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IOF-ESCEO POSITION PAPER

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

**Outcomes of an experts’ consensus meeting jointly organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Osteoporosis Foundation (IOF)**

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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; 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** Fracture risk assessment ∙ FRAX ∙ Treatment of osteoporosis ∙ Inhibitors of bone resorption ∙ Anabolic agents

**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 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 to antiresorptive treatments [10 11 12 13 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 randomized 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 Figure 1.

 **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 A1, with kind permission from Springer Science and Business Media.

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, 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].

Some agencies have been reluctant to reimburse treatments on the basis of fracture probability, particularly at younger ages where the 10-year probability of a major osteoporotic fracture is less than 10%. In the UK, for example, the intervention threshold for women age 50-54 years is 8.18%. At the same age, however, the remaining lifetime probability of a 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 29 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 Figure 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 these thresholds are given in the Appendix (Table A1) based on the weighted average of 5 European countries (Germany, France, Italy, Spain and the UK) but will vary by country.

**Fig. 2**. Infographic outlining 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 anti-resorptive 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 anti-resorptive 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.*

**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, Table A2). 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] (Figure 3).

Fig. 3 Treatment pathways according to the categorisation of fracture risk. For treatment modalities (inhibitors of bone resorption, anabolic agents etc) see Appendix, Table A2.

Non-pharmacological management should be considered for all patients but may be adapted according to the category 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, 44, 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]. Programs should continue over a duration of at least 50 hours, be progressive in nature, and include strength and balance training components [48, 49, 50].

The implications of the categorisation of risk on the use of anabolic regimens in this way are shown in Figure 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 age 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 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.

**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, and 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 age 60 years exposed to average doses of glucocorticoids and a femoral neck T-score of -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.

**Table 1** Examples of risk assessment in women from the UK (BMI set to 25kg/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

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, 5, 6, 7, 8, 53, 54, 55, 56, 57]. Thus, the incidence of 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 two 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 two 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).

**Table 2** 10-year probability of major osteoporotic fracture (MOF) for Icelandic women at different ages, categorized 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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | 10-year probability of MOF |  | Ratio |
| Age |  | (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 |

Risk stratification with NOGG guidelines\* BMI set at 25kg/m2

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.

**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 24kg/m2

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | Prior fracture in adult life |  | Recent clinical vertebral fracture |
| Age  |  | 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 |

**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, 61, 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.

**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/ARRRR 70/40%a | Fractures savedb |  | AR/ANRRR 40/70% | Fractures savedb |
| 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

**Conclusion**

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

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**Compliance with ethical standards**

*Competing interests*

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.

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**Appendix A**

**Table A1** Intervention thresholds as set byFRAX-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/m2 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/m2 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.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Ten-year fracture probability (%)** |  |  |
| **Age range****(years)** |  | **Intervention threshold\*** | **Lower assessment threshold** | **Upper assessment threshold\*\*** |  | **Lifetime risk at intervention 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 A2** Pharmaceutical interventions used in the management of postmenopausal osteoporosis. The list is not comprehensive but includes agents approved in Europe, the US 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* |  |  |
| Estrogen only MHT |  |  |
| Opposed MHT (with progestogen) |  |  |
| Tibolone |  |  |
| Bazedoxifene |  |  |
| Raloxifene |  |  |
|  |  |  |
| *Other* |  |  |
| Vitamin K |  |  |
| Calcitonin |  |  |
| Denosumab |  |  |

MHT, Menopause Hormonal Treatment; SERMs, Selective Estrogen Receptor Modulator

**Table A3** Number of postmenopausal women by age in a simulation cohort of 50633 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 | 50633 |
| 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 |