

Disparate Outcomes from Applying U.K. and U.S. Osteoporosis Treatment Guidelines

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Context: After the advent of absolute fracture risk calculators, guidelines for the management of osteoporosis released by the U.S.-based National Osteoporosis Foundation (NOF) and the U.K.-based National Osteoporosis Guidelines Group (NOGG) differ markedly in their approaches to treatment recommendations.

Objective: The aim of the study was to apply the NOF and NOGG guidelines to a cohort of older women and compare the treatment recommendations with fracture outcomes over 5 yr for each algorithm.

Design and Setting: We conducted a cohort study of women who participated in a 5-yr randomized controlled trial of calcium supplementation at a clinical research center.

Participants: We studied 1471 healthy, community-dwelling, older women with mean age of 74 yr and mean follow-up of 4.4 yr.

Main Outcome Measure: A total of 143 subjects (10%) sustained a nontraumatic osteoporotic fracture, and 21 sustained a nontraumatic hip fracture (1.4%).

Results: Applying the NOF guidelines required that 97% of participants undergo bone densitometry and 48% receive treatment. Seventy-six percent of hip fracture cases and 63% of osteoporotic fracture cases were identified for treatment. Applying the NOGG guidelines required that 13% of participants undergo bone densitometry and 21% receive treatment. Thirty-eight percent of hip fracture cases and 27% of osteoporotic fracture cases were identified for treatment.

Conclusion: Treatment recommendations and fracture outcomes in older, predominantly osteopenic women differ substantially according to the management guideline applied. The NOGG guidelines identify only a minority of fracture cases; the NOF guidelines identify the majority of fracture cases, but at the expense of greater resource utilization. Both strategies lead to recommendations for reassurance in significant numbers of women who subsequently sustain fragility fractures. (*J Clin Endocrinol Metab* 95: 1856–1860, 2010)

Recently, the World Health Organization-sponsored absolute fracture risk calculator, FRAX, was released. This tool estimates the 10-yr risks of major osteoporotic fracture and hip fracture by integrating 10 clinical risk factors [age, gender, body mass index (BMI), history of personal fracture, history of parental hip fracture, smoking status, glucocorticoid use, alcohol intake, and the presence of rheumatoid arthritis or secondary osteoporosis] and bone mineral density

(BMD) (1). FRAX can be used without BMD if BMD is not known (1).

Fracture risk prediction tools are designed to facilitate treatment of people at high absolute risk of fracture and reassurance of those at low risk. The introduction of absolute fracture risk calculators prompted the development of guidelines in the United States by the National Osteoporosis Foundation (NOF) (2) and in the United Kingdom by the National Osteoporosis Guidelines Group (NOGG)

NOGG Guidelines	NOF Guidelines
<p>1. Treat if previous fragility fracture.</p> <p>2. If clinical risk factors present, estimate 10 yr probability of major osteoporotic fracture using FRAX without BMD.</p> <p>If probability > intervention threshold: treat. If probability < assessment threshold: reassure. If probability falls between thresholds: measure BMD.</p> <p>3. If BMD measurement, re-estimate 10 yr probability of major osteoporotic fracture using FRAX with BMD.</p> <p>If probability > intervention threshold: treat. If probability < intervention threshold: reassure.</p>	<p>1. Treat if previous hip or vertebral fracture.</p> <p>2. For women age 65 and older, measure BMD.</p> <p>3. Treat if osteoporosis (BMD T-score ≤ -2.5 at proximal femur or lumbar spine).</p> <p>4. Treat if osteopenia (BMD T-score -1 to -2.5 at proximal femur or lumbar spine)</p> <p>AND</p> <p>FRAX-estimated 10 yr probability of hip fracture $\geq 3\%$ or major osteoporotic fracture $\geq 20\%$.</p>

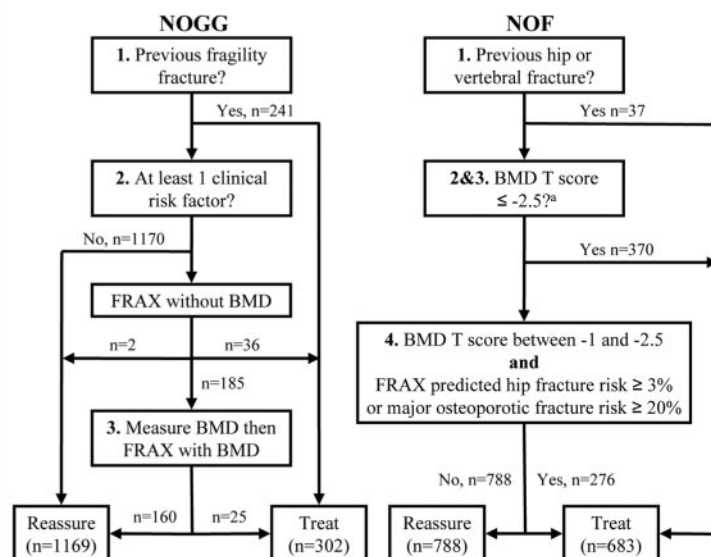


FIG. 1. Summaries of the NOGG and NOF guidelines for management of osteoporosis (left), with their application to a cohort of 1471 healthy older women (right). a, Nineteen women in the cohort were younger than 65 yr at baseline. The NOF guidelines recommend BMD measurement in women younger than 65 yr if there are concerns based on the risk factor profile. For the purposes of this analysis, we assumed that all these 19 women had a measurement of BMD for this reason.

(3, 4) that incorporate FRAX-derived risk calculations. However, the approaches taken to recommendations for intervention by these guidelines differ markedly, as summarized in Fig. 1. The NOF intervention thresholds are based upon economic cost-effectiveness analyses (5, 6), whereas the NOGG guidelines recommend intervention if the probability of fracture exceeds that of a person of the same age who has suffered a previous osteoporotic fracture (3). Thus, the NOGG intervention and assessment thresholds vary by age and gender, such that reassurance is recommended for older individuals at high risk of fracture, whereas intervention is recommended for younger individuals at lower risk of fracture.

Potentially, the differing approaches between guidelines might lead to different treatment recommendations and fracture outcomes. Two illustrative clinical cases are presented here. Patient 1 is female, aged 80 yr, in good health, with BMI of 23.8 kg/m², no personal or parental history of fracture, and a femoral neck BMD T score of -3. Her estimated 10-yr risk of major osteoporotic fracture using FRAX with BMD is 21% and of hip fracture is 9%. Applying the NOGG guidelines leads to a recommendation to reassure, whereas the NOF guidelines recommend treatment. Patient 2 is female, aged 65 yr, in good health, and also has a BMI of 23.8 kg/m², no personal or parental history of fracture, and a femoral neck BMD T score of -3. Her estimated 10-yr risk of major osteoporotic fracture is 16% and of hip fracture is 5%. Both the NOGG and NOF guidelines recommend treatment.

In the current work, we compared the recommended management, based on the NOF and NOGG guidelines, to fracture outcomes in a cohort of 1471 older postmeno-

pausal women who took part in a study of calcium supplementation (7).

Subjects and Methods

As previously described (7), participants were free from major medical conditions, with life expectancy greater than 5 yr, were not taking medications that might impact upon calcium metabolism, and had normal BMD for their age (BMD Z score above -2). At baseline, the mean (SD) age was 74 yr (4.2), BMI was 26.5 (4.3) kg/m², and femoral neck BMD T score was -1.3 (1.0). Twenty-seven percent had osteoporosis (T score ≤ -2.5 at hip or spine), 53% had osteopenia (T score between -1.0 and -2.5 at hip or spine), 29.6% had experienced a fracture since age 50 yr, 12% had a history of parental hip fracture, 3% smoked currently, 4% used at least 3 U/d of alcohol, 0.2% had rheumatoid arthritis, and none had secondary osteoporosis or used systemic glucocorticoids.

Over a mean duration of follow-up of 4.4 yr, 143 (10%) sustained a low-trauma osteoporotic fracture, and 21 sustained a low-trauma hip fracture (1.4%) (7). A low-trauma fracture was defined as a fall from standing height or less or equivalent injury, and an osteoporotic fracture was defined as any fracture except those of the head, hands, feet, and ankles (7). Nonvertebral fractures were verified radiologically, and vertebral fractures by semiquantitative morphometry. Fracture probabilities at baseline were calculated with the FRAX-UK tool. In women who sustained an incident fracture during follow-up, the mean (SD) estimated 10-yr risk of osteoporotic fracture was 15.8% (6.6) and of hip fracture was 5.3% (6.1). In women who did not sustain an incident fracture, the respective estimated risks were 13.0% (6.6) and 3.6% (4.6).

Results

Figure 1 shows the application of the guidelines to this cohort. Applying the NOF guidelines would have led to 97%

TABLE 1. Recommendations for management of skeletal health in older postmenopausal women, according to NOF and NOGG guidelines

	Entire cohort	Hip fracture	Osteoporotic fracture
n	1471	21	143
NOF guidelines			
Treated participants			
Hip/spine fracture	37	0	8
BMD T score ≤ -2.5	370	7	49
Osteopenia/fracture risk > intervention threshold ^a	276	9	33
Total treated (% of cohort)	683 (46)		
Fracture cases treated (%)		16 (76)	90 (63)
Reassured participants (% of cohort)	788 (54)		
Fracture cases reassured (%)		5 (24)	53 (37)
NOGG guidelines			
Treated participants			
Fragility fracture	241	8	36
FRAX without BMD > intervention threshold ^b	36	0	3
FRAX with BMD > intervention threshold ^b	25	0	0
Total treated (% of cohort)	302 (21)		
Fracture cases treated (%)		8 (38)	39 (27)
Reassured participants			
No clinical risk factors	1007	12	81
FRAX without BMD < NOGG assessment threshold ^b	2	0	0
FRAX with BMD < NOGG intervention threshold ^b	160	1	23
Total reassured (% of cohort)	1169 (79)		
Fracture cases reassured (%)		13 (62)	104 (73)

^a The NOF intervention threshold is FRAX-predicted 10-yr risk of hip fracture $\geq 3\%$ or major osteoporotic fracture $\geq 20\%$.

^b The NOGG intervention and assessment thresholds vary by age and gender (see text).

of women having a measurement of BMD and 46% being treated. Applying the NOGG guidelines (4) would have led to 13% of the cohort having a measurement of BMD and 21% being treated. The fracture outcomes that result from application of the guidelines are shown in Table 1. Applying the NOF guidelines identified 76% of women with hip fractures and 63% with osteoporotic fractures for treatment. Applying the NOGG guidelines identified only 38% of women with hip fractures and 27% with osteoporotic fractures for treatment. Applying the NOGG guidelines in the setting of primary fracture prevention, achieved by excluding the 241 women with previous fragility fractures, identified none of the women with hip fractures and only 3% of those with osteoporotic fractures for treatment.

In the 143 women who sustained an osteoporotic fracture, 34 were identified for treatment by both guidelines, five by NOGG only, and 56 by NOF only ($\kappa = 0.24$). In the 1328 women who did not sustain a fracture, 666 were identified for reassurance by both guidelines, 399 by NOG only, and 59 by NOF only ($\kappa = 0.24$). Under both NOF and NOGG guidelines, 87% of women identified for treatment using the respective algorithms did not sustain an osteoporotic fracture during follow-up.

Discussion

The two sets of guidelines produce markedly different recommendations and outcomes when applied to a cohort of

older postmenopausal women. The NOF approach required that almost all women (97%) undergo BMD measurement, recommended that almost one half of the women receive treatment, but recommended treatment for the majority of women who sustained hip or osteoporotic fractures during almost 5 yr of follow-up. The NOGG approach required few women (~13%) to have a BMD measurement, recommended that only one in five women receive treatment, but recommended treatment for only a minority of women who sustained hip or osteoporotic fractures. Both strategies led to recommendations for reassurance in substantial numbers of women who subsequently sustained fragility fractures. Given that the greatest numbers of fractures occur in the nonosteoporotic population (8, 9), of which our cohort is representative, these findings underline the limitations of the currently available tools for identifying individuals at risk of fracture, and therefore of reducing the fracture burden in the community.

The NOGG guidelines performed poorly in identifying women at risk of fracture in our cohort, especially in the setting of primary prevention, where they identified almost none of the women with subsequent hip or osteoporotic fracture. This finding calls into question the decision to base intervention thresholds on fracture risk in age-matched individuals who have already sustained a fragility fracture, in whom risk of subsequent fracture is about twice that of individuals without previous fracture

(10). Delaying intervention until an individual has sustained a fracture or has an estimated risk of fracture that exceeds that of an age-matched individual with a prevalent fracture seems highly unlikely to reduce the fracture burden in the general population. In the elderly population, the consequence of applying the NOGG guidelines is that fracture risk must be very high before treatment is recommended. It is not clear why such a high threshold has been chosen when treatment at lower thresholds is cost-effective (3, 6).

Applying the NOF guidelines to our cohort recommended treatment of almost half of the participants, and about two thirds of women who subsequently experienced a fracture. The NOF approach is based upon the majority of older women having a measurement of BMD and thus requires easy access to bone densitometry. Consequently, applying the NOF guidelines is more costly than applying the NOGG guidelines, but more likely to favorably impact on the community burden of fractures. The NOF guidelines were recently applied to the Study of Osteoporotic Fractures (SOF) cohort, resulting in the recommendation that 72% of women at least 65 yr old and 93% of women at least 75 yr old be treated (11). The differences between our findings and those of the SOF researchers are likely explained by the differences between the FRAX-US and FRAX-UK tools; the U.S. tool, which was used in the SOF analysis, generates higher risk estimates than the U.K. tool, because U.S. individuals are at higher risk of hip fracture than U.K. individuals (1). The recent update of the FRAX-US tool, based on updated fracture incidence data (12), produces lower estimated fracture probabilities than previous versions, particularly in younger persons (13). This change may lead to fewer people being recommended for treatment.

This analysis has limitations. We applied the FRAX-UK tool to a population of New Zealand women because the NOGG guidelines were developed with this tool and the epidemiology of hip fracture in the New Zealand population is similar to that of the U.K. population (1, 14). However, differences in mortality rates and the epidemiology of other osteoporotic fractures between the United Kingdom and New Zealand may affect the performance of the FRAX-UK tool in this cohort. The FRAX-NZ tool was released very recently. In our cohort, the estimated risk of hip fracture was similar using FRAX-UK and FRAX-NZ, but the estimated risk of osteoporotic fracture was lower using FRAX-NZ. When we repeated the analyses using the FRAX-NZ tool, the results obtained for both algorithms were very similar to those obtained using FRAX-UK. Using the FRAX-NZ tool, the NOF algorithm identified for treatment 45% of the cohort, 76% who sustained a hip fracture, and 61% who sustained an osteoporotic frac-

ture, whereas the NOGG algorithm identified for treatment 18% of the cohort, 38% who sustained a hip fracture, and 26% who sustained an osteoporotic fracture. Participants in our study were community-dwelling women who volunteered to take part in a clinical study and were at relatively low fracture risk (1.4% had hip fracture and 10% osteoporotic fracture over 4.4 yr of follow-up). Thus, our findings may not be applicable to the general population or to women at high risk of fracture. However, because most fragility fractures occur in women without osteoporosis (8, 9), the present findings are likely relevant to the aim of reducing fracture burden in the population. Finally, 23 women were not eligible to participate in our study because of low bone density (Z score < -2). We do not believe this would have affected our analyses.

In summary, application of the NOF and NOGG guidelines led to markedly different recommendations for management of skeletal health in a cohort of elderly women. The NOF guidelines identified the majority of women with fracture for treatment but required almost all women to have a measurement of BMD. In contrast, the NOGG guidelines required few women to have a measurement of BMD but recommended treatment for only a minority of women who subsequently experienced a fracture. The NOGG guidelines recommend treatment of younger people at low absolute risk, whereas denying older people with high absolute risk the benefits of effective therapies.

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