

Choice of osteoporosis guideline has important implications for the treatment decision in elderly women referred to a fall clinic

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ABSTRACT

INTRODUCTION: Different guidelines are used worldwide to make decisions on treating osteoporosis. Some are based on fracture risk calculations, whereas others use criteria based on bone mineral density (BMD) T-scores, risk factors, or fragility fractures. The aim of this study was to explore how osteoporosis treatment decisions in a group of elderly women with falls would be affected if fracture risk-based guidelines were used as compared to guidelines based on BMD T-scores.

METHODS: We studied 88 women attending a falls clinic. Dual energy X-ray absorptiometry and vertebral fracture assessment were performed and clinical risk factors were identified. We calculated the percentage of women recommended for treatment using five guidelines: Danish Bone Society (DBS-DK), UK National Osteoporosis Guideline Group (NOGG-UK), US National Osteoporosis Foundation (NOF-US); and we applied a 20% cut-off to fracture risk calculations by the Garvan Fracture Risk Calculator and Q-fracture 2012. Agreement was calculated using kappa statistics.

RESULTS: The median age (interquartile range) was 81 years (75–85.5 years). The proportion of women (95% confidence interval) recommended for treatment was DBS-DK 56% (44.7–66.3%), NOGG-UK 51% (40.1–62.1%), NOF-US 88% (78.5–93.5%), Garvan 91% (82.9–96.0%), Q-fracture 58% (47.0–68.4%). The guidelines agreed on treatment recommendations for 23 (26%) of the 88 women studied.

The kappa score was 0.13 ($p < 0.0001$).

CONCLUSION: This study showed that the choice of guideline has a major impact on the treatment decisions in elderly women with falls.

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garding assignment of patients for anti-osteoporotic treatment. However, it is important to recognise that the WHO T-score was designed as a diagnostic measure rather than an intervention threshold, for which a large variety of conditions should be taken into account. BMD is an imperfect measure for fracture prediction since more than half of the patients who experience a low energy hip fracture have a BMD above the osteoporotic range [2]. Furthermore, a low BMD is only one of a multitude of risk factors for fracture. Today, a number of clinical indicators are recognised as clinical risk factors for fracture [3, 4]. This has led to a shift from the WHO's T-score categorisation to absolute fracture risk determination in the assessment of osteoporosis.

For determination of fracture risk, several assessment tools that incorporate different clinical risk factors have been developed; e.g. the WHO Fracture Risk Assessment Tool (FRAX) [5], the Garvan Institute Fracture Risk Calculator (Garvan) [6], and the Q-fracture 2012 Risk Calculator (Q-fracture20) [7].

In recent years, several evidence-based guidelines have been launched for assignment of anti-osteoporotic medication that implement fracture risk calculation [8–10]. There is great diversity in how the assessment tools are incorporated and how the intervention threshold is defined.

To our knowledge, there are no studies investigating the impact of choice of osteoporosis treatment guideline on treatment recommendations, in a clinical setting among patients with a high risk for fracture.

The purpose of this study was to explore any possible differences with regard to treatment recommendations in a falls clinic between criteria-based guidelines based on the WHO T-score categorisation on the one hand and guidelines based on absolute fracture risk determination on the other. First, we investigated if the choice of guideline would influence the number of persons recommended for treatment. Second, we investigated the agreement between the guidelines with regard to who the guidelines would select for treatment.

METHODS

Data for this cross-sectional observational study were

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Falls and osteoporosis are common and important conditions in older people, sharing the serious clinical endpoint of fracture. Assessment of osteoporosis is essential when examining patients with recurrent falls and vice versa.

According to the World Health Organization (WHO), osteoporosis is diagnosed when a value for bone mineral density (BMD) T-score ≤ -2.5 [1]. Thus, the BMD is a pivotal factor in physicians' decision-making process re-

collected among 195 women who were admitted to the Falls Clinic at Odense University Hospital, Denmark, (May 2012 -January 2013) due to falls and instability. Women aged 65 years or older were recruited consecutively. We excluded women who were unable to give informed consent or could not be transferred onto the dual energy X-ray absorptiometry (DXA) scanner. Eligible women were interviewed about their clinical risk factors as required for fracture risk assessment. To minimise recall bias or memory decay, information on prior fractures and comorbidity was validated through information from hospital records.

The BMD of the hip and spine was measured by DXA (Hologic Discovery A). The women were assessed with lateral scans of the spine T4-L4 by the DXA equipment. All scans were performed on the same device by a trained technician. We used National Health and Nutrition Examination Survey (NHANES) reference values and reference values provided by the manufacturer for calculations of the T-score for the hip or spine, respectively. Lateral scans of the spine were analysed using the Genant semi-quantitative visual grading method [11]. We classified grade two and three as clinically relevant vertebral fractures. When in doubt, X-rays were performed.

We assessed fracture risk using the FRAX, Garvan and Q-fracture on-line calculators. The clinical risk factors considered with the different tools are listed in **Table 1**. We calculated fracture risk by FRAX, with femoral neck BMD (FN-BMD), using the country-specific tool for Denmark (DK-FRAX), the United Kingdom (UK-FRAX) and the United States (US-FRAX).

Garvan calculates fracture risk with the FN-BMD; but when the FN-BMD was not available, we calculated fracture risk using weight as suggested by the calculator. Since our data did not allow for the use of all response categories available according to Garvan and the Q-fracture tool for falls and alcohol, and tobacco use, we adjusted information on falls, tobacco and alcohol use. To fit the Garvan tool, we adjusted our data on falls within the past 12 months. Women who reported having two-four falls within the past year were classified as having two falls. Women reporting more than four falls were classified as having three or more falls. Those who reported zero or one fall were classified as such. Using the Q-fracture assessment, we classified all current smokers as light smokers as we were unable to make any further subdivision of smokers, and those who reported an alcohol consumption exceeding two units a

 **TABLE 1**

Overview of the guidelines in terms of criteria for measuring bone mineral density, initiation of treatment, the fracture risk assessment tool used, and clinical risk factors considered in the guidelines.

Guideline	Criteria for measuring BMD	Criteria for initiating treatment	1. Assessment tool 2. Risk factors considered
DBS-DK	≥ 1 CRF	Prior fragility fracture of the hip or spine. BMD T-score ≤ -2.5 (total hip or spine) Glucocorticoid treatment and BMD T-score between -1 and -2.5 BMD T-score ≤ -4,0 and no CRF	1. None 2. Family history of osteoporosis, age > 80 yrs, prior fragility fracture, menopause < 45 yrs, BMI < 19 kg/m ² , smoking, alcohol, glucocorticoid treatment, falls among aged, secondary osteoporosis
NOF-US (women)	All women aged ≥ 65 yrs or postmenopausal women, based on risk factor profile	Prior hip or vertebral fracture T-score ≤ -2,5 (femoral neck, total hip or spine) Postmenopausal women and T-score between -1 and -2.5 and 10-year hip fracture risk ≥ 3% or 10-year risk of major osteoporotic fracture ≥ 20%	1. FRAX 2. Age, sex, BMI, parental fractured hip, prior fracture, smoking, alcohol, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, BMD
NOGG-UK (women)	Postmenopausal women with a probability of major osteoporotic fracture between lower and upper assessment threshold using FRAX	Women with a prior fragility fracture Women with risk of major osteoporotic fracture above intervention threshold without BMD testing Women with risk of major osteoporotic fracture above intervention threshold, fracture risk assessed after BMD testing	1. FRAX 2. Age, sex, BMI, parental fractured hip, prior fracture, smoking, alcohol, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, BMD
Garvan20		Estimated fracture risk ≥ 20%	1. Garvan20 2. Age, sex, falls, prior fracture, BMI/BMD
Q-fracture20		Estimated fracture risk ≥ 20%	1. Q-fracture20 2. Age, sex, BMI, ethnicity, parental fractured hip/osteoporosis, prior fracture, smoking, alcohol, nursing or care home resident, falls, co-morbidity ^a , medication ^b

BMD = bone mineral density; BMI = body mass index; CRF = clinical risk factors; DBS-DK = Danish Bone Society; FRAX = Fracture Risk Assessment Tool; Garvan20 = Garvan Institute Fracture Risk Calculator 2012; NOF-US = US National Osteoporosis Foundation; NOGG-UK = UK National Osteoporosis Guideline Group; Q-fracture20 = the Q-fracture 2012 Risk Calculator.

a) Diabetes, dementia, cancer, lung diseases, cardiovascular diseases, liver or kidney diseases, gastrointestinal or endocrine problems, rheumatoid arthritis, systemic lupus, epilepsy or Parkinson's disease.

b) Glucocorticoids, antidepressants, oestrogens/hormone replacement therapy.

day were classified as 3-6 units a day. We were unable to make further subdivision into 7-9 units a day, or more than nine units a day.

We calculated the fraction of women eligible for treatment according to five different guidelines: Danish Bone Society (DBS) [12], UK National Osteoporosis Guideline Group (NOGG-UK) criteria [9], US National Osteoporosis Foundation (NOF-US) guideline [10], Garvan (Garvan20) [6] and Q-fracture20 [7]. The Q-fracture20 and Garvan20 guidelines were constructed by applying a fixed threshold of 20% for treatment eligibility. Women who had a calculated fracture risk $\geq 20\%$ by the Garvan20 or the Q-fracture20 tool were recommended for treatment by the guideline. The main aspects of each guideline are presented in Table 1. We studied the agreement between the guidelines in the women identified for treatment by calculating kappa scores and by plotting each patient into a Venn diagram representing the different guidelines.

The study was approved by The Regional Ethics Committee of Southern Denmark (S-20120262), The Danish Data Protection Agency (2008-58-0035).

Trial registration: ClinicalTrials.gov (NCT01600547).

RESULTS

We included 117 women in this study. A total of 88 women completed the full assessment, including DXA and lateral scans of the spine. The women not assessed with DXA ($n = 29$) and therefore not included in the analysis; and they did not differ significantly on FRAX ten-year probability of major osteoporotic fracture calculated without BMD (median (interquartile range (IQR)) 39% (27.5-45.0%) versus 40% (32.0-44.0%) $p = 0.54$). Of the 88 women included in the analysis, lateral scans of the spine were missing for 11 women because of poor quality, and six women did not have an FN-BMD because of bilateral hip prosthesis. The characteristics of the study population are described in **Table 2**.

The median (IQR) 10-year risk percentage of major/any-osteoporotic fractures calculated with BMD was: DK-FRAX 29.0% (20.0-35.0%), UK-FRAX 18.0% (13.0-25.0%), US-FRAX 21.0% (14.0-26.0%), Q-fracture 21.9% (15.8-31.1%), and Garvan 48.4% (31.1-67.9%). The median (IQR) 10-year risk percentage of hip fracture was DK-FRAX 11.0% (5.6-17.0%), UK-FRAX 7.4% (3.2-11.0%), US-FRAX 6.4% (3.2-11.0%), Q-fracture 14.5% (7.3-23.0%) and Garvan 26.4% (10.4-53.3%).

The proportion of women (95% confidence interval (CI)) recommended for treatment was NOGG-UK 51% (40.1-62.1%), NOF-US 88% (78.5-93.5%), Danish Bone Society (DBS-DK) 56% (44.7-66.3%), Garvan20 91% (82.9-96.0%) and Q-fracture20 58% (47.0-68.4%). The guidelines agreed on recommendations for 28 (32%) pa-



TABLE 2

Characteristics of the cohort ($N = 88$).

Age, yrs, median (IQR)	81 (75-85.5)
BMI, kg/m ² , mean (\pm SD)	27.2 (\pm 5.8)
T-score ≤ -2.5 total hip, femoral neck, or spine, n (%)	44 (50.0)
Prior hip fracture, n (%)	12 (13.6)
Vertebral fracture ^a , n (%)	13 (14.8)
Osteoporosis ^b , n (%)	57 (64.8)
Persons with falls within the past 12 months, n (%)	80 (90.9)
Persons with recurrent falls ^c , n (%)	58 (65.9)
Prior fragility fracture, n (%)	51 (58.0)
Parental history of fracture, n (%)	9 (10.2)
Currently smoking, n (%)	14 (15.9)
Use of oral glucocorticoids, n (%)	6 (6.8)
Rheumatoid arthritis, n (%)	1 (1.1)
Secondary osteoporosis, n (%)	23 (26.1)
Alcohol ≥ 3 units a day, n (%)	8 (9.1)

BMI = body mass index; DXA = dual energy X-ray absorptiometry;

IQR = interquartile range; SD = standard deviation.

a) Assessed with lateral spine DXA.

b) T-score ≤ -2.5 total hip, femoral neck, or spine, or fragility fracture of hip or spine.

c) > 1 fall within the past 12 months.

tients: recommending treatment for 23 (26%) and no treatment for five (6%) of the 88 patients participating in the study (**Figure 1**). The kappa score was 0.13 ($p < 0.0001$) indicating slight agreement.

DISCUSSION

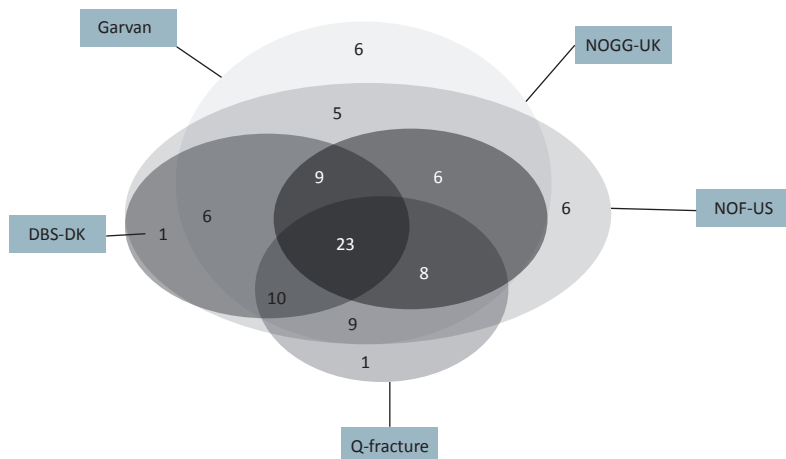
To our knowledge, this is the first study to address the impact of different guidelines in a sample of persons admitted to a falls clinic. Our data showed that the choice of guideline has a major impact on treatment decisions. The guidelines only agreed on recommending treatment in 23 cases (26%). Comparing different guidelines can be problematic, i.e. the UK NOGG guidelines are based on intervention thresholds based on age, whereas the US-NOF approach uses a set threshold. Clinicians should be aware of these issues before deciding which approach is suitable for their patients.

Other studies have also evaluated the impact of NOF and NOGG guidelines on the proportions of persons recommended for treatment. The treatment rates of the NOF guidelines ranged from 33% to 46%, whereas treatment rates for NOGG guidelines ranged from 21% to 47% [13-16]. None of these studies were done in a clinical setting, and our study showed considerably larger proportions of persons identified for treatment than other studies, probably due to differences in age and morbidity in the samples studied.

Several issues are important to consider when comparing different guidelines between different countries.

FIGURE 1

Venn diagram showing the actual number of persons recommended for treatment by the different guidelines. We assessed 88 patients. Guidelines agreed on recommending treatment for 23 (26%). The kappa score was 0.13 ($p < 0.001$).



DBS-DK = Danish Bone Society; Garvan20 = Garvan Institute Fracture Risk Calculator; NOF-US = US National Osteoporosis Foundation; NOGG-UK = UK National Osteoporosis Guideline Group.

Clinical guidelines take into account local conditions such as epidemiologic differences, i.e. the prevalence of the disease, mortality and morbidity related to the disease. FRAX is the only tool that considers epidemiologic differences between countries, which is reflected in the differences in the calculated median fracture risk. For guidelines that recommend FRAX, some of the differences in treatment eligibility are related to these factors. Furthermore, some tools such as FRAX take into account life expectancy, which is not the case for other tools. This is potentially important for older populations such as the population in our study where mortality and fracture carry equal weight. Other conditions that affect clinical guidelines are organisational differences such as access to DXA and medical care. The NOF guideline is based on cost effectiveness analysis. It considers expenditure related to fractures, drugs, physician visits and BMD testing. The threshold defined depends on the willingness to pay within the society [17]. It may therefore be inappropriate to apply the NOF-US guideline to Non-US societies with other priorities. Differences between guidelines also reflect different approaches to the identification of scientific evidence, the assessment of data quality and the translation of information when clinical practical guidelines are developed [18].

The discrepancy between treatment recommendations raises the question which guideline would be the most appropriate in Denmark. Since DBS-DK is based on the WHO T-score categorisation, the guideline is limited by the low sensitivity of DXA, and it therefore only targets some of those who will experience fractures. A less

rigorous interpretation of the WHO T-score threshold in high-risk populations might be beneficial. FRAX is a possible alternative. However, the ability of FRAX to increase accuracy of fracture risk prediction is much debated, and little is known about the efficacy of anti-osteoporotic medication in patients selected for treatment due to a high risk score [19, 20]. If DK-FRAX had been used as decision tool in this sample with 20% risk of major fracture as the intervention threshold, 76% would have been recommended for treatment. The agreement between the DBS-DK and the DK-FRAX is 65.9% ($\kappa = 0.28$).

Our study has some limitations. First, FRAX has an upper age limit of 90 years for calculation of fracture risk. Four participants were older than 90 years. However, they would all be treated according to the NOGG-UK or NOF-US guidelines because of prior fragility fracture or low-spine BMD; this inaccuracy in FRAX score therefore does not affect the proportions of women recommended for treatment. Second, we had to adjust categorisation on falls, tobacco and alcohol consumption when calculating the fracture risk using the Garvan and Q-fracture risk tools. These adjustments could have led to underestimation of fracture risk and the proportions of participants eligible for treatment. Only two women, who were not recommended for treatment according to the Garvan20, reported a number of falls within the past 12 months in the range of 2-4 falls. Applying a worst-case scenario would increase the proportion of women eligible for treatment by 2%. We tested the impact of the inaccuracy of information on tobacco and alcohol consumption on the proportion of women eligible for treatment according to the Q-fracture tool. We calculated fracture risk with the Q-fracture tool applying the worst-case scenario (heavy smoker or > 9 units of alcohol/day) to the women who reported current smoking or alcohol consumption > two units/day and with a calculated fracture risk < 20% according to Q-fracture. The impact of this inaccuracy increased the proportion of persons treated according to Q-fracture20 from 58% to 59%.

The strengths of our study are: First, it considers several guidelines and three different risk assessment tools. Each guideline represents different principles for recommending patients for treatment or not. Second, we used country-specific FRAX calculations for calculating the UK-NOGG and the US-NOS treatment rates as recommended by the guidelines. Our results therefore reflect the actual discrepancy in treatment rates between countries. Third, the women were assessed with lateral spine DXA to identify asymptomatic vertebral fractures which influence treatment decisions according to the guidelines. However, we are aware that the method does not permit precise thoracic spine evaluation, and the number of vertebral fractures could have

been underestimated. Fourth, the study was applied in a clinical setting and in a population considered to be at high risk for fractures and it therefore reflects the clinicians' dilemma regarding treatment recommendations.

CONCLUSION

In summary, our study shows that the choice of guideline and fracture risk assessment tool will have a substantial impact on the proportion and selection of women recommended for treatment in a falls clinic population. Clinicians should be aware of these differences as the choice of tool and guideline will determine treatment decisions.

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