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ORIGINAL ARTICLE

# Comparison of the proportion of patients potentially treated with an anti-osteoporotic drug using the current criteria of the Belgian national social security and the new suggested FRAX® criteria

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**Abstract** To assess the number of anti-osteoporosis treatments that would be reimbursed by the Belgian social security if either FRAX® or the current criteria were used to determine access to reimbursement. This is a retrospective study based on data from 1,000 women randomly selected from an outpatient hospital specialized in bone metabolism in Belgium. Proportions of potentially refunded treatments between FRAX® and current criteria were compared. Out of the 1,000 women files, 890 have sufficient information to assess FRAX®. In Belgium, current criteria include a bone mineral density (BMD) *T* score below −2.5 at the lumbar spine, the femoral neck or the total hip and/or at least a prevalent vertebral fracture. Using these criteria, 167 women (18.8 %) would have access to reimbursement. Using the criteria based on the validated Belgian FRAX® tool, only 116 women (13.0 %) would have access to reimbursement, meaning that access to reimbursement based on FRAX® criteria would reduce by 30 % the anti-osteoporosis drug expenses covered by the national social security. Interestingly, only 65 women out of the 116 (56.0 %) selected with the FRAX® criteria were also selected with the current criteria of the national social security. A substantial proportion of individuals that would potentially receive a reimbursement for their treatment using the FRAX® criteria do not have access to any refund for their treatment with the current criteria. Since patients identified with the FRAX® tool are those with the highest risk profile for future fractures, reappraisals of treatment reimbursement guidelines are expected in Belgium.

**Keywords** FRAX · Osteoporosis · Drug · Economic evaluation · Reimbursement

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## Introduction

Osteoporotic fractures are an important cause of morbidity and are linked with significant risk for subsequent fracture and mortality, in both women and men. In 1994, the World Health Organization (WHO) proposed an operational definition for osteoporosis based on bone mineral density (BMD) [1], measured by dual X-ray absorptiometry (DXA). The limits for osteoporosis were set when the BMD value fell below 2.5 standard deviations (*T* score −2.5) of the mean value found in young healthy adult women [1]. It has been used not only as a classification tool, but as a diagnostic criteria and an intervention threshold to determine who should be treated.

Even though a low BMD is strongly associated with the risk of fracture, it is well recognized that different risk factors, such as age, history of a prior fragility fracture, steroid use, and many others, are independent contributors to the risk of fracture and added to the BMD measurement improve the sensitivity of the identification of patients at high risk of fracture [2]. Recently, the importance of additional risk factors such as age and prior fractures have been incorporated into some clinical guidelines (e.g., National Institute for Health and Clinical Excellence (NICE) Osteoporosis Technology Appraisals) or been used in a more subjective way by specialists to rationalize

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**Table 1** 10-year probabilities (in %) of a major osteoporotic fracture and a hip fracture calculated with the Belgian FRAX® model

| Variables | Age (years) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 |
| Major osteoporotic fracture | 7.4 | 9.9 | 12 | 15 | 18 | 20 | 16 | 31 | 30 |
| Hip fracture | 1.1 | 1.8 | 2.4 | 3.7 | 5.7 | 8.4 | 11 | 14 | 14 |

approaches to treatment. The introduction of the FRAX® algorithm has resulted in a more reliable way to estimate fracture risk. The FRAX® tool (www.shef.ac.uk/FRAX) stratifies fracture risk more accurately than is possible with the use of BMD alone [3]. FRAX® computes the 10-year probability of a hip fracture or a major osteoporotic fracture, the latter comprising a clinical spine, hip, forearm, or humerus fracture. The risks of fracture and death vary with the different regions of the world, so that the tool needs to be calibrated to the epidemiology of the region [4]. A validation of the FRAX® tool has been launched recently in Belgium [5, 6].

Because of limited available resources, strict conditions of reimbursement of drugs against osteoporosis are applied in many countries, including Belgium. Until recently, the majority of clinical guidelines for the management of osteoporosis were oriented on refunded interventions based on BMD *T* score. The FRAX® tool provides new opportunities to improve management but requires a reappraisal of clinical guidelines [3]. Now, some guidelines integrate risks factor, but it is not the case in Belgium.

The objective of this study is to assess the number of anti-osteoporosis treatments that would be reimbursed by the Belgian social security if either FRAX® or the current criteria were used to determine access to reimbursement.

## Materials and methods

This is a retrospective study based on data from 1,000 women randomly selected from an outpatient hospital specialized in bone metabolism in Belgium. Initially, this bone metabolism center has data on more than 10,000 subjects, mainly women. The bone metabolism center is specialized in the screening, diagnosis, and management of bone diseases.

We have planned to analyze about 10 % of the data to obtain a representative subset of 1,000 records. Medical records were excluded if they were related to men or to subjects aged less than 40 years. These 1,000 medical files were selected using a systematic random sampling method.

BMD was measured at the spine, the femoral neck, and the total hip using a Hologic QDR-4500 densitometer. *T* score was calculated with the use of the National Health and Nutrition Examination Survey (NHANES) data.

The 10-year risk of hip fracture and of any other major osteoporotic fracture (spine, wrist, or humerus) was calculated using the FRAX® tool (www.shef.ac.uk/FRAX/) accessed on April 2010. The clinical risk factors and the femoral neck BMD needed to calculate FRAX® results were taken from medical records.

In Belgium, a treatment against osteoporosis is reimbursed by the Belgian social security if the woman has a BMD *T* score below −2.5 at the lumbar spine, the femoral neck or the total hip, and/or at least a prevalent vertebral fracture. Recently, treatment consideration based on FRAX® results has been suggested for Belgian women [7]. The FRAX® probabilities according to the age of the subject that have been used in this study are presented in Table 1.

Complete information was available for 890 women. From these 890 files, two analyses were done based on the potential reimbursement of anti-osteoporotic treatment. The first analysis was based on the current Belgian criteria for reimbursement and the other analysis was based on the FRAX® criteria. The primary objective of this study was to assess the number of treatments that would be reimbursed by the Belgian social security if either FRAX® or the current criteria were used to determine access to reimbursement. The difference between the proportions of refunded treatments in the two analyses was assessed by a $\chi^2$ test. Analyses of variance were used to compare their clinical characteristics.

## Results

Out of the 1,000 women included in this study, information obtained to calculate the FRAX® results was available for 890 (89 %). Women were aged 62.6 ± 9.9 years, had a body mass index of 26.1 ± 4.8 kg/m$^2$, and a *T* score of −1.17 ± 1.01. The 10-year probability of a major osteoporotic fracture was 8.31 ± 5.78 and the probability of a hip fracture was 2.10 ± 3.14. The FRAX® profile of the 890 subjects is detailed in Table 2.

Using the current Belgian criteria for reimbursement, 167 women (18.8 %) have access to drug reimbursement. Using the potential criteria based on the FRAX® tool, only 116 women (13.0 %) would have access to refunds ($p = 0.0009$ between the two groups). Women selected

**Table 2** FRAX® profile of the 890 subjects selected in this study

| Variables | % |
|---|---|
| Prior fracture | 27.7 |
| Parental history of fracture | 2.7 |
| Smoking | 8.0 |
| Glucocorticoids | 1.8 |
| Rheumatoid arthritis | 0.6 |
| Secondary osteoporosis | 0.0 |
| Alcohol | 0.3 |

with the current criteria were significantly older ($p < 0.0001$), had a lowest BMD $T$ score ($p = 0.007$), had less prevalent fracture ($p = 0.002$), and parental history of hip fracture ($p = 0.01$) and were less likely to smoke ($p = 0.008$) (Table 3). No other significant difference was observed. In particular, the 10-year probabilities of a major or a hip fracture were not significantly different between the two groups.

Out of the 116 women selected with the FRAX® criteria, 51 (44.0 %) were not selected with the current criteria of the national social security. This means that a substantial proportion of individuals that should potentially receive a treatment using the FRAX® criteria do not have access to any drugs reimbursement using the current criteria. Interestingly, this proportion was even more important at younger age (Table 4).

Moreover, only 38.9 % (65 out of 167) of the women who have access to refunds with the current criteria would potentially be reimbursed if the FRAX® criteria were used. This proportion falls to zero after the age of 85 years (Table 5).

**Table 3** Comparison between characteristics of the women selected with the FRAX tool and those selected with the current criteria

| Variables | Women selected with the FRAX tool | Women selected with the current criteria | $p$ value |
|---|---|---|---|
| Age (years) | 57.5 ± 9.2 | 65.2 ± 10.1 | <0.0001 |
| BMI (kg/m$^2$) | 23.5 ± 4.6 | 23.9 ± 4.8 | 0.517 |
| Femoral neck $T$ score | −2.2 ± 0.8 | −2.2 ± 0.8 | 0.541 |
| Lumbar $T$ score | −1.8 ± 1.4 | −2.3 ± 1.5 | 0.007 |
| Hip $T$ score | −1.8 ± 1.0 | −1.9 ± 1.0 | 0.749 |
| Prior fracture (%) | 60.3 | 41.3 | 0.002 |
| Parental history of fracture (%) | 10.3 | 3.0 | 0.011 |
| Smoking (%) | 22.4 | 10.8 | 0.008 |
| Glucocorticoids (%) | 4.3 | 2.4 | 0.366 |
| Rheumatoid arthritis (%) | 3.4 | 1.8 | 0.379 |
| Alcohol (%) | 0.9 | 0 | 0.229 |
| 10-year probability of major fracture (%) | 14.3 ± 8.0 | 13.3 ± 7.4 | 0.267 |
| 10-year probability of hip fracture (%) | 5.7 ± 6.4 | 5.3 ± 5.6 | 0.505 |

**Table 4** Proportion of individuals who have access to drugs reimbursement using the current criteria among those potentially selected to receive a treatment using the FRAX® criteria

| Variables | Age (years) | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | 50 | 55 | 60 | 65 | 70 | 75 | 80 | |
| Proportion of individuals current/FRAX® criteria | 6/26 (23.1 %) | 11/20 (55.0 %) | 18/31 (58.1 %) | 13/19 (68.4 %) | 6/8 (75.0 %) | 7/8 (87.5 %) | 4/4 (100 %) | 65/116 (56.0 %) |

**Table 5** Proportion of individuals potentially selected to receive a treatment using the FRAX® criteria among those who have access to drugs reimbursement using the current criteria

| Variables | Age (years) | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | 50 | 55 | 60 | 65 | 70 | 75 | 80 | 85 | 90 | |
| Proportion of individuals FRAX®/ current criteria | 6/10 (60.0 %) | 11/17 (64.7 %) | 18/37 (48.6 %) | 13/25 (52.0 %) | 6/21 (28.6 %) | 7/26 (26.9 %) | 4/20 (20.0 %) | 0/10 (0 %) | 0/1 (0 %) | 65/167 (38.9 %) |

## Discussion

Our study showed that, in Belgium, access to reimbursement based on FRAX® criteria would reduce the number of women that would receive a refund for an anti-osteoporosis treatment. Taking into account the hypothesis that the identification of patients at highest risk of fracture is more accurate with the FRAX® tool than with BMD alone, access to reimbursement based on the FRAX® criteria could be more efficient than based on the current criteria. Interestingly, we also showed that almost 50 % of individuals that potentially could receive a treatment with reimbursement using the FRAX® criteria do not receive a refunded treatment with the current criteria.

Until recently, the majority of clinical guidelines for the management of osteoporosis were oriented on refunded interventions based on BMD *T* scores. There have been several approaches to the development of guidelines based on fracture probability. A method commonly used is to "translate" current practice in light of the FRAX® tool. In 2008, the National Osteoporosis Guideline Group (NOGG) in collaboration with many Societies in the United Kingdom recommended an approach for decision making based on fracture probabilities derived from a FRAX® assessment that can be applied to men and women [8]. The NOGG provided intervention thresholds (the fracture probability at which intervention is recommended) and assessment thresholds (the fracture probabilities at which a BMD test might or might not be recommended).

In Belgium, the identification of patient at highest risk of fracture and the criteria for anti-osteoporotic treatment reimbursement are still based on BMD and/or the presence of a prevalent fracture. Setting a treatment cut-off based on a *T* score alone does select patients at increased probability of fracture. However, it also categorizes patients with an equal or higher fracture probability as non-eligible for treatment if additional clinical risk factors are not taken into account in the fracture risk assessment. The determination of the individual 10-year fracture probability with the FRAX® tool would at least ensure that patients at equal risk would have equal opportunities to get the appropriate treatment.

In the field of osteoporosis, treatment access is usually restricted to patients that present the same criteria than subjects included in clinical trial (i.e., low bone mass measured by DXA and/or prevalent vertebral fractures). Although we acknowledge, we have no direct evidence that women identified by the FRAX® tool will respond to available treatments as well as patients identified based on current classical criteria. Interestingly, post hoc analyses based on health economics evaluation of treatment based on the FRAX® tool have recently been published [7, 9–11]. They showed enhanced effectiveness of pharmacologic intervention in patients with higher fracture probabilities as determined by the FRAX® tool.

In our study, we have shown that women selected with the current criteria of the national social security have not the same characteristics compared to women selected by the FRAX® tool. Indeed, treatment selection based on FRAX® would lead to treat younger women with better lumbar BMD and more risk factor of fracture (i.e., prevalent fracture, parental history of hip fracture, and smoking). Interestingly, even if the 10-year probability of fractures was not significantly different between groups, selection based on FRAX® would potentially reduce the number of treatment reimbursed.

The application of fracture probability to clinical practice demands a consideration of the thresholds for intervention [12]. Moreover, in many countries, treatment for osteoporosis competes with other health care priorities, which are usually based on a health economic argument [13]. In the United Kingdom, for example, a treatment that costs £20,000–30,000 per quality-of-life year gained is considered to be cost-effective. Using this criterion, a 10-year probability of a major osteoporotic fracture of about 7 % or more provides a cost-effective threshold for men and women in the United Kingdom, though this varies slightly with age [14]. In the USA, the guidelines of the National Osteoporosis Foundation have been amended recently to accommodate in part the incorporation of fracture probability. Patients with a prior hip or vertebral fracture are recommended for treatment as are men and women with a *T* score for BMD of −2.5 SD or below. Conversely, no treatment recommendation is provided for those with a *T* score of −1.0 SD or above. In the remainder of the US guidelines, recommendations for intervention are guided by fracture probabilities that are based on a health economic analysis. As a matter of fact, treatments are recommended when FRAX® probabilities are equal or greater than 20 % for major osteoporotic fractures or equal or greater than 3 % for hip fracture in untreated patients with low bone mass (osteopenia) at the hip or spine and without a history of low trauma fractures of either the hip or spine [15, 16]. With the FRAX® Belgium tool, the proposed intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture and therefore rises with age [8].

In United Kingdom, using the FRAX® tool, the proportion of the female population potentially treated varied from 24 % to 47 %, depending on age [14]. In our study, the proportion of women to be treated would be of 13 % using the FRAX® criteria and are about 18 % using the current criteria. The drug expenses supported by the national social security for osteoporosis management would in that case be reduced by 30 % using the FRAX® criteria. However, a more sophisticated economics analysis

ran in a Belgian setting is needed to assess the global interest of switching from the current criteria to the FRAX® criteria.

In Switzerland, a study shows that the level of 10-year fracture probability equivalent to that currently accepted for reimbursement of BMD measurement by DXA is achieved with several clinical risk factor profiles and combinations [17]. These include risk factors not (yet) accepted for reimbursement in Switzerland, such as a parental history of fracture, tobacco and/or alcohol abuse, and rheumatoid arthritis. This suggests that, with an identical 10-year fracture probability, adequate diagnostic workup is not equally accessible to all patients presenting an identical fracture risk. Consequently, with current access to osteoporosis diagnosis, too few patients at increased probability of fracture are adequately identified and subsequently treated [17].

A recent study tried to determine which men on androgen deprivation therapy (ADT) would be identified as treatment candidates, based on DXA or on FRAX® assessments calculated with or without femoral neck *T* score [18]. They showed that using DXA, 33 % of men would need treatment. When the FRAX® tool was used including the femoral neck *T* score, only 17.4 % of the men met the criteria for treatment. However, when the FRAX® tool was applied without the *T* score, 54.9 % of the men met the criteria for treatment.

There are limitations to the present study. First, we used a sample of women from one clinic, specialized in osteoporosis management. Patients attending this clinic could be different from the general population. Second, we did not interview the subjects directly. Instead, some risk factor information was derived from the medical record. However, as this outpatient hospital is specialized in bone diseases management, the medical staff is used to record all clinical risk factors for fractures. However, we acknowledge that some risk factors in the medical file were reported by the patient themselves and this could explain some underreporting (e.g., less than 1 % of women reported a consumption of alcohol that could be considered as risk factor). Third, some patients might have attended the clinic more than once if they had a *T* score just under the limit of treatment reimbursement. By attending a later visit, they might then have been in the conditions of drug reimbursement. However, these subjects would not have been asked to attend again the clinic with a BMD *T* score in the normal range. Fourth, economics modeling would be needed to assess the real global benefit of these results.

We conclude that there are ethical and economic needs of additional reappraisal to translate current guidelines for the management of osteoporosis into guidelines based on fracture probability.

**Conflict of interest** The authors declare that they have no conflict of interest.

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