the management of osteoporosis. Where available, systematic reviews, meta-analyses and randomised controlled trials have been used to provide the evidence-base with the available literature updated using PubMed to identify systematic reviews and meta-analyses from January 2017 to December 2018, subsequent to the generation of the recent European Guidelines. The recommendations in this guidance have been endorsed by the Scientific Advisory Board of ESCEO and the Committee of Scientific Advisors and the Committee of National Societies of the IOF.
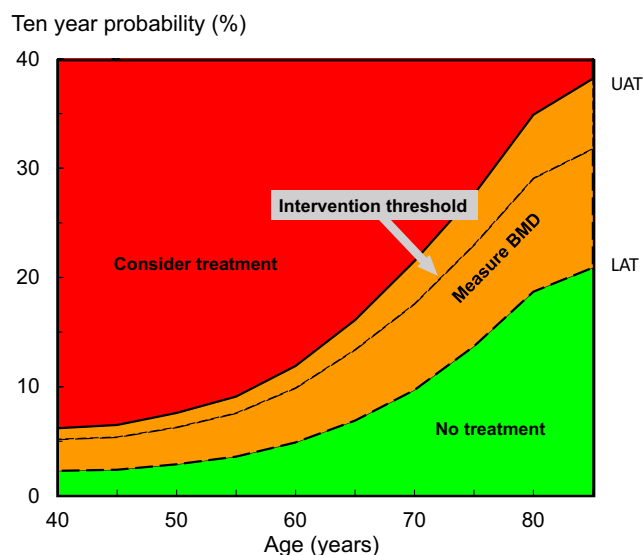
Risk assessment

The IOF and ESCEO recommend that risk of fracture should be expressed as an absolute risk, i.e. probability of fracture over a ten-year interval [1]. The absolute risk of fracture depends upon age and life expectancy as well as the current fracture risk. The period of 10 years was chosen to cover the likely length of treatment and the time over which benefits may continue or risks arise if treatment is stopped [17]. Algorithms that integrate the weight of clinical risk factors for fracture risk, with or without information on BMD, were developed in 2007 by the then WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield. The resulting FRAX tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture, the latter comprising a clinical spine, hip, forearm or humerus fracture. The tool has been externally validated in independent cohorts [18] and calibrated to the epidemiology of fracture and death in 67 countries covering more than 80% of the world population at risk [19].

Intervention and assessment thresholds

FRAX has been incorporated into more than 100 guidelines worldwide but the approach to intervention thresholds has varied widely [19, 20]. For the purposes of this report, the guidance of the IOF and ESCEO [1] is used as an example and shown in Fig. 1.

In the European guidance, it is recommended that postmenopausal women with a prior fragility fracture should be treated without further assessment, although BMD measurement and incorporation into the FRAX calculation is sometimes appropriate, particularly in younger postmenopausal women. In women without a previous fragility fracture, the management strategy should be based on assessment of the ten-year probability of a major osteoporotic fracture (clinical spine, hip,

Fig. 1 Assessment guidelines based on the ten-year probability of a major osteoporotic fracture (%). The dotted line denotes the intervention threshold. Where assessment is made in the absence of BMD, a BMD test is recommended for individuals where the probability assessment lies in the orange region i.e. between the lower assessment threshold (LAT) and the upper assessment threshold (UAT). The intervention threshold and BMD assessment thresholds used are those derived from [1] and reproduced in the Appendix, Table 5, with kind permission from Springer Science and Business Media

forearm or humerus). Women with 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 [1]. The age-dependent intervention threshold is set at a risk equivalent to that associated with a prior fracture in a woman of the same age with average BMI and, therefore, rises with age [21]. The same thresholds are used in men since the cost-effectiveness of interventions is broadly similar in men and women [22, 23].
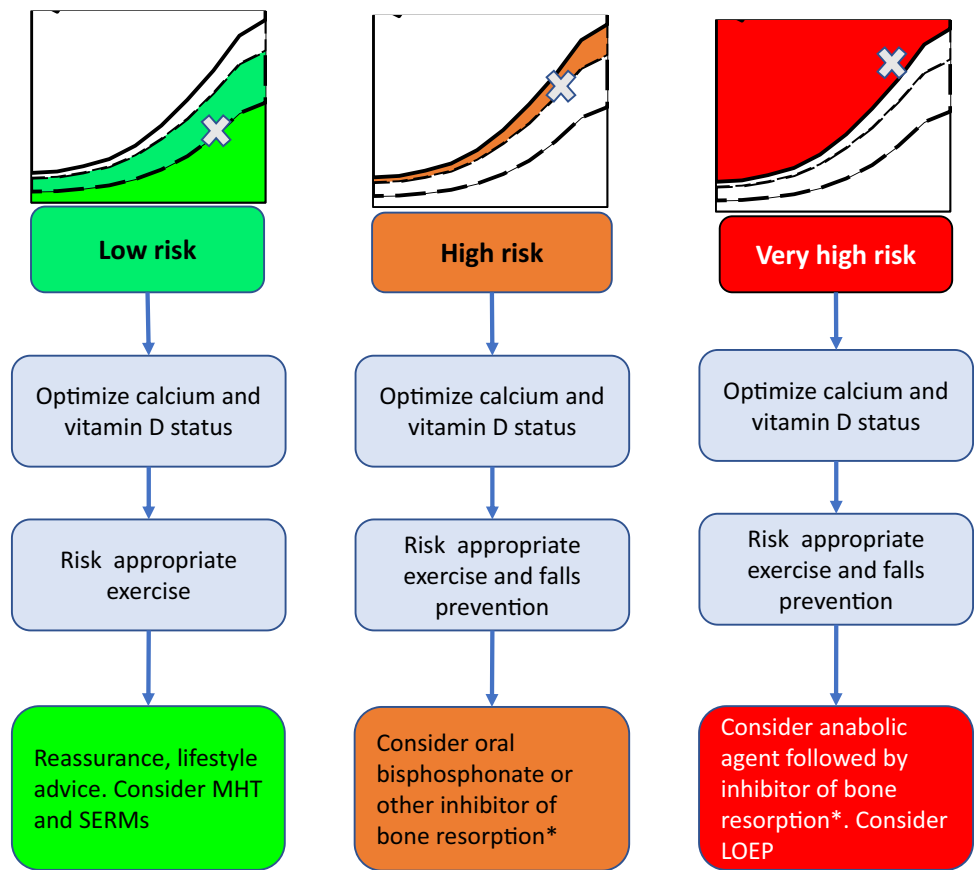
Fig. 2 Infographic outlining of the characterisation of fracture risk by ▶ FRAX major osteoporotic fracture probability in postmenopausal women. Initial risk assessment uses FRAX with clinical risk factors alone. FRAX probability in the red zone indicates very high risk and that an initial course of anabolic treatment followed by antiresorptive therapy may be appropriate. FRAX probability in the green zone suggests low risk, with advice to be given on lifestyle, calcium and vitamin D nutrition and menopausal hormone treatment considered. FRAX probability in the intermediate (orange) zone should be followed by BMD assessment and recalculation of FRAX probability including femoral neck BMD. After recalculation, risk may be in the red zone (very high risk), orange zone (high risk, which suggests initial antiresorptive therapy) or green zone (low risk, either in the original green zone or in the original orange zone but below the intervention threshold). *Note that patients with a prior fragility fracture are at least designated at high risk and possibly at very high risk dependent on the FRAX probability*
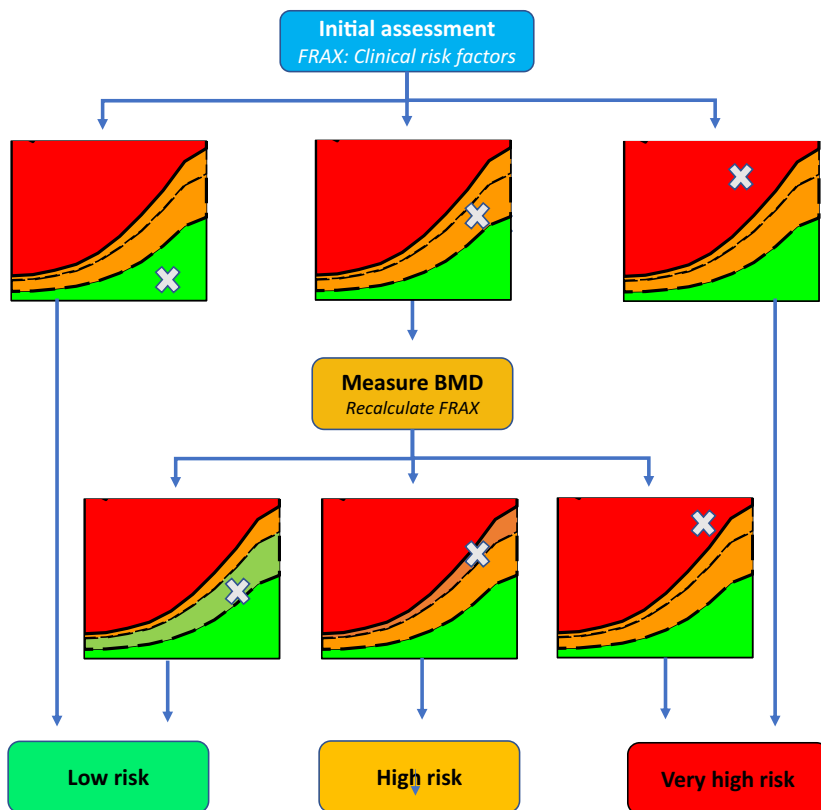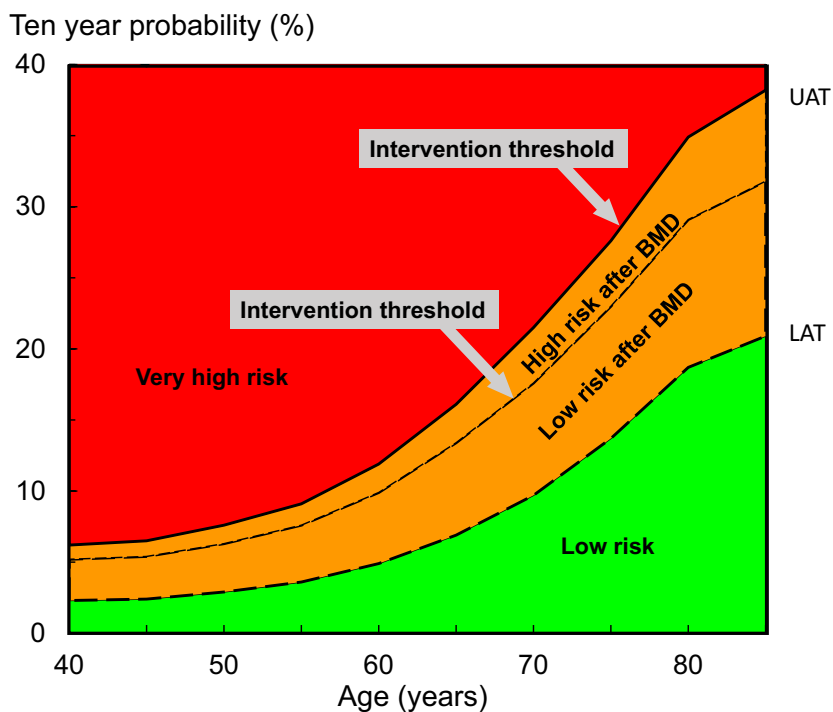
Some agencies have been reluctant to reimburse treatments on the basis of fracture probability, particularly at younger ages where the 10-yea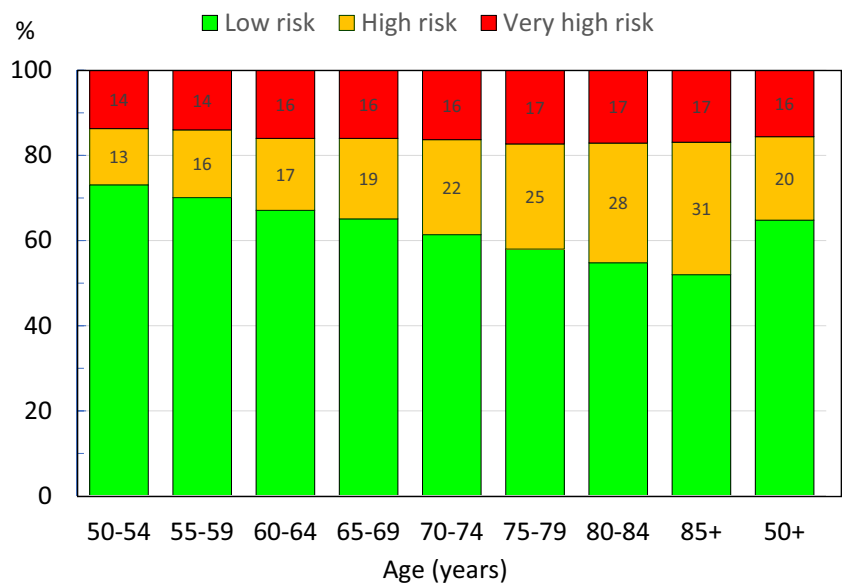r probability of a major osteoporotic fracture is less than 10%. In the UK, for example, the intervention threshold for women aged 50–54 years is 8.18%. At the same age, however, the remaining lifetime probability of a

Fig. 3 Treatment pathways according to the categorisation of fracture risk. For treatment modalities (inhibitors of bone resorption, anabolic agents, etc.), see Appendix, Table 6

Low risk

Optimize calcium and vitamin D status

Risk appropriate exercise

Reassurance, lifestyle advice. Consider MHT and SERMs

High risk

Optimize calcium and vitamin D status

Risk appropriate exercise and falls prevention

Consider oral bisphosphonate or other inhibitor of bone resorption*

Very high risk

Optimize calcium and vitamin D status

Risk appropriate exercise and falls prevention

Consider anabolic agent followed by inhibitor of bone resorption*. Consider LOEP

MHT, menopausal hormone therapy;
SERM, selective estrogen receptor modulator;
LOEP, local osteo-enhancement procedure
* See Appendix, table A2

Fig 4 Proportion (%) of postmenopausal women by age in a simulated normal population of 50633 women from the UK [51] characterised at low, high and very high risk. The high-risk category includes women with a prior fracture not characterised at very high risk. Numbers in the high and very high risk categories refer to the percentage so characterised at each age interval

major fracture is high (57%). Moreover, there are cost-effective scenarios for treatment available at these levels of risk [1].

In addition to the 10-year probability of a major osteoporotic fracture, the European guidance also provides intervention thresholds that are based on the 10-year probability of hip fracture. Either or both thresholds can be used; indeed, the screening for prevention of fractures in older women (SCOOP) trial showed that a screening strategy decreased the incidence of hip fracture (but not other fractures), based on treatment targeted by hip fracture probability [24].

To enhance fracture risk assessment, relatively simple arithmetic adjustments have been developed, which can be applied to conventional FRAX estimates of probabilities of hip fracture and a major fracture to adjust the probability assessment with knowledge of

> High, moderate and low exposure to glucocorticoids [25]
> Concurrent data on lumbar spine BMD [26, 27]
> Trabecular bone score of the lumbar spine [28–30]
> Hip axis length [31]
> Falls history [32]
> Immigration status [33]
> Type 2 diabetes [34, 35]
> Chronic kidney disease [36]
> Recency of fracture [9, 37]

Categorisation of risk

The assessment strategy above permits the classification of risk. In addition to the categories of low and high risk espoused in the current IOF-ESCEO guideline, very high risk can be identified as outlined in Fig. 2. Very high risk is defined as a fracture probability that lies above the upper assessment threshold after a FRAX assessment, with or without the inclusion of BMD, i.e. where BMD testing is unavailable, the same probability threshold can be used. The numerical data for

Table 2 10-year probability of major osteoporotic fracture (MOF) for Icelandic women at different ages, categorised by (A) a clinical vertebral fracture within the previous 2 years and (B) a prior fracture of undetermined recency. The right-hand column provides the ratio by which to adjust FRAX probabilities by virtue of a recent clinical vertebral fracture. From [59], with kind permission from Springer Science and Business Media

Age	10-year probability of MOF		Ratio
	(A) Recent vertebral fracture	(B) Prior fracture in adult life	
50	29.0	11.7	2.47
60	36.1	19.4	1.86
70	41.9	27.6	1.52
80	42.5	34.2	1.24
90	34.7	33.3	1.04

these thresholds are given in the Appendix (Table 5) based on the weighted average of 5 European countries (Germany, France, Italy, Spain and the UK) but will vary by country.

Impact on treatment

The rationale for the more refined characterisation of risk is to direct appropriate interventions. Thus, initial treatment recommendations for women at high risk might most usually start with an inhibitor of bone resorption. For example, the UK National Institute for Clinical Excellence (NICE) and the IOF/ESCEO guidelines recommend oral bisphosphonates [1, 38, 39] but a very large range of pharmacological interventions are recommended worldwide (Appendix, Tables 6 and 7). In contrast, women at very high risk might be more suitably treated with an anabolic treatment followed thereafter by an inhibitor of bone resorption [40] (Fig. 3).

Non-pharmacological management should be considered for all patients but may be adapted according to the category

Table 1 Examples of risk assessment in women from the UK (BMI set to 25 kg/m²). Risk factors include prior fracture (of uncertain recency), prior clinical vertebral fracture within the past two years, family history of hip fracture, exposure to glucocorticoids, exposure to higher than average doses of glucocorticoids and bone mineral density (BMD) T-score at the femoral neck

Age (years)	Prior fracture	Recent spine fracture	Family history	GC	GC high dose	BMD (T-score)	10-year probability (%)	Category of risk
70	Yes					-	20	Low[1]
70			Yes			-	17	Low
70	Yes		Yes			-	30	Very high
70		Yes				-	30	Very high
60				Yes		− 1.5	10	Low
60				Yes		− 2.0	13	High
60				Yes	Yes	− 2.0	15	Very high

[1] Qualifies for treatment by virtue of a prior fracture

Table 3 Unadjusted probabilities of a major fracture in women with a prior fragility fracture by age using the UK FRAX model together with the categories of risk and adjusted FRAX probabilities for women with a recent clinical vertebral fracture. BMI set at 24 kg/m^{2}

Age	Prior fracture in adult life		Recent clinical vertebral fracture	
	Probability (%)	Category of risk	Probability (%)	Category of risk
50	7.3	High	18.0	Very high
60	12.2	High	22.7	Very high
70	20.3	High	30.9	Very high
80	27.6	Very high	34.2	Very high
90	33.9	Very high	35.3	Very high

of fracture risk [41, 42]. For all patients, education on osteoporosis (e.g. knowledge of osteoporosis, medications, diet and exercise) and advice for daily weight-bearing physical activity are appropriate [43–45]. Where indicated, the addition of fall prevention measures, including supervised exercise and/or rehabilitation, has been shown to be useful in reducing falls [46, 47] but the effects on fracture risk remain uncertain [47]. Programmes should continue over a duration of at least 50 hours, be progressive in nature and include strength and balance training components [48–50].

The implications of the categorisation of risk on the use of anabolic regimens in this way are shown in Fig. 4 as applied to the age-specific NOGG guidance [21]. As would be expected, the proportion of women characterised at low risk decreased with age and, conversely, those at high risk increased with age. The proportion of women characterised at very high risk increased with age though the quantum of effect was modest. Overall, in women aged 50 years or more, 64.8% were categorised at low risk, 19.7% at high risk and 15.6% at very high risk. Numerical data by age are given in the Appendix (Table 6).

Examples of very high risk

A prior fragility fracture provides informative examples of the categorisation of risk and recommendations for treatment which are illustrated for a woman age 70 years in Table 1. A prior fragility fracture of undetermined recency is associated with a 10-year probability of a major osteoporotic fracture of 16%. Whereas this probability is designated as low, treatment with an inhibitor of bone resorption is indicated by the IOF-ESCEO guidance and many other guidelines by virtue of the prior fracture [19]. A family history of hip fracture in the absence of any other risk factors provides a similar fracture probability is characterised at low risk and lifestyle advice recommended. The combination of a prior fragility fracture of uncertain recency and a family history of hip fracture is associated with a much higher risk than either risk factor alone or falls into the category of very high risk where an anabolic regimen might be recommended.

A further example of the interaction of risk factors on the categorisation of risk is provided in the context of exposure to glucocorticoids (see Table 1). A woman aged 60 years exposed to average doses of glucocorticoids and a femoral neck T-score of −

Table 4 The effect on hip fracture (number/1000 patient years) of an anabolic agent (AA) given for the first 18 months followed by an antiresorptive (AR) for a total of 10 years. The clinical scenario is a postmenopausal woman from the UK with a recent major osteoporotic fracture. The efficacy (RRR) of the anabolic agent is modelled at 70% and

that of the antiresorptive at 40%. The time course of a subsequent hip fracture is non-linear as given in [58]. The two right-hand columns show the effects of an antiresorptive followed by an anabolic agent for the last 18 months of a 10-year treatment

	Untreated	AA/AR RRR 70/40%[a]	Fractures saved[b]	AR/AN RRR 40/70%	Fractures saved[b]
Age	N/1000	N/1000	N/1000	N/1000	N/1000
50	8.1	2.4	5.7	4.7	3.4
55	12.8	3.8	9.0	7.5	5.3
60	20.4	6.1	14.3	11.9	8.5
65	31.3	9.4	21.9	18.3	13.0
70	48.3	14.5	33.8	28.3	20.0
75	73.6	22.1	51.5	43.1	30.5
80	104.7	31.4	73.3	61.2	43.5
85	160.4	48.1	112.3	93.8	66. 6
90	180.9	54.3	126.6	105.8	75.1

[a] It is assumed that the effect of the anabolic agent is maintained with the subsequent antiresorptive agent

[b] First fractures

1.5 would be characterised as being at low risk in the absence of other clinical risk factors. A lower T-score of − 2.0 would place her in the category of high risk. However, for high doses (> 7.5 mg daily), probabilities should be upward-revised by about 15% [25, 52] which would place the patient at very high risk.

There is now a substantial body of evidence that the risk of a subsequent osteoporotic fracture is particularly acute immediately after the index fracture and wanes progressively with time [4–8, 53–57]. Thus, the incidence of a second fracture in those who will sustain a further fracture is particularly high in the first 2 years after the index event [58]. In the case of hip fracture, 61% of subsequent fractures over a 10-year time horizon will occur within the first 2 years. For forearm, spine and humerus fractures the recurrence within two years is 54, 42 and 53%, respectively. A recent population-based study demonstrated that the phenomenon of immediate risk was also age dependent [9]. For a woman at age 70 years, a prior clinical vertebral fracture within the past 2 years is associated with a 1.52-fold higher fracture probability than for a woman of the same age with a prior fragility fracture of uncertain recency [59] (Table 2). Thus, a recent clinical vertebral fracture uplifts the fracture probability from 16 to 24% and would place the woman in the category of very high risk (see Table 1).

Risk stratification with NOGG guidelines* BMI set at 25 kg/m^2

The ratios given in Table 2 can be used to adjust fracture probabilities derived from FRAX for recency of clinical vertebral fracture. Table 3 gives the current probabilities of a major fracture in women with a prior fragility fracture of uncertain recency using the UK FRAX model together with the adjusted probabilities for women with a clinical vertebral fracture within the past two years.

Impact of sequential treatment on fracture

In patients at very high risk of fracture, starting treatment with an anabolic agent seems most appropriate to promptly reduce the fracture risk [60–62]. Given that treatments with anabolic agents are limited to 12–24 months and that efficacy will wane once treatment is stopped, the real potential of the anabolic treatments is that their greater effect on BMD and fracture can be maintained with the inhibitors of bone turnover once anabolic treatment is stopped [11, 63, 64]. Take for example a hypothetical anabolic agent that reduced the risk of hip fracture by 70% (relative risk reduction, RRR = 70%). In this case, the anabolic agent, followed by an antiresorptive to maintain the effect for a total of 10 years, might be expected to save 33.8 hip fractures/1000 patient years in women age 70 years with a recent fragility fracture. In contrast, an antiresorptive (RRR = 40%) followed by an anabolic regimen for the last 18 months of a 10-year treatment would save only 20.0 hip fractures/1000 patient years. The difference illustrates the

importance of the sequence. The assumptions used and data for other ages are given in Table 4.

Conclusion

The risk categorisation of individuals deemed to merit treatment into high and very high risk and aids the targeting of anabolic therapy followed by antiresorptive medications.

Compliance with ethical standards

Conflicts of interest NM Al-Daghri G Adib, C Campusano, M Chandran, F Jiwa, H Johansson, JK Lee, E Liu, D Pinto, N Veronese, W Xia, L Zakraoui have no conflicts of interest to declare.

O Bruyère received research grants from Biophytis, IBSA, MEDA, Servier and SMB and consulting or lecture fees from Amgen, Biophytis, IBSA, MEDA, Servier, SMB, TRB Chemedica and UCB.

C Cooper reports personal fees from Alliance for Better Bone Health, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and UCB.

B. Dawson-Hughes has received grant support from Pfizer and DSM and consulting fees from TTY Biopharma Co, Ltd, Intrinsic Therapeutics and Agnovos.

NC Harvey has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Radius Health, Servier, Shire, UCB, Consilient Healthcare and Internis Pharma.

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OD Messina has received honoraria from Amgen, Lilly, Novartis and Pfizer

O Minski received honorary fees for lectures, from Abbvie, Roche, Pfizer, Pierre Fabre, Janssen, Novartis and MSD.

D Prieto-Alhambra's research group has received research grants from Amgen, Servier and UCB; speaker fees from Amgen and UCB; educational grants from Johnson & Johnson and consultancy fees from Amgen and UCB.

J-Y Reginster has received advisory board or consulting fees from IBSA-Genévrier, Pierre Fabre, Radius Health, TEVA and Mylan; lecture fees from Agnovos, IBSA-Genévrier, Mylan, CNIEL, Dairy Research Council (DRC) and Theramex and institutional grant support from IBSA-Genévrier, Mylan, CNIEL and Radius Health.

R Rizzoli has received consulting fees or advisory board fees from Radius Health, Labatec, Danone, Nestlé, CNIEL and Sandoz.

K Saag reports grant support from Amgen and Radius and consulting fees from Amgen, Radius and Roche.

Appendix

Table 5 Intervention thresholds as set by FRAX-based 10-year probability (%) of a major osteoporotic fracture equivalent to women with a previous fracture (no other clinical risk factors, a body mass index of 24 kg/m^2 and without BMD). The lower assessment thresholds set by FRAX is based on the 10-year probability (%) of a major osteoporotic fracture equivalent to women without clinical risk factors (a body mass index of 24 kg/m^2 and without BMD). The upper assessment threshold is set at 1.2 times the intervention threshold. The UK FRAX model is used. From [1], with kind permission from Springer Science and Business Media.

Age range (years)	Ten-year fracture probability (%)			Lifetime risk at intervention threshold*
	Intervention threshold*	Lower assessment threshold	Upper assessment threshold**	
50–54	7.8	4.0	9.4	57
55–59	11	5.3	13.2	54
60–64	14	7.3	16.8	50
65–69	19	9.8	22.8	47
70–74	22	12	26.4	43
75–79	26	16	31.2	39
80–84	31	20	37.2	36
85–89	33	18	39.6	34

*Threshold for high risk

**Threshold for very high risk

Table 6 Pharmaceutical interventions used in the management of postmenopausal osteoporosis. The list is not comprehensive but includes agents approved in Europe, the USA and member countries represented by the authors

Inhibitors of bone resorption	Stimulators of bone formation
Vitamin D derivatives	
Alfacalcidol	Abaloparatide
Calcidiol	Teriparatide (including biosimilars)
Calcitriol	Romosozumab
Bisphosphonates	
Alendronate (including effervescent formulation)	
Clodronate	Uncertain action
Neridronate	Strontium ranelate
Risedronate (including gastric resistant formulation)	
Ibandronate	
Zoledronate	
MHT and SERMs	
Oestrogen only MHT	
Opposed MHT (with progestogen)	
Tibolone	
Bazedoxifene	
Raloxifene	
Other	
Vitamin K	
Calcitonin	
Denosumab	

MHT, menopause hormonal treatment; SERMs, selective oestrogen receptor modulator

Table 7 Number of postmenopausal women by age in a simulation cohort of 50,633 women from the UK [51] and the proportion (%) characterised at low, high and very high risk. The high risk category includes women with a prior fracture not characterised at very high risk

	Age (years)								
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+	Total
Number	8799	8384	8552	6671	5792	4784	3807	3844	50,633
Low risk (%)	73.0	70.1	67.1	65.1	61.4	58.0	54.8	52.0	64.8
High risk (%)	13.4	15.9	17.0	19.1	22.2	24.7	28.2	31.1	19.7
Very high risk (%)	13.7	14.0	16.0	16.0	16.3	17.3	17.1	16.9	15.6

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