

Bone Mineral Density Thresholds for Pharmacological Intervention to Prevent Fractures

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Background: Treatment intervention thresholds for prevention of osteoporotic fractures can be derived from reports from the World Health Organization (diagnostic criteria) and National Osteoporosis Foundation (treatment criteria). It is not known how well these thresholds work to identify women who will fracture and are therefore candidates for treatment interventions. We used data from the National Osteoporosis Risk Assessment (NORA) to examine the effect of different treatment thresholds on fracture incidence and numbers of women with fractures within the year following bone mineral density measurement.

Methods: The study comprised 149 524 white postmenopausal women aged 50 to 104 years (mean age, 64.5 years). At baseline, bone mineral density was assessed by peripheral bone densitometry at the heel, finger, or forearm. New fractures during the next 12 months were self-reported.

Results: New fractures were reported by 2259 women, including 393 hip fractures; only 6.4% had

baseline T scores of -2.5 or less (World Health Organization definition for osteoporosis). Although fracture rates were highest in these women, they experienced only 18% of the osteoporotic fractures and 26% of the hip fractures. By National Osteoporosis Foundation treatment guidelines, 22.6% of the women had T scores of 2.0 or less, or -1.5 or less with 1 or more clinical risk factors. Fracture rates were lower, but 45% of osteoporotic fractures and 53% of hip fractures occurred in these women.

Conclusions: Using peripheral measurement devices, 82% of postmenopausal women with fractures had T scores better than -2.5 . A strategy to reduce overall fracture incidence will likely require lifestyle changes and a targeted effort to identify and develop treatment protocols for women with less severe low bone mass who are nonetheless at increased risk for future fractures.

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OSTEOPOROTIC FRACTURES cause substantial clinical and economic burdens for society.^{1,2} More than 50% of women with hip fractures never completely return to their prefracture function; 25% are admitted to nursing homes and 20% die within 1 year after fracture.³ Vertebral fractures are also associated with increased morbidity and mortality.^{1,4} The number of osteoporotic fractures and cost for their treatment are expected to continue to rise because of the aging of the population and secular increases in the incidence of fractures.^{5,6}

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The single most important predictor of osteoporotic fractures in postmenopausal women without a previous fracture is bone mineral density (BMD). There is a strong, continuous relationship between BMD and osteoporotic fractures,^{7,8}

with a 1.5- to 2.6-fold increase in fracture risk for every standard deviation decrease in BMD; differences depend on the site where BMD is measured and the location of the fracture.⁹⁻¹¹

Although it is well established that the risk of fracture is highest in women with the BMD levels usually used for the diagnosis of osteoporosis, women with higher BMD levels, such as those used for the diagnosis of osteopenia, are also at increased risk for fracture. In a previous analysis of 200 160 postmenopausal women in the National Osteoporosis Risk Assessment (NORA) study, women with osteoporosis (BMD levels at peripheral sites, ≤ -2.5) had 2.74 times higher 1-year risk of fracture, and women with osteopenia (BMD, -1 to -2.49) had 1.73 times higher risk of fracture, compared with women with normal BMD, independent of demographic and clinical factors.¹²

The BMD level appropriate for intervention with pharmacological treatment in postmenopausal women at increased

fracture risk is a critical issue when assessing the potential for reducing the overall fracture rate in the population. Several medications have been shown to prevent bone loss or reduce the risk of fracture in postmenopausal women with low bone mass or osteoporosis.¹³⁻²⁰ However, there is no agreement on the ideal BMD measurement at which to initiate pharmacological therapy. The lack of consensus on treatment intervention thresholds reflects the trade-offs between the known and potential benefits and risks of these treatments, the willingness of patients to initiate and continue therapy, and the available resources to pay for medications.

Treatment threshold levels available for consideration in clinical practice emerge principally from 2 sources. The first is derived from reports developed by the World Health Organization (WHO), and the second is from the National Osteoporosis Foundation (NOF). The WHO provided an operational definition of osteopenia and osteoporosis in 1994.²¹ A postmenopausal woman with a BMD 2.5 SDs or more below the young adult mean (ie, T score, ≤ -2.5) at any site (spine, hip, or mid radius) is considered to have osteoporosis, and a woman with a BMD between -2.49 and -1.0 is considered to have osteopenia. Although the WHO cutpoints were designed as diagnostic thresholds and were not developed to provide criteria for selecting patients in whom to initiate therapy, many clinicians and reimbursement sources use the WHO level for osteoporosis (T score, ≤ -2.5) as the treatment intervention threshold.

The NOF developed treatment thresholds by combining BMD measured at the hip with clinical risk factors for fracture (eg, prior fracture as an adult, family history of fracture, body weight <127 pounds, cigarette smoking).^{2,22} According to NOF recommendations, women with a T score of -2.0 or less or -1.5 or less with at least 1 risk factor should be considered for treatment. The rationale for these particular threshold levels was evidence-based and influenced by cost-effectiveness considerations.²

It is not known how well the WHO- and NOF-derived treatment cutpoints identify women who will fracture in the near future and are therefore candidates for therapy to reduce fracture risk. In this article, we use information from NORA in an initial attempt to address this question. We examine fracture incidence and numbers of women with fractures within the year following a peripheral BMD measurement, comparing BMD thresholds derived from WHO and from NOF.

METHODS

NORA is a longitudinal, observational study. The cohort is composed of 200 160 postmenopausal women (defined as having no menstrual period, bleeding, or spotting during the 6 months before enrollment), residing in 49 states who were at least 50 years old who did not have a previous diagnosis of osteoporosis or a BMD measurement within the 12 months preceding enrollment. Participants were recruited from the practices of 4236 primary care physicians in 34 states and the District of Columbia between September 1997 and March 1999. Physicians were identified based on having large numbers of postmenopausal women in their practices and not having in-office bone densitometry equipment. Approximately 17% of invited physicians

agreed to consider participating, and 75% to 80% of this group participated. With scientific support from NORA personnel, each physician office generated randomly selected names of up to 300 eligible women, of whom between 40 and 100 agreed to enter the study. There were no general health or preexisting medical condition exclusions, although women had to be ambulatory and able to visit their physicians' offices. Women treated with a bisphosphonate, calcitonin, or raloxifene hydrochloride were ineligible for participation, but current estrogen use was not an exclusion criterion. The study protocol and consent documents were approved by the national Essex Institutional Review Board, Lebanon, NJ. A detailed description of the study design and initial results of BMD and fracture outcomes have been reported previously.^{12,23,24}

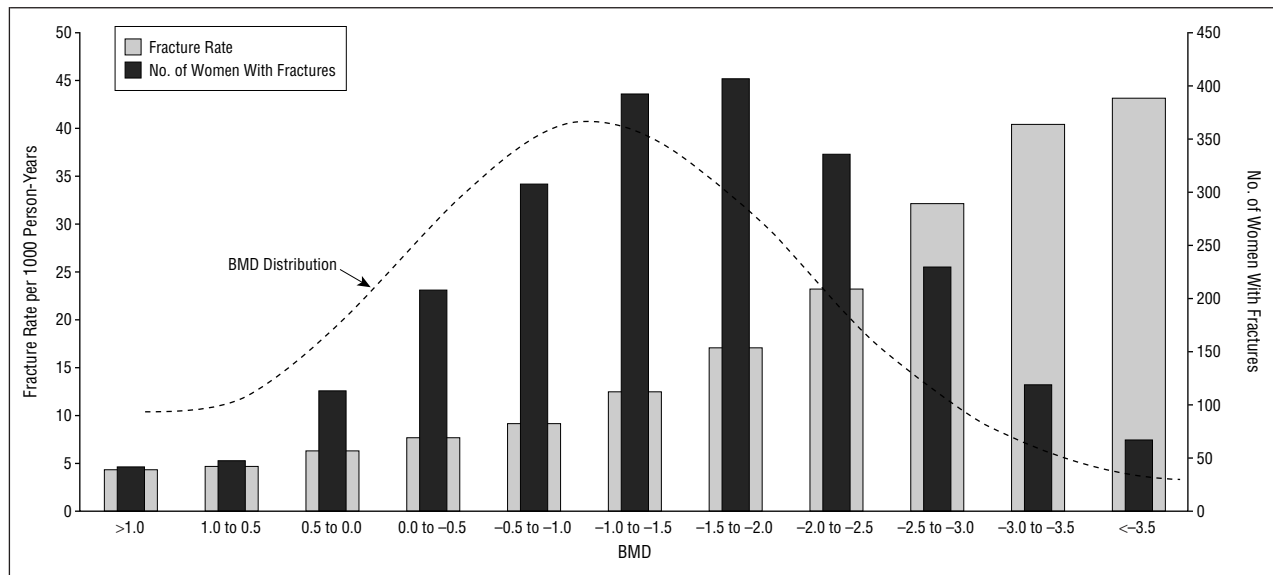
At baseline, each woman completed questionnaires that included demographic data and risk factors for osteoporosis, including personal and family history of fracture, lifestyle behaviors, and medication use. The questionnaires had been pilot tested before use in NORA to assure comprehensibility of the questions. Each subject had one of the following BMD measurements at a peripheral site conducted in her primary care physician's office: heel, using single x-ray absorptiometry (Osteoanalyzer; Norland Medical Systems Inc, White Plains, NY) or ultrasonography (Sahara; Hologic Inc, Bedford, Mass); forearm, using peripheral dual-energy x-ray absorptiometry (DXA) (pDEXA; Norland Medical Systems Inc); or finger, using peripheral DXA (AccuDEXA; Schick Technologies Inc, Long Island City, NY). Instruments were calibrated daily and in each new location and were standardized with device-specific phantoms. Testing was performed by NORA field personnel who were licensed technicians who had completed training by the equipment manufacturers and by the International Society for Clinical Densitometry. Quality assurance was maintained by staff at the quality assurance center at Synarc Inc, Portland, Ore, who monitored scans from all technicians according to a rigorous formal protocol.²⁵ T scores were calculated from the young adult normal white reference databases as reported by the equipment manufacturers. Our group has previously reported that each of these peripheral BMD measurements was equally predictive of increased risk of fracture during the year after the baseline evaluation.^{12,23}

Approximately 12 months after enrollment, each participant received a follow-up questionnaire that included the following questions about new fractures:

Since you joined NORA, have you broken any bone? Please tell us which bone(s) you broke and the month and year you broke the bone. If you were hospitalized for broken bone(s), please tell us about how many days you stayed overnight in the hospital. (a) Hip; (b) Spine; (c) Rib; (d) Wrist; (e) Forearm; (f) Other Bone.

Reported new fractures were compared with fractures that had been described at baseline. If the sites were identical, the fracture was considered to be preexisting and was not included in the present analysis. If a participant reported 4 or more new fractures, these data were also excluded from analysis because these fractures were likely to be due to major trauma. For these analyses, osteoporotic fractures included self-reported fractures at the wrist or forearm, rib, spine, or hip. Patients who reported hip fractures were contacted by telephone for confirmation. This analysis was limited to white women (89.7% of the NORA cohort) to minimize any effect of ethnic variation. Among these 179 471 white women, 149 524 (83%) completed the follow-up survey and reported fracture status.

Proportions of women, fracture incidence rates, and proportions of fractures were calculated for the following BMD T-score thresholds: ≤ -2.5 ; ≤ -2.0 ; ≤ -2.0 or ≤ -1.5 with at least 1 additional risk factor such as prior fracture as an adult, family history of fracture, low body weight (<127 lbs [57 kg]), and ciga-



Bone mineral density (BMD), osteoporotic fracture rate, and number of women with fractures.

rette smoking (NOF treatment criteria); and ≤ -1.0 . Proportions of women, fracture incidence rates, and proportions of fractures were also computed and displayed graphically for BMD T scores of >1.0 , <-3.5 , and every 0.5 increment between 1.0 and -3.5 . Fracture rates and proportions of fractures were computed for all osteoporotic fractures (including hip fractures) and specifically for hip fractures. Fracture rates were calculated per person, not total number of fractures (ie, if a participant reported 2 new fractures, this was counted as 1 fracture event), and weighted for duration of follow-up. All analyses were conducted using SAS version 6.12 (SAS Institute, Cary, NC).

RESULTS

The mean \pm SD age of these women was 64.5 ± 9.3 years (range, 50-104 years). Bone mineral density T scores were obtained using single x-ray absorptiometry (heel) in 79 185 women (53%), peripheral DXA (distal forearm) in 51 941 women (35%), peripheral DXA (finger) in 10 836 women (7%), and ultrasonography (heel) in 7 562 women (5%). New osteoporotic fractures ($n=2340$) were reported by 2259 women. Of these, 393 reported a hip fracture, representing 17.4% of all women who reported a fracture.

The **Figure** illustrates graphically the strong continuous relationship between lower BMD and higher fracture rate, expressed as the number of women who fractured per 1000 person-years of follow-up. The Figure also shows the distribution of BMD T scores within the NORA population, which approximates a normal distribution. The absolute number of women who sustained an incident fracture within a given T-score range is a function of the fracture rate multiplied by the population distribution within that T-score range. The fracture rates were highest in women with the lowest T scores, as expected. Nevertheless, 82% of the 2259 women who reported fractures at 1 year had peripheral T scores greater than -2.5 , and 67% had T scores greater than -2.0 .

Estimates of the fracture rate and proportion of all osteoporotic fractures and hip fractures occurring at various levels of BMD thresholds are shown in the **Table**. Only 6.4% of participants had T scores of -2.5 or less.

Although fracture rates were 35.7 per 1000 person-years for osteoporotic fracture and 8.8 per 1000 person-years for hip fracture in these women, they contributed only 18% of the osteoporotic fractures and 26% of the hip fractures. Twenty-three percent of women met NOF treatment guidelines (ie, T score, ≤ -2.0 , or ≤ -1.5 with ≥ 1 risk factors); fracture rates were somewhat lower in this group (24.7 per 1000 person-years for osteoporotic fracture and 5.1 per 1000 person-years for hip fracture). However, 45% of the osteoporotic fractures and 53% of hip fractures occurred in these women who met the NOF treatment guidelines. If a T-score cutpoint of -1.0 or less was applied, 70% of women with osteoporotic fractures and 77% of those with hip fractures were identified; however, fracture rates for osteoporotic fracture and hip fracture were even lower: 17.4 per 1000 person-years and 3.6 per 1000 person-years, respectively.

COMMENT

In this large cohort recruited from primary care practices in the United States, 82% of women who sustained osteoporotic fractures of the wrist or forearm, hip, rib, or spine within 1 year after peripheral BMD testing had T scores greater than -2.5 . Only 18% of the NORA women who had fractures would have been treatment candidates if the intervention threshold had been set at -2.5 or less. This would result in no intervention in 82% of the women who actually experienced a new fracture during the first year after BMD was measured. Therefore, treatment of only women with T scores of -2.5 or less would have a limited effect on reducing the number of women who sustain osteoporotic fractures, including hip fractures. Recent results from the Study of Osteoporotic Fractures showed a similar observation in older women (lowest age, 65 years), in which 54% of the women with hip fractures and 74% of the women with any nonvertebral fracture had a total hip T score greater than -2.5 .²⁶

The NOF guidelines recommend pharmacological intervention in women with T scores of -2.0 or less, or

Fracture Rates, Proportions of Population, and Percentages of Fractures, According to T-Score Groups

T Score	Proportion of Population, %	Osteoporotic Fracture Rate*	Osteoporotic Fracture, %†	Hip Fracture Rate*	Hip Fracture, %
≤-2.5	6.4	35.7	18	8.8	26
≤-2.0	14.5	28.6	33	6.5	44
National Osteoporosis Foundation Guidelines‡	22.6	24.7	45	5.1	53
≤-1.0	45.3	17.4	70	3.6	77

*Per 1000 person-years.

†Self-reported fractures of wrist or forearm, hip, spine, or rib.

‡T score ≤-2.0 or ≤-1.5 with ≥1 risk factors.

-1.5 or less with prior fracture as an adult, family history of fracture, low body weight (<127 pounds), or cigarette smoking. Cutpoints in the present study based on these recommendations identified 45% of women with osteoporotic fractures and 53% of those with hip fractures. This threshold increased the number of candidates for medical intervention to 22.6% of the NORA population, capturing nearly half of those who fractured with intervention in less than a quarter of the population. If the treatment threshold is shifted further to below -1.0, 70% of the women who experienced osteoporotic fractures and 77% of those with hip fractures would have been identified as treatment candidates, but this would require treating nearly half of the women, substantially increasing cost.

The observation that more than half (52%) of the NORA women experiencing an incident osteoporotic fracture within 1 year had a BMD T score of -1.0 to -2.5 underscores the unmet need to identify those women who are most likely to fracture and might benefit from targeted pharmacological intervention. Although the fracture rate per 1000 person-years is lower than that for women with T scores below -2.5, most of the fractures occur in this middle area of the BMD distribution (Figure), because most the women are in this T-score range. It will be necessary to determine methods for risk stratification, based on combining BMD data with those risk factors that best serve to predict the risk of future fracture, to allow more efficient application of therapeutic resources. Other risk factors have been reported to be predictive of fractures independent of BMD, including age,^{11,27} prior fracture,^{28,29} body size,^{8,29} and factors related to falls.³⁰

Fracture prevention will require not only better targeting of high-risk women with less severe BMD T-score levels but also evidence that treatments lower fracture risk in those women. Most clinical trials with fracture outcomes have been conducted in women with T scores of -2.0 or less, measured at the spine or hip, or in women with prevalent vertebral fractures.^{13,14} Little data exist to show that available agents are effective at reducing the risk of fracture in women with BMD T scores greater than -2.0, because such women have not been the focus of most clinical trials with first-fracture outcomes. In prevention trials, antiresorptive agents maintain or increase BMD in women with low bone mass, contrasted with the loss of bone density observed with placebo.³¹⁻³³ Preservation of bone mass with attendant preservation of bone architecture over time would be expected to afford protection against fracture. Recent findings from the Women's Health Initiative trial¹⁷

showed a reduction of clinical fractures and hip fractures with hormone therapy in women unselected for osteoporosis by BMD or prior fracture criteria, which suggests that treatment of women with osteopenia reduces fracture risk. With large enough studies or long enough studies, other antiresorptives would be expected to provide similar benefit to women with osteopenia.

Despite the advantages of a large population of women ranging from age 50 to 104 years from throughout the United States, this study has some limitations. First, NORA included only women with personal physicians and excluded women who had a prior diagnosis of osteoporosis or were receiving specific treatment for osteoporosis. Therefore, NORA women may be healthier, with lower fracture rates and better BMD, than the US population. Second, peripheral devices were used to assess BMD in NORA, and comparability of these peripheral BMD test to the gold standard measurements of central hip and spine BMD is still under study. However, the WHO diagnostic criteria were established based on central (hip and spine) and peripheral (forearm) BMD measurement devices.²¹ T scores obtained by peripheral devices may not always be as low as T scores determined from central DXA devices, resulting in prevalences of WHO-defined osteoporosis using peripheral device-specific databases of 3% to 14%, compared with prevalences based on hip measurements for white women of 16% to 20%.^{34,35} The discrepancies between T-score calculations among various BMD devices are well recognized and exist among different central DXA skeletal sites and devices as well.³⁶⁻⁴⁰ As previously reported, prediction of fracture risk in NORA, including risk of hip fracture, with peripheral BMD measurements was similar to that reported in other studies^{12,23} with hip BMD measurements. Third, fractures in NORA were self-reported, without radiological confirmation, so fractures may have been overestimated (eg, sprains or arthritis reported as fractures) or underestimated (unrecognized or subclinical fractures). It has previously been shown, however, that self-report of fractures is generally reliable.⁴¹⁻⁴³ Because most spine fractures are asymptomatic or at least unrecognized, NORA cannot address the value of risk factors or peripheral BMD to predict nonclinical spine fractures. Over the long term, clinical and subclinical vertebral fractures are associated with increased morbidity and mortality.^{4,44} Finally, the data in this analysis are derived from information from white postmenopausal women, and generalization to other ethnic groups should be made with caution, if at all, until analyses from those groups become available.

We conclude that substantial reductions in the population burden of osteoporotic fractures experienced by postmenopausal women cannot be accomplished simply by aggressively treating women with T scores of -2.5 or less. There will have to be a targeted effort toward better identification and treatment of women with moderate levels of low bone mass, who are nonetheless at an increased risk for future fracture. We believe that non-pharmacological approaches, including weight-bearing exercise, strength training, and a healthy diet, including adequate calcium, should continue to be encouraged. The NOF treatment intervention guidelines, as defined in the present study, provide a reasonable strategy for targeting and treating women at high risk for fractures. Future research is required to develop strategies to risk-stratify women with osteopenia (T scores, -2.5 to -1.0) who are at substantial risk for fracture and who constitute most of those who sustain fractures.

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