

# Multidisciplinary Portuguese recommendations on DXA request and indication to treat in the prevention of fragility fractures

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## INTRODUCTION

Osteoporosis (OP) is a metabolic skeletal disease characterized by low bone mass and microarchitecture deterioration leading to increased bone fragility and susceptibility to fracture. In Portugal, the annual hip fragility fracture incidence is estimated to be between 154 to 572 per 100.000 women and 77 to 232 per 100.000 men, depending on age<sup>1</sup>. More than 10.000 patients are admitted every year to the Portuguese National Health Service due to hip fragility fractures, justifying annual total health care expenditures of over 220 million euro<sup>2</sup>. This corresponded to 1.4% of the total national health care expenditure in 2013, including private and public services, according to Portuguese Health Statistics<sup>3</sup>. The total expense with fragility fractures is much higher, as hip fractures only account for about 39.1% of the total number of fragility fractures observed in Portugal according to a recent study<sup>4</sup>.

Altogether, osteoporotic fractures currently represent an enormous social and economic burden in Por-

tugal, despite the fact that this country has one of the lowest incidences of fragility fractures in Western Europe<sup>1</sup>. The size of the problem will tend to increase relentlessly due to the increasing ageing of the population and other societal changes<sup>5</sup>, unless effective preventive measures are put in place.

This paper reports on the work of an Expert Committee convened to foster such measures, by providing physicians with practical and valid recommendations regarding the initiation of pharmacological treatment for osteoporosis and/or the request of DXA evaluation, in order to optimize the efficiency of interventions and minimize the costs and risks for individuals and society.

Since the last publication of recommendations for the diagnosis and treatment of osteoporosis in Portugal in 2007<sup>6</sup>, the FRAX<sup>®</sup> tool has been incorporated in the clinical guidelines for OP of several countries<sup>7,12</sup>. In fact, over half of the subjects who experience a fragility fracture do not have OP as defined by BMD<sup>13</sup>. FRAX<sup>®</sup> integrates a set of well-proven clinical risk factors for fracture, independent of BMD: age, gender, body mass

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index, prior fragility fracture, parental history of hip fracture, long-term use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking and alcohol intake, with or without BMD. It provides an estimate of the risk of major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and of hip fracture in the subsequent 10 years<sup>14,15</sup>. FRAX® provides valid predictions without BMD values<sup>16,17</sup>, although its accuracy increases when BMD is also considered<sup>18</sup>. This algorithm is applied upon the fracture epidemiology and death rates of each country, to provide locally optimized estimates of fracture probability. The FRAX® was derived from population-based cohort studies from Europe, North America, Asia and Australia and has been validated in 62 countries and adopted by many as the key basis for decisions on whom to treat.

With this in mind, we have recently validated the FRAX model for the estimation of osteoporotic fracture probability in the portuguese population – FRAX®Port<sup>15</sup> (<http://www.shef.ac.uk/FRAX/tool.aspx?country=53>). Through systematic literature review and meta-analysis<sup>19</sup>, as well as consensus discussion we have decided that FRAX® is the most appropriate instrument to achieve similar purposes in Portugal. Among its advantages lies the possibility of using it even in the absence of BMD, allowing its output to decide if and when DXA is needed.

We have also performed a nation-wide careful evaluation of the costs of hip fractures and their impact upon quality of life and mortality<sup>2</sup>. The fracture risk probabilities above which the different interventions become cost-effective, in the actual Portuguese settings, were defined based on matured economic methodology, assisted by internationally renowned experts<sup>2</sup>.

These developments laid the optimal ground for a timely review of the Portuguese recommendations regarding the risk threshold for DXA investigation and pharmacological treatment of osteoporosis.

On these bases, we now recommend that decisions regarding the performance of dual X-ray absorptiometry (DXA) or the initiation of treatment are based on estimates of the actual risk of fracture and the economic implications of fractures and the different preventive strategies.

This report does not cover all possible management options and is not intended to override the individual physician's responsibility towards the patient or the

personal choice of each patient. The authors wish to emphasize that formal guidance for every specific situation or co-morbidity cannot be provided due to lack of appropriate evidence. Judicious clinical judgment is required in such conditions.

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A total of 10 recommendations were produced (Table I).

## METHODS

### DEVELOPMENT OF GUIDELINES

A number of national experts on osteoporosis and all the relevant Portuguese scientific societies were invited and accepted to participate in the development of these recommendations: Rheumatology; Orthopaedics and Traumatology; Endocrinology, Diabetes and Metabolism; Gynaecology; Internal Medicine; Physical and Rehabilitation Medicine; Family Medicine, National Observatory for Rheumatic Diseases and Portuguese Society for Osteoporosis and Metabolic Bone Diseases. The only national patient organization active in the field of osteoporosis, Associação Portuguesa Contra a Osteoporose – APOROS, also participated in the Committee. Altogether, the Committee had 17 voting members, all of whom are co-authors of this report.

Relevant questions to be addressed by the recommendations were defined by consensus in a first round of e-mail consultations upon a draft prepared by the Principal Investigator (JAPS) and the research fellow (AM). A thorough literature review was performed in order to address each question (AM and JAPS) and made available to the committee members prior to the meeting. The electronic search was performed in PubMed MEDLINE (2006- January 15<sup>th</sup> 2015). The search strategies included the following medical descriptors: “Osteoporosis”, “Osteoporotic fractures”, “Risk Assessment”, “Algorithms”, “Recommendations”,

**TABLE I. SUMMARY OF RECOMMENDATIONS ON DXA REQUEST AND INDICATION TO TREAT IN THE PREVENTION OF FRAGILITY FRACTURES**

Recommendation	Votes	Average agreement
1 The implementation of general, non-pharmacological, preventive measures for osteoporosis, such as diet, vitamin D supplementation, exercise, falls prevention and monitoring the use of any bone active drug should apply to all ages, whenever correctable risk factors are identified, irrespective of FRAX® and BMD.	Approved 17/17 favorable votes	97.0% (75-100)
2 Pharmacological treatment for osteoporosis should be recommended, unless contraindicated, in all subjects over the age of 50, who have previously experienced either: A. $\geq 1$ fragility fracture of the hip or $\geq 1$ symptomatic vertebral fragility fracture or B. $\geq 2$ fragility fractures, independently of the site of fracture or the absence of symptoms (e.g. two asymptomatic vertebral fractures).	Approved 17/17 favorable votes	95.6% (70-100)
3 All Portuguese women and men over the age 50 should have their ten-year risk of osteoporotic fracture estimated with the FRAX®Port tool, with or without DXA.	Approved 17/17 favorable votes	95.9 % (80-100)
4 For FRAX®Port estimates, without DXA, between 7% and 11% for major osteoporotic fracture AND between 2.0% and 3% for hip fracture, BMD of the femoral neck should be obtained and entered into a new FRAX®Port ten-year risk estimation (see Figure 2). DXA may be justified in additional special conditions, as described in text.	Approved 16 favorable votes and one abstention	90.9% (60-100)
5 A. In men and women with a fracture risk estimate (without BMD) below 7% for major osteoporotic fractures AND 2% for hip fracture a decision not to treat with pharmacological agents may be warranted, without the need to perform DXA. Applicable general preventive measures should be applied.	Approved 16 favorable votes and one abstention	95.0% (50-100)
5 B. In such cases, FRAX®Port estimates should be repeated with a frequency that depends on how close the previous estimate is to lower limit of indication to DXA and also on the occurrence of significant changes in clinical risk factors. (see Figure 2A).	Approved 16 favorable and 1 abstention	93.8% (60-100)
6 In men and women with a fracture risk estimate, without DXA, above, 11% for major osteoporotic fracture OR 3% for hip fracture, pharmacological treatment with generic alendronate is cost-effective and should be advised (unless contra-indicated), without the need to perform DXA. (see figure 2A).	Approved 16 favorable votes and one abstention	95.3% (80-100)
7 In men and women with a FRAX®Port ten-year risk estimate, including DXA, at or above 9% for major osteoporotic or 2.5% for hip fractures pharmacological treatment for osteoporosis with generic alendronate is cost-effective and should be advised (unless contra-indicated). (see Table I and Figure 2B).	Approved 17/17 favorable votes	93.2% (60-100)
8 The decision to start anti-osteoporotic treatment with agents other than generic alendronate should be informed by their respective cost-effectiveness thresholds (see Table III).	Approved 16 favorable votes and one against	88.1% (0-100)
9 A. In men and women with a FRAX®Port ten-year risk estimate, including DXA, below 9% for major osteoporotic AND below 2.5% for hip fractures, pharmacological agents are not cost-effective and a decision not to use them may be warranted. Applicable general preventive measures should be applied.	Approved 17/17 favorable votes	96.5% (80-100)
9 B. In such patients, DXA and FRAX®Port assessments should be repeated every 2 years or whenever clinical risk factors change significantly (see figure 2). DXA may not be needed in case the previous BMD values are reassuring.	Approved 16 favorable votes and one abstention	92.8% (75-100)
10 While using FRAX®Port for the sake of these recommendations, health professionals should be aware of several limitations of this tool and considerer judicious adjustments of the risk estimates provide by this tool in specific circumstances, described below.	Approved 17/17 favorable votes	97.6% (70-100)

“Guidelines”, “Treatment”, “Cost-effectiveness”, “Bone Mineral Density” and “DXA”. Original articles, reviews and guidelines regarding threshold for treatment initiation and DXA request were included in this review. References cited in published Systematic Reviews or in original articles were also checked.

Possible alternative answers to the elected questions, according to the collected evidence, were drafted by the principal investigator and submitted, together with the respective evidence, to the Expert Committee in a second round of emails. Committee members were asked to appraise the supportive evidence and alternative recommendations or to propose additional ones. All alternatives were circulated in a third round of e-mails, prior to the final face-to-face meeting.

This meeting was held on the 13<sup>th</sup> March 2015 to discuss the generated evidence, vote on the possible answers and thus generate a set of recommendations. The meeting was recorded for documentation and future clarification of doubts. The votes of individual representatives and degree of agreement regarding each recommendation were registered. Portuguese data on the cost-effectiveness of interventions according to different fracture risk thresholds were disclosed to the panel, for the first time, only after all the guiding principles, presented below, had been irrevocably established. They were only known to three of the members, who performed the study (AM, OL, JAPS). This strategy was adopted to guarantee that the cost-effectiveness basis for the decision to intervene was based on the grounds of guiding principles and not contaminated by considerations of the percentage of the population eligible for intervention, its overall costs, or the (dis)similarity of our intervention thresholds *vis-a-vis* other published guidance.

A final round of e-mails was conducted to refine some recommendations.

Finally, this paper was drafted and circulated among the committee members until a final version was reached and submitted to the individual societies' and associations' approval and endorsement.

## **UNDERLYING CONCEPTUAL DEFINITIONS: GUIDING PRINCIPLES**

As a preparatory phase for the definition of the recommendations, the Committee planned and developed a detailed discussion dedicated to the establishment of a number of guiding principles and concepts. These are presented below:

### **GUIDING PRINCIPLE 1**

**Risk factors for osteoporosis, as those related with diet, exercise, sun exposure, medications, should be assessed by health professionals and patients throughout life, and corrected when appropriate**

This guiding principle was approved by all committee members 17/17 votes.

Many risk factors for osteoporosis influence bone health from the earliest phases and throughout life, even if the consequences of osteoporosis only become apparent later in life. This is the case, for example, of diet (calcium, protein), exercise, vitamin D status, and medications such as glucocorticoids. All these conditions have health implications far beyond the limits of bone health and should, therefore, be considered as a medical routine. The correction of these risk factors is an integral part of osteoporosis management, usually referred to as “General Measures”.

### **GUIDING PRINCIPLE 2**

**The decision to institute pharmacological treatment in osteoporosis should be based on the individual's ten-year risk of subsequent osteoporotic fracture as estimated by the FRAX®Port tool**

This guiding principle was approved by all committee members 17/17 votes

FRAX® is an algorithm developed by the Centre for Metabolic Bone Diseases, University of Sheffield, UK, which allows the estimation of the individual risk of osteoporotic fractures over the subsequent 10 years on the basis of 11 clinical risk factors (CRFs) that have been shown, through individual studies and meta-analyses, to influence the risk of fracture, independently of BMD. They are all easily available in clinical practice: age, weight, height, prior fragility fracture, parental history of hip fracture, current tobacco smoking,  $\geq 3$  months glucocorticoids use, rheumatoid arthritis, causes of secondary osteoporosis (type I diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease) and alcohol consumption. FRAX® can be used with or without BMD (Figure 1).

When calculated using only CRFs, i.e. without considering BMD, FRAX® has been shown to have a better performance than BMD alone in predicting major fracture risk<sup>20</sup>. The development of this tool was based on excellent methodology<sup>14</sup> and its validity has been ex-

**FIGURE 1.** Screen page for input of data and risk estimation in the Portuguese version of the FRAX® tool (Portuguese model, version 3.9. <http://www.shef.ac.uk/FRAX/tool.aspx?country=53>) [With permission of the Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK]

ternally confirmed, up until now, by twenty-six studies performed in different countries and cohorts<sup>14,21-43</sup>. A total of 62 countries and/or ethnic models, are currently available and several others are being developed<sup>5</sup>.

A recent systematic literature review and meta-analysis performed by some of the Committee members<sup>19</sup> clearly demonstrated that FRAX is the most robust and accessible tool available to predict the risk of osteoporotic fractures. Its accuracy is well established and demonstrated by area under the curve (AUCs) from receiver operating characteristic (ROC) analysis for fracture prediction that range from 0.71 to 0.79 in meta-analysis. This performance in only surpassed by the QFracture tool<sup>19</sup>, but this instrument requires the consideration of 31 clinical risk factors and has only been validated for the UK and Ireland.

The FRAX®Port tool is the Portuguese version of FRAX®, developed to incorporate the actual epidemiology of hip fractures and mortality in the general Portuguese population<sup>15</sup>. The methodology and results of this adaptation have been endorsed by the Sheffield

University department responsible for FRAX® and by all Portuguese scientific societies and patients' organizations related to osteoporosis. It is readily available online.

### GUIDING PRINCIPLE 3

**The presence of previous fragility fractures justifies the consideration of pharmacological treatment, irrespective of the risk-estimate by the FRAX®Port tool**

This guiding principle was approved by 15 favorable votes, one against and one abstention.

Several studies support the conclusion that it is cost-effective to treat individuals with a prior hip or vertebral fragility fracture<sup>8,9,44</sup>. Vertebral fractures, for example, are a very strong risk factor for subsequent hip and vertebral fracture<sup>45,46</sup>, whereas forearm fractures predict future vertebral and hip fractures<sup>47</sup>.

The vote against was justified on the basis that previous fractures are already accounted for in FRAX®.

The time elapsed since the last previous fracture is

also relevant: the risk of further fractures is greatest during the first 2–3 years but remains significantly elevated for up to 10–15 years (most notably for proximal femoral fractures, vertebral fractures, and humeral fractures)<sup>48,49</sup>.

#### GUIDING PRINCIPLE 4

**Physicians should be aware of the limitations of FRAX® and of DXA, and make judicious informed adaptations of the fracture risk estimate when such limitations apply**

This guiding principle was approved by all committee members 17/17 favorable votes.

#### GUIDING PRINCIPLE 5

**Portuguese intervention thresholds should be based on a similar FRAX® ten-year risk estimate for all ages. This principle should only be overruled if the health-economics evaluations demonstrated that the intervention threshold for any given age&gender group differs more than 50% from the value recommended on the basis of the overall population**

This guiding principle was approved by 10 of the 17 committee members, 4 voted against and three abstained.

This was one of the most controversial points in the consensus meeting. The final recommendation is similar to the guidelines adopted by the National Osteoporosis Foundation – USA<sup>12</sup> and Canada<sup>11</sup>. In both these cases, the threshold for intervention was defined as the level of risk above which the cost per QALY gained was within the national acceptable limits. In both these guidelines, a similar value of estimated risk of fracture was adopted as the threshold for intervention for all ages and both genders, despite there being small age- and gender-related differences in the levels of risk that defined cost-effectiveness.

The recommendations issued by the United Kingdom's Royal College of Physicians<sup>44</sup>, the Swiss association Against Osteoporosis<sup>9</sup> and the French National Authority for Health<sup>7</sup> adopted a different conceptual drive: Treatment is recommended for all people whose 10-year FRAX® estimated risk is equal or superior to that of a female patient of similar age, who has already suffered a fragility fracture. This concept is based on the fact that treatment in people with a previous fragility fracture has been shown to be cost-effective. Given that the risk of fracture increases with age, all other things being equal, this approach determines that the intervention threshold increases substantially with age. As

an example, according to the UK guidance referred above, treatment will be recommended for a 50 year old whose 10-year risk of fracture is 7.5% but not for a 70 year-old whose ten-year estimated risk is 24%. The majority of our committee refused this philosophical approach. This was based mainly on the argument that the gain of one Quality-adjusted life year (QALY) should be considered of the same value for all ages. It was emphasized that age, as well as mortality are already considered in FRAX® and thus influence the fracture risk estimate. Overall, the majority of the committee decided to stand by the concept that, for the sake of equity, similar gains in health, as measured by QALYs, should justify similar financial efforts by society, irrespective of age.

#### GUIDING PRINCIPLE 6

**The Portuguese intervention thresholds should be based on cost-effectiveness data**

This guiding principle was approved by all committee members 17/17 votes.

By doing this, the Committee decided to accept that the threshold for intervention, at a population level, should be informed by economic considerations, rather than on a «political» perspective of a level of risk that would justify intervention, irrespective of its costs and societal willingness to pay. The committee thus acknowledges that the cost of intervention and the societal willingness to pay needs to be taken into account in decisions to treat or not to treat.

This principle implies that decisions to treat should have a similar foundation in all realms of medicine in our country – the impact of interventions in terms of QALYs gained should be calculated, the cost per QALY gained (or Incremental Cost-Effectiveness Ratio – ICER) determined and, naturally, a similar willingness to pay for a QALY should be applied, whatever the disease and intervention under consideration.

#### GUIDING PRINCIPLE 7

**The intervention thresholds should be based on data reflecting the Portuguese reality on fractures, mortality, costs and treatment efficacy**

This guiding principle was approved by all committee members 17/17 votes.

Recommendations on the level of fracture risk above which pharmacological intervention become cost-effective are inextricably dependent on dimensions that vary enormously at a national level, such as: epidemio-

logy of fractures, general mortality, mortality associated with fractures, medical interventions used in fracture cases, costs of caring for fractures, costs of preventive interventions, health policies, cost per QALY gained (ICER), economic status of the country and willingness to pay. This imposes the need to consider national data when making such decisions, and requires that intervention-threshold recommendations for Portugal had to wait until such data became available.

#### **GUIDING PRINCIPLE 8**

**The threshold for pharmacological treatment of osteoporosis shall be established at ten-year risk estimates that correspond to a Willingness to Pay per QALY gained of €32,000.**

**The cheapest of all pharmacological interventions should be taken as the basis to decide on the actual intervention threshold for the Portuguese population.**

This guiding principle was approved by 16 committee members and one abstention.

Cost-effectiveness of a given intervention can only be established by comparing its impact to a set value of willingness to pay for a QALY gained<sup>50</sup>. There is no established Portuguese national policy establishing Willingness to Pay for QALYs. So, the panel decided to endorse the recommendations issued by WHO, that this should be set at 2 fold the National Gross Product per capita<sup>51</sup> – 32.000€ is a rounding up of  $2 \times 16.400\text{€}$ , the Portuguese Gross domestic product (GDP) for year 2014<sup>52</sup>.

The choice for the cheapest intervention as a reference is based on the fact that the costs as well as the effectiveness of each of the available alternatives are taken into account while establishing the respective Cost per QALY (ICER).

All the above decisions were made before the actual cost-effectiveness studies for Portugal were presented to the Committee.

#### **GUIDING PRINCIPLE 9**

**DXA should be performed when it has a reasonable probability of changing the decision to treat/not to treat that can be taken on the basis of the FRAX®Port risk estimation made without DXA**

This guiding principle was approved by 16 favorable votes and one abstention.

Adding DXA to CRFs in FRAX® results, according to our meta-analysis, in the improvement of the AUC from 0.74 to 0.79<sup>19</sup>. DXA may also assist the clinician

in gauging the probability of secondary osteoporosis, in quantifying response to therapy and motivating the patient to treatment. The Committee considered that performing one DXA examination, at the time of deciding whether to treat, represents a relatively minor cost in view of the overall burden of the disease, which is compensated by the benefits than can be derived from that exam. This perspective led to a less stringent recommendation on when to perform DXA.

*Based on this guiding principle the following concepts were defined for the purposes of these recommendations:*

- **Intervention threshold:** A FRAX®Port ten-year risk-estimate value, with BMD, above which pharmacological treatment is warranted.

- **Range of fracture risk indicating the need for DXA:** A range of FRAX®Port ten-year risk-estimate, without BMD, within which DXA is justified, because it holds a reasonable probability of changing the decision to treat or not-to-treat.

Ideally, the lower and upper threshold for DXA evaluation would be based on real life Portuguese data establishing the probability of BMD inducing a change in the decision to treat/not to treat, around the intervention threshold. In the absence of such data, and taking into account the issues described above, the Committee consensually decided to establish these values at 2% and 0.5% above and below the intervention threshold for major osteoporotic and for hip fractures respectively.

#### **COST-EFFECTIVENESS ANALYSIS**

Once the above Guiding Principles were adopted, the Portuguese cost-effectiveness analysis with generic alendronate (the less expensive intervention) versus no treatment was presented to the Committee (Table II).

A detailed study in a representative sample of Portuguese patients with hip fractures was performed to establish the impact of osteoporotic fractures in terms of resource consumption (direct and indirect costs), mortality and quality of life. A societal perspective was adopted, i.e. all costs were considered irrespective of the payer being the patient or the security system<sup>2</sup>.

These data were incorporated in a previously validated Markov economic model<sup>53</sup> which synthesized relevant available data, such as the incidence of fractures and their age distribution, the general population mortality, the cost, effectiveness and risk of adverse events



**TABLE II. COST-EFFECTIVE INTERVENTION THRESHOLDS EXPRESSED AS THE 10-YEAR PROBABILITY OF A MAJOR /HIP FRACTURE (%) AT WHICH INTERVENTION WITH GENERIC ALENDRONATE BECOMES COST-EFFECTIVE IN COMPARISON TO NO TREATMENT, ADOPTING A WILLINGNESS TO PAY OF €32,000.00/QALY**

Age	10-year probability of a major fracture (%)	10-year probability of a hip fracture (%)
50	8.6	2.6
55	8.7	2.4
60	10.4	3.0
65	9.2	2.3
70	8.6	2.3
75	8.1	2.1
80	7.1	1.7
85	5.9	1.3
All ages	8.8	2.5

The intervention threshold for “All ages” is not the arithmetic mean of the individual age-groups values but the result of QALY calculations including the overall population. Adapted from <sup>54</sup>

of the different medications, need for co-medications and control procedures and drop-out rates. This model allows the estimation of Incremental Cost-Effectiveness Ratio – ICER, for each intervention, a concept that can be understood as the cost paid for each QALY gained, in comparison to no treatment. The results were used to establish the levels of estimated risk of fracture at which each given intervention becomes cost effective, i.e. results in costs per QALY within the established willingness to pay.

Based on the published results<sup>54</sup>, the Committee decided to adopt the FRAX®Port risk estimates of 9% for major osteoporotic fractures and 2.5% for hip fractures as the intervention thresholds for generic alendronate, in Portugal – Table II. The values for assessment threshold were established as 2% and 0.5% above and below the threshold of intervention for major osteoporotic or hip fractures, respectively.

## RECOMMENDATIONS

### RECOMMENDATION 1

**The implementation of general, non-pharmacological, preventive measures for osteoporosis, such as diet, vitamin D supplementation, exercise, falls prevention and monitoring the use of any bone active drug should apply to all ages, whenever correctable risk factors are identified, irrespective of FRAX® and BMD**

This recommendation was approved by all committee

members the 17/17 votes and an average agreement of 97 % (min.-máx.= 75-100) .

### RECOMMENDATION 2

**Pharmacological treatment for osteoporosis should be recommended, unless contraindicated, in all subjects over the age of 50 who have previously experienced either:**

- A.  $\geq 1$  fragility fracture of the hip or  $\geq 1$  symptomatic vertebral fragility fracture or**
- B.  $\geq 2$  fragility fractures, independently of the site of fracture or the absence of symptoms (e.g. two asymptomatic vertebral fractures).**

This recommendation was approved by all committee members the 17/17 votes and an average agreement of 95.6 % (70-100).

#### *Specifications to Recommendation 2*

For this purpose, a fragility fracture is defined as a fracture occurring spontaneously or following minor trauma, i.e similar or inferior to that of a fall from body height, after exclusion of pathological local causes of fracture such as neoplasia.

This recommendation implies that the presence of such fractures overrides the FRAX®Port, i.e treatment should be considered in these patients irrespective of FRAX®Port risk-estimate or DXA measurements. This does not imply that FRAX® or DXA should not be performed, as they may provide useful information to guide further investigation and choice of therapeutic interventions.

Recommending treatment for people who have al-



ready endured a fragility fracture, irrespective of FRAX® is common to all of the abovementioned recommendations: NOF-USA<sup>8</sup>, Canada<sup>11</sup>, France<sup>7</sup> and Switzerland<sup>9</sup>. This concept is inherent to the NOGG/UK recommendations<sup>44</sup>. The exact definition varies between documents. No evidence was found to propose the inclusion of  $\geq 2$  fragility fractures (other than hip or clinical vertebral) for treatment without further assessment. This was a consensus recommendation, based on the authors' opinion and experience.

### RECOMMENDATION 3

**All Portuguese women and men over the age 50 should have their ten-year risk of osteoporotic fracture estimated with the FRAX®Port tool, with or without DXA**

This recommendation was approved by all committee members 17/17 votes and an agreement of 95.9 % (80-100).

#### Specifications to recommendation 3

The decision to perform DXA should, ideally, be based on this initial FRAX®Port without BMD, as described below. However, if a recent BMD is already available, its value should be entered in the FRAX®Port calculation. The decision process for treatment should, in such case, be based on Recommendations 7, 8 and 9. DXA values can be acceptable for this purpose for up to two years, unless significant events for bone metabolism take place meanwhile.

Physicians are strongly recommended to strictly adhere to the definitions of clinical risk factors as described in the FRAX® website.

### RECOMMENDATION 4

**For FRAX®Port estimates, without DXA, between 7% and 11% for major osteoporotic fracture and between 2% and 3% for hip fracture, BMD of the proximal femur, and, if possible and indicated, the spine should be assessed and the results of femoral neck T-score entered into FRAX®Port. (Figure 2). DXA may be justified in additional special conditions, as described below.**

This recommendation was approved by 16 favorable votes and one abstention with an average agreement of 90.9 % (60-100).

#### Specifications to recommendation 4

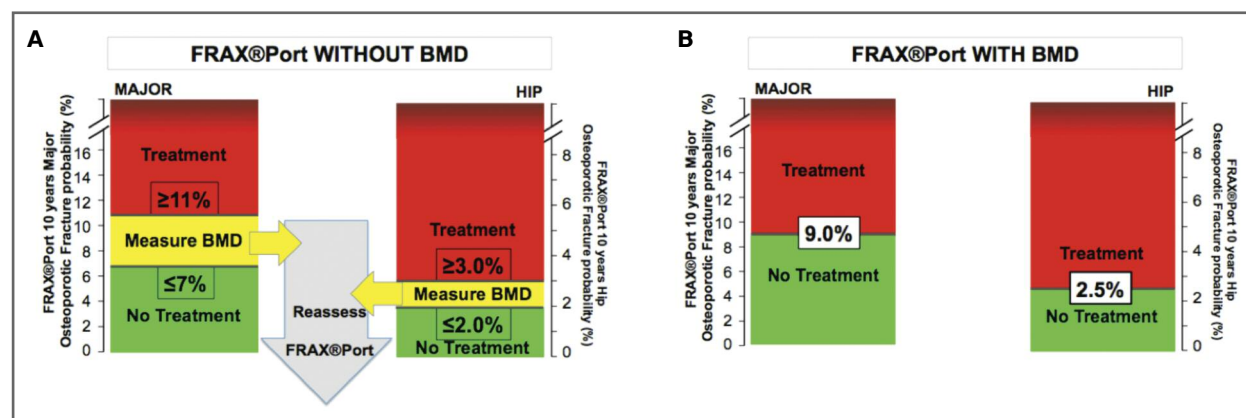
For the purposes of this recommendation, BMD should be assessed by dual x-ray absorptiometry (DXA).

The spine and proximal femur, are the sites recommended for DXA evaluation<sup>55</sup>. Spine DXA is prone to overestimate BMD in the presence of osteoarthritis, vertebral fractures and other calcifying changes overlaying the sites of interest.

The T score value for the femoral neck should be used for FRAX®Port.

In the context of decision to/not-to treat, DXA results must be considered in the context of FRAX®Port and not in isolation. This principle implies that the diagnosis of osteoporosis or osteopenia based on densitometry does not, *per se*, warrant the initiation of pharmacological treatment for osteoporosis.

The use of DXA for monitoring therapy is controversial, it is rarely justifiable at intervals of less than 2-3 years and may be dispensable altogether if the



**FIGURE 2.** Use of FRAX®Port ten-year estimated risk of major osteoporotic and hip fractures to decide on request of DXA and on initiation of pharmacologic treatment for osteoporosis. A: Estimates without BMD. B: Estimates with BMD.

adherence to effective therapy is guaranteed (for more info on the appropriate use and interpretation of DXA see references<sup>18,56,57</sup>).

The committee considers that performing DXA may occasionally be justified outside these FRAX boundaries or irrespective of them, including in the conditions described in Table III.

**Other conditions**, with less well-established relationship with osteoporosis, may also justify the performance of DXA as part of the diagnostic work-up. These include Cystic fibrosis; Ehlers-Danlos; Gaucher's disease; Glycogen storage diseases; Hemochromatosis; Homocystinuria; Hypophosphatasia; Marfan syndrome; Menkes steely hair syndrome; Porphyria; Riley-Day syndrome; Athletic amenorrhea; Hyperprolactinemia; Panhypopituitarism; Turner's and Klinefelter's syndromes; Cushing's syndrome; Thyrotoxicosis; Gastric bypass; Gastrointestinal surgery; Pancreatic disease; Primary biliary cirrhosis; Hemophilia; Leukemia; Lymphomas; Monoclonal gammopathies; Multiple myeloma; Sickle cell disease; Systemic mastocytosis; Thalassemia; Ankylosing spondylitis; Systemic lupus erythematosus; Amyloidosis; Chronic metabolic acidosis; Chronic obstructive lung disease; Congestive heart failure; Depression; End-stage renal disease; Hypercalciuria; Idiopathic scoliosis; Post-

-transplant bone disease; Sarcoidosis; type I diabetes mellitus.

**Some medications** with less well-established relationship with osteoporosis, may also justify the performance of DXA in special cases. These include: Aluminum (in antacids); Anticoagulants (heparin); Barbiturates; Cancer chemotherapeutic drugs; Depomedroxyprogesterone; Lithium; Cyclosporine A and tacrolimus; Methotrexate; Parental nutrition; Proton pump inhibitors; Selective serotonin reuptake inhibitors; Tamoxifen®; Thiazolidinediones (such as Acetos®); Thyroid hormones (in excess).

## RECOMMENDATION 5

**A. In men and women with a fracture risk estimate (without BMD) below 7% for major osteoporotic fractures and 2% for hip fracture a decision not to treat with pharmacological agents may be warranted, without the need to perform DXA.**

**Applicable general preventive measures should be applied**

This recommendation was approved by 16 favorable votes and one abstention with an average agreement of 95 % (50-100).

**B. In such cases, FRAX®Port estimates should be repeated with a frequency that depends on how close the previous estimate is to lower limit of indication to DXA and also on the occurrence of significant changes in clinical risk factors. (Figure 2a)**

This recommendation was approved by 16 favorable votes and one abstention with an average agreement of 93.8 % (60-100).

Regarding recommendation 5B the Committee presumes that FRAX®Port reassessments will, on average, in such cases, be justified every 5 years from age 50 to 70 and every two to three years thereafter, in the absence of relevant intercurrents.

## RECOMMENDATION 6

**In men and women with a fracture risk estimate, without DXA, above, 11% for major osteoporotic fracture or 3% for hip fracture, pharmacological treatment with generic alendronate is cost-effective and should be advised (unless contra-indicated), without the need to perform DXA. (Figure 2a)**

This recommendation was approved by 16 favorable

**TABLE III. CONDITIONS/DISEASES AND TREATMENTS WITH IMPACT UPON BMD, AS ESTABLISHED BY SYSTEMATIC LITERATURE REVIEWS AND/OR META-ANALYSIS**

Patients with the following conditions/diseases	Patients starting or under the following medications
Fragility fracture age ≤50 years (58)	Androgen deprivation therapy (59-61)
Prolonged immobilization and paralysis(62, 63)	Glucocorticoids (64)
Falls history (5, 6, 8, 11, 18)	Anticonvulsants (65)
Anorexia nervosa (66, 67)	Gonadotropin-releasing hormone analogues (GnRH) (68-70)
Calcium and vitamin D deficiency (5, 8, 71, 72)	Aromatase inhibitors (73-77)
Intestinal malabsorption (8, 78)	Antiretroviral therapy (72, 79)
Rheumatoid arthritis (80)	
Hyperparathyroidism (81, 82)	

votes and one abstention and an average agreement of 95.3 % (80-100).

#### RECOMMENDATION 7

**In men and women with a FRAX®Port ten-year risk-estimate, including DXA, at or above 9% for major osteoporotic or 2.5% for hip fractures pharmacological treatment for osteoporosis with generic alendronate is cost-effective and should be advised (unless contra-indicated).**

(See Table II and Figure 2B)

This recommendation was approved by all committee members 17/17 votes with an average agreement of 93.2 % (60-100).

#### RECOMMENDATION 8

**The decision to start anti-osteoporotic treatment with agents other than generic alendronate should be informed by their respective cost-effectiveness thresholds (Table IV)**

This recommendation was approved by 16 favorable votes and one against with an average agreement of 88.1 % (0-100).

#### Specifications to recommendation 8

This recommendation does not preclude the decision to prescribe these medications at lower risk-estimates, based on clinical grounds, such as formal-contraindication to less expensive alternatives, or conditions making the selected choice especially appropriate. The individual physician may also decide to adopt a different willingness to pay.

This specification was approved by 16 favorable votes and one against and an average agreement of 99.3% (90-100).

The cost per QALY associated with different medications is affected by their cost and effectiveness in different clinical settings. IV presents the risk-estimate levels at which treatment with zoledronic acid, denosumab and teriparatide become cost-effective in comparison to no-treatment and may, thus, be recommended on cost-effectiveness grounds, as described by Marques et al<sup>54</sup>.

The authors want to highlight that no national data is available on cost-effectiveness thresholds for other drugs. The only alternative is to extrapolate based on indicators of effectiveness, persistence and cost of those alternative drugs compared to the studied options.

#### RECOMMENDATION 9

**A. In men and women with a FRAX®Port ten-year risk estimate, including DXA, below 9% for major osteoporotic and below 2.5% for hip fractures, pharmacological agents are not cost-effective and a decision not to use them may be warranted.**

**Applicable general preventive measures should be applied**

This recommendation was approved by all committee members the 17/17 votes and an average agreement of 96.5 % (80-100).

**B. In such patients, DXA and FRAX®Port assessments should be repeated every 2 years or whenever clinical risk factors change significantly (Figure 2).**

**DXA may not be needed in case the previous BMD values are reassuring**

This recommendation was approved by 16 favorable votes one abstention and an agreement of 92.8% (75-100).

**TABLE IV. COST-EFFECTIVENESS THRESHOLDS FOR SEVERAL MEDICATIONS, BASED ON THE FRAX®PORT TEN-YEAR OSTEOPOROTIC FRACTURE RISK ESTIMATE, BASED ON A WILLINGNESS TO PAY OF 32.000€/QALY AND CURRENT COST OF MEDICATION. ADAPTED FROM <sup>54</sup>**

	Cost basis/year (€)	Without DXA		With DXA	
		Major %	Hip %	Major %	Hip %
Generic alendronate	99	11	3	9	2.5
Zoledronic acid	347	22	12	20	10
Denosumab	552	37	25	35	23
Teriparatide	4234	80	65	78	63

# RECOMMENDATION 10

While using FRAX®Port for the sake of these recommendations, health professionals should be aware of several limitations of this tool and considerer judicious adjustments of the risk estimates provide by this tool in specific circumstances, described below

This recommendation was approved by all committee members the 17/17 favorable votes with an average agreement of 97.6 % (70-100).

## Specifications of recommendation 10

1. The limitations of FRAX®Port are the same as those of FRAX®. Some of these may be resolved in future revisions of the tool;
2. FRAX® does not take into account the number of prior fragility fractures<sup>18</sup>, but this limitation is overcome by the Committees decision to recommend previous fragility fracture as an independent criterion to start treatment.
3. FRAX® has not been validated to be used in patients under osteoporotic treatment or for monitoring the effects of treatment<sup>18</sup>.

This specification was approved by 16 favorable votes, one abstention and an average agreement of 100%.

4. Falls are an important clinical risk factor for fractures and are not included in the FRAX® tool<sup>9</sup>. No formal recommendation can be made for this purpose, due to lack of appropriate scientific evidence. The best reference values that we can be provided are based on calculations performed with the QFracture®2013<sup>83</sup>, a validated and accurate fracture risk estimation tool, which considers falls. In this context, the presence of a "history of falls", multiplies by a factor of around 1.5, the 10-year fracture risk estimate made in its absence.

This specification was approved by 17 favorable votes and an average agreement of 92.1 % (0-100).

5. The FRAX tool does not take into account the corticosteroid dose above 5mg Prednisolone equivalent for three months. The Committee recommends that the 10-year probabilities of a hip fracture or a major osteoporotic fracture be adjusted according to the dose of glucocorticoids as described in Table V. No adjustments regarding duration of treatment can be proposed, due to lack of appropriate evidence.

This specific recommendation was approved by 16 favorable votes, one abstention and an average agreement of 87.5% (50-100).

6. FRAX® algorithm uses T-score for femoral neck BMD

**TABLE V. RECOMMENDED ADJUSTMENT OF 10-YEAR PROBABILITIES FOR MAJOR OSTEOPOROTIC FRACTURE OR HIP FRACTURE FOR ALL AGES, ACCORDING TO DAILY DOSE OF GLUCOCORTICOID. ADAPTED FROM <sup>5,84</sup>. MULTIPLY THE FRAX®PORT FRACTURE RISK ESTIMATE BY THE PROVIDED ADJUSTMENT FACTOR**

Prednisolone equivalent (mg/day)	Adjustment factor for ten year-probability estimates (for all ages)	
	Major osteoporotic fracture	Hip fracture
<2.5	0.8	0.65
2.5–7.5	No adjustment	
≥7.5	1.15	1.20

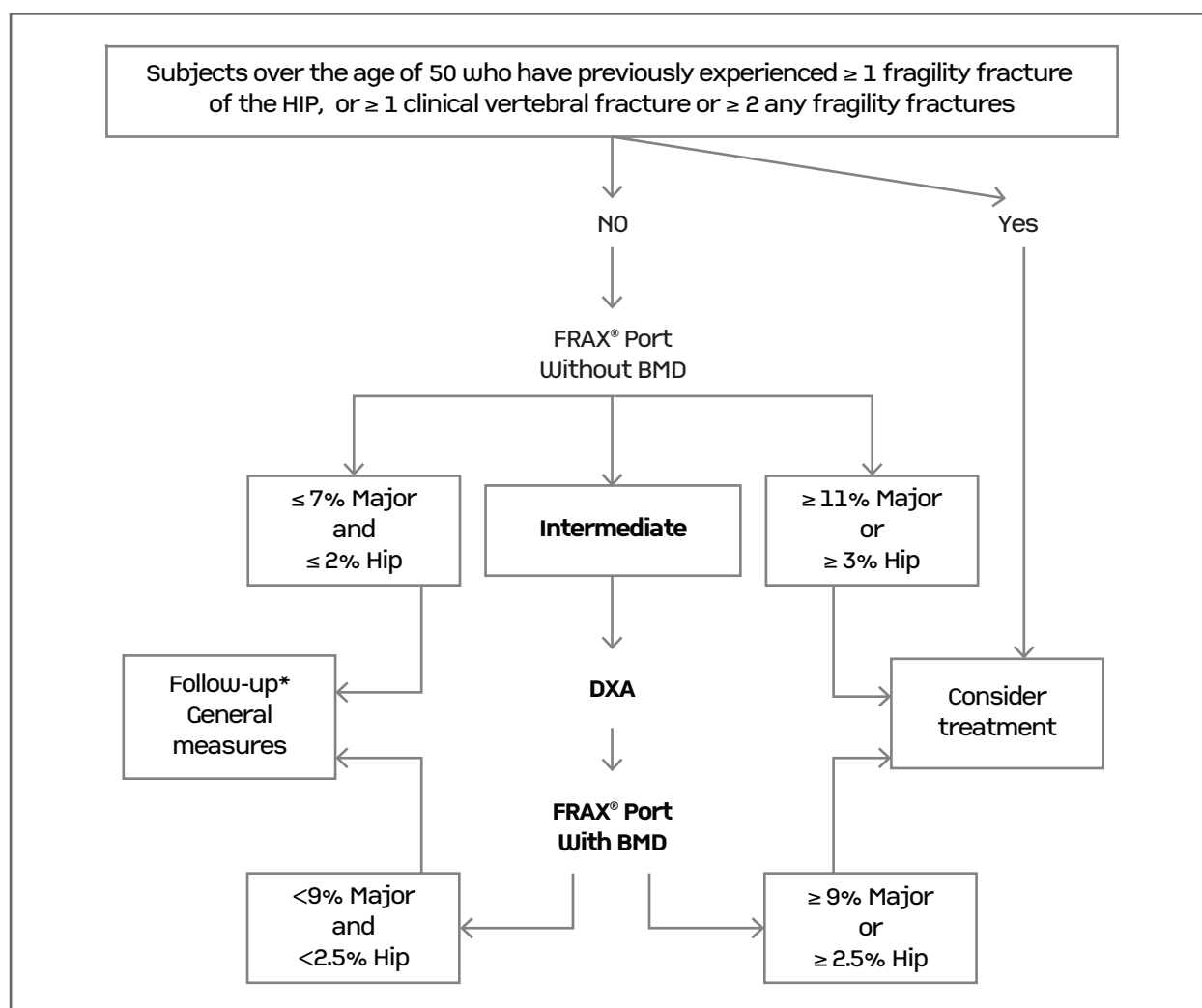
and does not take into account the lumbar spine BMD. However, when there is a large discordance (> 1SD) in the T-score of femoral neck and lumbar spine, it is proposed that the clinician may increase/decrease FRAX® estimate for major osteoporotic fractures by 10% for each rounded T-score difference between the lumbar spine and femoral neck<sup>5,85</sup>.

For example if T-score femoral neck = -1.5 and T-score lumbar spine = -2.8, the FRAX® estimate for major osteoporotic fractures should be increased by 10% percent (for example from 7% to 7.7%). If the values were -1.5 and -1.9 respectively, no changes should be made (difference <0.5 T). If femoral neck T score = -2.3 and lumbar spine T score = -3.9, the difference (1.6) is rounded to 2 T score and the major osteoporotic fractures risk estimate should be increase by 20% (for example from 8% to 9.6%, justifying medication according to the present recommendations).

As in all other circumstances, it is important to guarantee the quality and validity of lumbar spine DXA.

This specification was approved by 17 favorable votes and an agreement of 91.5% (75-100).

In Figure 3 we present a simplified integrated flow chart of decisions on treatment and DXA assessment according to the current recommendations. Take into account that the intervention thresholds are based on calculations for generic alendronate. Please refer to recommendation 8 to adapt for other medications.



**FIGURE 3.** Integrated approach of osteoporosis intervention thresholds and DXA request for Portuguese patients according to the current recommendations. Intervention thresholds described in this figure are appropriate for generic alendronate. Consider recommendation 8 (Table IV) for other agents.

BMD = bone mineral density; DXA= Dual-energy X-ray absorptiometry; \*Follow up – Repeat assessments as suggested in recommendations 5B and 9B

## DISCUSSION AND FINAL REMARKS

Ten recommendations regarding who to treat for osteoporosis and who to examine with DXA in daily clinical practice have been developed for Portuguese patients, based on consensualized guiding principles and updated epidemiologic and economic evaluations in the Portuguese setting (Table I). The recommendations are practical, evidence-based and supported by a panel of experts and representatives of all Portuguese scientific societies and patients' associations with an interest in Osteoporosis.

Evidence was used as the basis for recommendations as much as possible and this was supplemented by collegial decisions of the experts when decisive evidence was lacking. Considerable effort was put in to trying to keep the recommendations as simple, but also comprehensive, i.e capable of responding to most of the practicing clinicians needs.

These recommendations provide a much more robust and rationale basis for treatment decisions than considering solely the bone mineral density (BMD) or asking clinicians to base decisions on a subjective weighting of clinical risk factors. FRAX® allows the in-

tegration of a large number of clinical risk factors for fractures, whose relevance has been proven by evidence and whose impact has been estimated by meta-analysis. Moreover, the Portuguese version of FRAX incorporates the actual epidemiology of fragility fractures and mortality in the target population. The consideration of cost-effectiveness analyses of interventions in our actual epidemiologic and economic context, responds to the responsibility of making judicious use of the limited resources available for health care. These calculations were performed using state-of-the-art economic models and prestiged economic counseling. The adopted willingness to pay follows international recommendations.

A certain degree of arbitrariness was used in establishing the same cost-effective intervention threshold for all ages, despite there being considerable variability between the age groups. The same applies to the amount adopted as willingness to pay (WTP): some practitioners may have a different view and the WTP may change according to GDP and national health policies. Expert users may wish to produce a more precise definition of cost-effective threshold for specific individual cases, taking into account the patient's age, the medication being considered or a WTP of their own choice. This can be achieved through the use of a dedicated tool made available by Marques et al<sup>54</sup> <https://dl.dropboxusercontent.com/u/4287154/OsteoporoseThrCalc/ThreshComputationPortugalFINAL.xlsx>.

These recommendations represent an important paradigm shift, which was made possible by the development of FRAX®, its Portuguese adaptation and the economic evaluations described above. We believe that the potential of this change towards supporting a more efficient use of human and financial resources in the combat to the ever-growing epidemics of osteoporotic fractures is truly enormous. However, it all depends on the use that health professionals, both individually and as a community, make of these new tools. It is expected that the endorsement of these recommendations by all the experts and societies represented will increase their dissemination and implementation into national clinical practice, thus expanding their potential to foster progress on the current standard of osteoporosis management in our country.

We will be greatly indebted to all health professionals who may be willing to share their views and experiences on using these recommendations and offer suggestions on how to improve their reach on behalf of public health ([reuma@huc.min-saude.pt](mailto:reuma@huc.min-saude.pt))

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