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ORIGINAL ARTICLE

Use of pharmacologic agents for the primary prevention of osteoporosis among older women with low bone mass

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Abstract
Summary We examined the use of pharmacologic agents for the primary prevention of osteoporosis among older women with osteopenia. We found that these individuals were not managed in concordance with the National Osteoporosis Foundation (NOF) guidelines and that self-perceived osteoporosis risk and lower bone density were strongly associated with receipt of treatment.
Introduction Although osteoporosis medications are used for the primary prevention of osteoporosis among persons with low bone mass (osteopenia), their use may be discordant with clinical practice guidelines.
Methods We studied women 55 years and older participating in the Global Longitudinal Study of Osteoporosis in Women (GLOW). Eligible participants had a dual energy x-ray absorptiometry (DXA) test performed at the University of Alabama at Birmingham hospital and had an osteopenia diagnosis based on their DXA test results.

Participants' demographics, fracture risk factors, and exposure to osteoporosis medications were determined from the GLOW survey. We examined the proportions of women managed in concordance with the National Osteoporosis Foundation 2008 guidelines, and we assessed factors independently associated with osteoporosis treatment decisions. Women with a prior spine or hip fracture were excluded.

Results Among 597 eligible women from GLOW, the mean age ± standard deviation (SD) was 70±7 years. Among all subjects, 309 (52 %) were treated in concordance with the NOF 2008 guidelines. Greater self-perceived osteoporosis risk and lower bone mineral density were significantly and consistently associated with receipt of osteoporosis treatment, both for those considered appropriate and for those considered inappropriate for treatment based on the NOF guidelines.
Conclusions We found significant discordance between NOF 2008 guidelines and pharmacologic management of women with osteopenia. A person's self-perceived osteoporosis risk and bone mineral density were most strongly associated with receipt of osteoporosis medication use among women with low bone mass.

Keywords Clinical guidelines · Low bone mass · Osteoporosis medication · Self-perceived osteoporosis risk

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Introduction

The 2008 US National Osteoporosis Foundation (NOF) guidelines recommend the use of pharmacologic treatment in individuals with low bone mineral density (BMD) (hereafter referred to as osteopenia) if coupled with a 10-year predicted hip fracture risk of 3 % or greater or a predicted major osteoporotic fracture risk of 20 % or greater. The risk prediction is based on BMD or body mass index with additional clinical risk factors present in the FRAX® calculator [1].

Osteopenia affects half of women 50 years or older; almost three times that of women with osteoporosis [2]. Therefore, although women with osteoporosis have a higher fracture risk, at a population level, an estimated 82 % of fractures occurred in women whose peripheral T-score was greater than −2.5 [3]. Further, in two separate analyses, women with osteopenia accounted for 50 % of all older women meeting the NOF 2008 criteria for treatment [4, 5].

Despite national recommendations that many women with osteopenia may be candidates for pharmacologic prevention of osteoporosis, data on the utilization of osteoporosis medications in this population are limited. In a cohort of women 55 years of age with osteopenia by BMD and without a history of hip or spine fractures after age 45 years, we conducted a cross sectional study to determine the extent to which use of pharmacologic agent for primary prevention of osteoporosis was concordant with the NOF clinical guidelines. In addition, we assessed factors associated with the observed discordance between osteoporosis treatment received and the care recommended by the NOF guidelines. The two types of discordance considered were treatment of women for whom treatment was not recommended, and absence of treatment of women for whom treatment was recommended, according to the NOF 2008 clinical guidelines.

Methods

Study population

The study population consisted of participants in the Global Longitudinal Study of Osteoporosis in Women (GLOW) recruited from the study site of Birmingham, AL, USA. Primary care physician practices were recruited through primary care networks at the University of Alabama at Birmingham (UAB). These practices provided lists of women 55 years of age or older who had been seen in their practice at least once in the prior 2 years. Stratified sampling at each site was performed to achieve a ratio of 1:2 for women 55–64 years of age to women 65 years or older. Participants were contacted via mailed questionnaires and telephone follow-up of those who did not respond by mail. Baseline surveys were mailed between 2006 and 2008, and the subjects were contacted annually thereafter for four additional years. Detailed descriptions of the GLOW study have been previously published [6]. A total of 5,061 subjects were recruited at the Birmingham, Alabama site [6]. Additional eligibility criteria for the current study were at least one dual energy x-ray absorptiometry (DXA) test performed at the UAB hospital within 2 years prior to assessment of osteoporosis medication use and fracture risk factors from a GLOW survey questionnaire (baseline, first, or second follow-up) and an osteopenia diagnosis based on their DXA test results. An osteopenia diagnosis was defined as having the lowest T-score at the femoral neck, total hip, spine, or one-third radius (if measured) that was between −1.0 and −2.5. If a subject had more than one DXA test at the UAB hospital, only the first DXA test was included. Subjects who had a self-reported history of hip or spine fracture were excluded since a history of one of these fractures would potentially qualify a subject for treatment and not for primary prevention. The study was approved by the UAB institutional review board.

Exposure to osteoporosis medications and covariates

Current and past exposures to osteoporosis medications were queried at baseline and all succeeding GLOW surveys. On the GLOW baseline survey, the study participants were provided a list of medications approved for the treatment and prevention of osteoporosis and were asked if they were currently using any medication or had used it in the past but discontinued. At each GLOW follow-up mail survey, participants were asked again about current medications and any changes that had occurred in their treatment regimen in the previous 12 months. As a result, current and past use of osteoporosis medications were collected prospectively and updated annually. Medications queried were risedronate, ibandronate, alendronate, zoledronic acid, teriparatide, calcitonin, and raloxifene.

Subject demographic characteristics ascertained at the GLOW baseline survey included age, height, race, and educational attainment. Similar to the use of osteoporosis medications, most fracture risk factors were assessed at baseline and all subsequent follow-up surveys, including personal and parental history of fracture, number of falls in the past 12 months, smoking, and alcohol use. Subjects were also asked about their self-perceived fracture risk, self-perceived osteoporosis risk, and how concerned they were about osteoporosis. Weight was self-reported at baseline and at the second follow-up survey. FRAX risk scores for 10-year fracture risk were calculated at baseline. Due to the inability to accurately capture data on chronic glucocorticoid use, only current glucocorticoid use was ascertained.

Statistical analysis

Since treatment guidelines were updated (in 2008) during the GLOW survey time period, we assessed the proportions of women managed in concordance with the NOF 2008 guidelines. Concordance was defined as current or past receipt of treatment among those recommended for treatment and no receipt of treatment among those not recommended for treatment. Univariate odds ratios (ORs) for the receipt of treatment and corresponding 95 % confidence intervals (CIs) were calculated and Kappa statistics were calculated.

Among those recommended for treatment, we examined factors, including subjects' demographic characteristics, their fracture risk factors, and their self-perceived osteoporosis risk, that were associated with not receiving treatment. Among subjects not recommended for treatment, we examined factors associated with receipt of treatment. Univariable and multivariable logistic regressions (reduced model produced using backward elimination with a 0.05 p value threshold for variable

retention) were used to identify these factors in both sets of analyses.

Because self-perceived fracture risk and self-perceived osteoporosis risk were strongly and significantly correlated, self-perceived fracture risk was not included in the main analysis. We conducted a sensitivity analysis including self-perceived fracture risk. In addition, we assessed concordance to NOF 2003 guidelines because some of the women may have been managed in concordance to the 2003 guidelines prior to the 2008 update.

Results

A total of 1,533 women had at least one DXA test performed at UAB within 2 years of at least one GLOW survey. Among these survey participants, 809 had osteopenia. After excluding those who reported a hip or vertebral fracture since age 45 years ($N=39$) and those who did not have complete data for fracture risk assessment ($N=173$) sequentially, a total of 597 survey participants were eligible for these analyses. Figure 1 shows the attrition at each step during the process to identify eligible subjects for the current analysis. Of those, 175 (29.3 %) had data derived from surveys completed in 2007, 259 (43.4 %) in 2008, 161 (27.0 %) in 2009, and 2 (0.3 %) in 2010. The mean participant age ± standard deviation (SD) was 70±7 years, and the median, the lower, and upper quartile for the duration from date of DXA test to date of GLOW survey completion were 165, 82, and 247 days.

A total of 308 (52 %) were managed in accordance with the NOF 2008 guidelines, including 168 recommended for treatment who ever used therapy and 140 not recommended for treatment who never used therapy. Those who met NOF 2008 criteria were not more likely to have ever received treatment

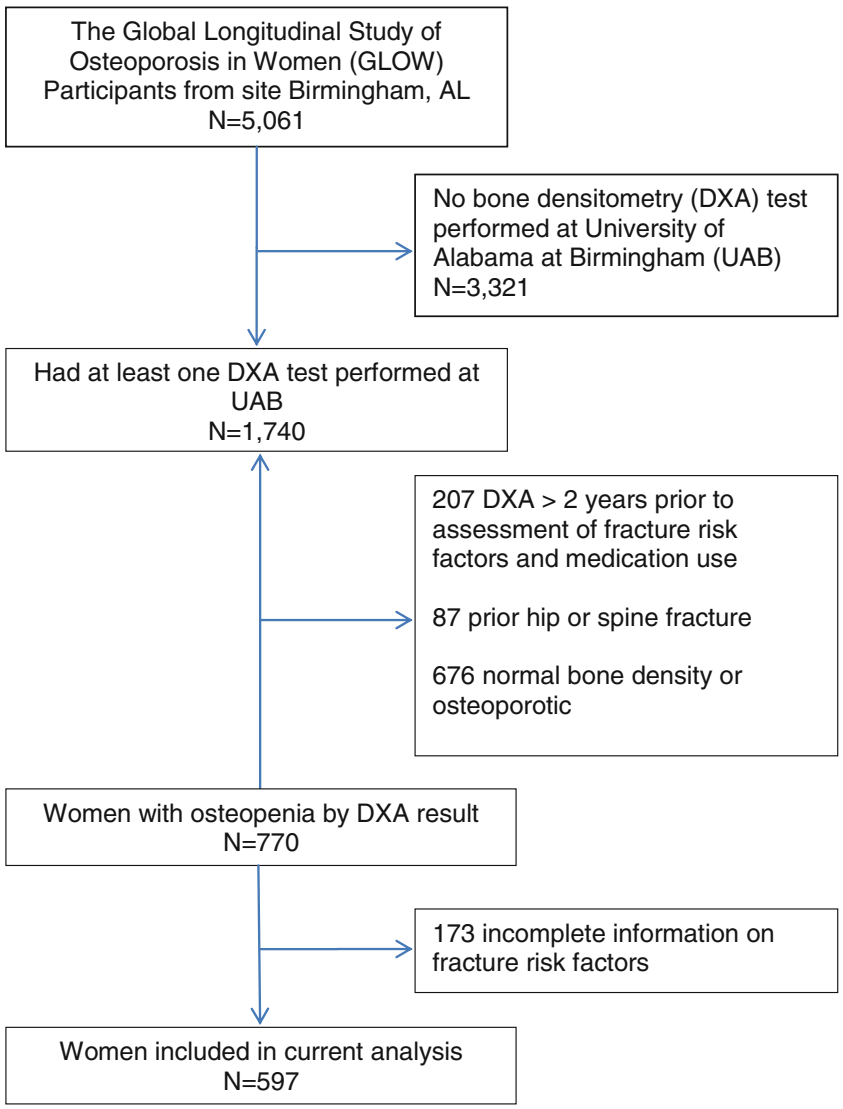

Fig. 1 Flow diagram of the process to identify eligible study participants

(OR, 1.1; 95 % CI, 0.8–1.6) than those who did not meet the criteria (Table 1). The Kappa coefficient was 0.03 indicating poor agreement [7]. Results from sensitivity analysis found a greater proportion (61 %) of women managed in concordance with the NOF 2003 guidelines, including 215 recommended for treatment who ever used therapy and 147 not recommended for treatment who had never used therapy (Table 1). The Kappa coefficient was 0.21.

Among women with osteopenia who were not recommended for treatment based on the NOF 2008 guidelines, high self-perceived osteoporosis risk, lower BMD, and being a nonsmoker were independently associated with receipt of osteoporosis medications in multivariable analysis (Table 2). Among women recommended for treatment, weighing more than 125 lb, absence of parental hip fracture, higher BMD, and low self-perceived osteoporosis risk were significantly associated with never receiving treatment (Table 3).

The results from sensitivity analysis replacing self-perceived osteoporosis risk with self-perceived fracture risk were consistent with those of the main analysis and indicated that medication use was strongly associated with greater amount of concern about osteoporosis and self-perceived fracture risk.

Discussion

In this cross sectional study of a large longitudinal cohort of community-based women 55 years of age or older with osteopenia, we found that nearly half of these women were not managed in concordance with the NOF 2008 guidelines. As anticipated, we confirmed that BMD was independently associated with the receipt of treatment. This may be a partial explanation for the greater degree of observed discordance when 2008 guidelines were applied compared to when the 2003 guidelines were considered, since the 2003 guidelines relied heavily on BMD and the 2008 guidelines rely more on an amalgam of other risk factors.

We found that participants' self-perceived osteoporosis risk was significantly and strongly associated with treatment, both among those recommended and not recommended for treatment based on the NOF guidelines. The finding suggests that women may pursue and be provided care that is not guideline based. In contrast, many other known fracture risk factors, including age, were not independently associated with receipt of treatment. For clinicians who commonly encounter women with reduced bone density but not yet osteoporotic, assuming relevance of the NOF treatment guidelines, our findings suggest room for improvement in the management of osteopenic women through increased use of the FRAX tool to assist in fracture risk assessment and in making treatment decision.

Table 1 Unadjusted associations between meeting and not meeting National Osteoporosis Foundation criteria and receipt of osteoporosis treatment

	Total no.	No. ever treated (% of total)	Odds ratio for treatment receipt (95 % CI)
NOF 2003 Guidelines			
Overall			
Treatment recommended	350	215 (61.4)	2.3 (1.7–3.3)
Treatment not recommended	247	100 (40.5)	Reference
By BMD category and presence of major risk factors[a]			
Treatment recommended			
T-score ≤−2.0	210	136 (64.8)	3.8 (2.4–6.1)
−2.0<T-score≤−1.5 and presence of at least one risk factors[a]	140	79 (56.4)	2.7 (1.6–4.4)
Treatment not recommended			
−2.0<T-score≤−1.5 and no risk factor*	121	59 (48.8)	2.0 (1.2–3.3)
−1.5<T-score<−1.0	126	41 (32.5)	Reference
NOF 2008 Guidelines			
Overall			
Treatment recommended	310	168 (54.2)	1.1 (0.8–1.6)
Treatment not recommended	287	147 (51.2)	Reference
By FRAX risk score			
Treatment recommended			
10-year probability of hip fracture ≥3 % and 10-year probability of major osteoporotic fracture ≥20 %	153	98 (64.1)	1.7 (1.1–2.5)
Either 10-year probability of hip fracture ≥3 % or 10-year probability of major osteoporotic fracture ≥20 %, but not both	157	70 (44.6)	0.8 (0.5–1.3)
Treatment not recommended			
10-year probability of hip fracture <3 % and 10-year probability of major osteoporotic fracture <20 %	287	147(51.0)	Reference

[a] Risk factors include parental hip fracture, body weight <125 lb, current smoking, and current glucocorticoid use

The inconsistency we observed between therapy recommended by the NOF guidelines and treatment received likely reflects the lack of definitive evidence supporting the utilization of pharmacologic agents for primary prevention in individuals with osteopenia. The US Food and Drug Administration has approved a number of medications for the prevention of osteoporosis. However, because clinical trials typically do not include those with T-score >−2.0 or those

Table 2 Factors associated with ever receiving treatment among 287 women 55 years or older with osteopenia NOT RECOMMENDED for treatment based on NOF 2008 guidelines

	Ever treated $N=147$	Never treated $N=140$	Univariate OR (95 % CI) $N=287$	Adjusted OR (95 % CI)[a] $N=268$
Demographics				
Age group				
55–64	78 (53.1)	73 (52.1)	1.5 (0.5–4.9)	
65–74	64 (43.5)	60 (42.9)	1.5 (0.5–5.5)	
75+	5 (3.4)	7 (5.0)	Reference	
Black versus white	19 (13.2)	36 (25.9)	0.4 (0.2-0.8)	
Education				
College or more	72 (49.0)	52 (37.4)	1.9 (1.0–3.4)	
Some college	47 (32.0)	49 (35.3)	1.3 (0.7–2.5)	
High school or less	28 (19.0)	38 (27.3)	Reference	
Fracture risk factors				
Bone mineral density				
>−1.5 and <−1.0	22 (15.0)	51 (36.4)	0.3 (0.1–0.6)	0.3 (0.1–0.6)
>−2.0 and ≤−1.5	74 (50.3)	57 (40.7)	0.8 (0.5–1.4)	0.8 (0.4–1.4)
>−2.5 and ≤−2.0	51 (34.7)	32 (22.9)	Reference	Reference
Weight <125 lb	21 (14.3)	11 (7.9)	2.0 (0.9–4.2)	
Fracture since 45[b]	12 (8.2)	8 (5.7)	1.5 (0.6–3.7)	
Parental history of FX	17(11.6)	17(12.1)	1.0 (0.5–1.9)	
Current smoker	3 (2.0)	11 (7.9)	0.2 (0.1–0.9)	0.2 (0.1–1.0)
Current steroid use	3 (2.1)	4 (2.9)	0.7 (0.2–3.2)	
Rheumatoid arthritis	14 (9.5)	16 (11.4)	0.8 (0.4–1.7)	
Diabetes	3 (2.0)	5 (3.6)	0.6 (0.1–2.4)	
Early menopause	26 (17.7)	40 (28.6)	0.5 (0.3–0.9)	
Aromatase inhibitor	6 (4.1)	7 (5.0)	0.8 (0.3–2.5)	
Current estrogen use	26 (17.7)	27 (19.3)	0.9 (0.5–1.6)	
Fall in previous 12 months	51 (34.7)	54 (38.8)	0.8 (0.5–1.4)	
Self-perceived fracture risk				
Osteoporosis concern				
Very concerned	63 (42.9)	49 (35.5)	4.5 (1.4–14.5)	
Somewhat concerned	80 (54.4)	75 (54.3)	3.7 (1.2–11.8)	
Not at all concerned	4 (2.7)	14 (10.1)	Reference	
Self-rated risk of osteoporosis compared with women of same age				
Much higher	25 (17.6)	17 (12.7)	4.7 (1.5–14.1)	4.8 (1.5–16.0)
A little higher	42 (29.6)	23 (17.2)	5.8 (2.0–16.5)	6.2 (2.0–19.0)
About the same	50 (35.2)	55 (41.0)	3.3 (1.1–7.8)	3.2 (1.1–9.5)
A little lower	19 (48.7)	20 (51.3)	3.0 (1.0–9.1)	4.1 (1.2–13.7)
Much lower	6 (24.0)	19 (76.0)	Reference	Reference

[a] Reduced model using backward elimination to retain covariates with a threshold p value of 0.05.

[b] Fracture at a site other than hip or spine

without history of a prior fracture, data on the efficacy in fracture prevention from treating those with bone density in the range between −1.0 and −2.0 are limited. Examining data from randomized trials, risedronate significantly reduced the risk of fragility fractures among postmenopausal women with osteopenia [8]. However, because trial participants either had to have low BMD (T-score ≤−2.0) or fracture risk factors, the study participants do not represent the general osteopenic population of interest for this analysis.[8] The Fracture Intervention Trial included women with T-score <−1.6, and alendronate was not associated with reduced risk of clinical fracture at any site or morphometric vertebral fracture in osteopenic women without history of vertebral fracture [9]. In addition, the study reported a significant interaction between treatment efficacy and initial bone density such that 4 years of alendronate treatment did not reduce the risk of clinical fracture among those whose T-score was greater than −2.5 [9].

As a result of this paucity of evidence, clinical guidelines for management of osteopenic individuals vary. The 2010

Table 3 Factors associated with never receiving treatment among 310 women 55 years or older with osteopenia RECOMMENDED for treatment based on NOF 2008 guidelines

	Ever treated $N=168$	Never treated $N=142$	Univariate OR (95 % CI) $N=310$	Adjusted OR (95 % CI)[a] $N=288$
Demographics				
Age group				
55–64	14 (8.3)	7 (4.9)	0.6 (0.2–1.6)	
65–74	84 (50.0)	77 (54.2)	1.1 (0.7–1.8)	
75+	70 (41.7)	58 (40.8)	Reference	
Black versus white	7 (4.2)	9 (6.3)	1.5 (0.6–4.3)	
Education				
College or more	59 (35.1)	58 (41.1)	1.4 (0.8–2.4)	
Some college	47 (28.0)	40 (28.4)	1.2 (0.7–2.2)	
High school or less	62 (36.9)	43 (30.5)	Reference	
Fracture risk factors				
Bone mineral density				
>−1.5 and <−1.0	19 (11.3)	34 (23.9)	3.6 (1.8–7.1)	2.5 (1.2–5.4)
>−2.0 and ≤−1.5	64 (38.1)	66 (46.5)	2.1 (1.3–3.5)	1.6 (0.9–2.8)
>−2.5 and ≤−2.0	85 (50.6)	42 (29.6)	Reference	Reference
Weight <125 lb	40 (23.8)	22 (15.5)	0.6 (0.3–1.0)	0.4 (0.2–0.9)
Fracture since 45[b]	58 (34.5)	42 (29.6)	0.8 (0.5–1.3)	
Parental history of FX	65 (38.7)	30 (21.1)	0.4 (0.3–0.7)	0.5 (0.3–0.8)
Current smoker	10 (6.0)	10 (7.1)	1.2 (0.5–3.0)	
Current steroid use	12 (7.4)	6 (4.2)	0.6 (0.2–1.5)	
Rheumatoid arthritis	14 (8.3)	14 (9.9)	1.2 (0.6–2.6)	
Diabetes	2 (1.2)	7 (5.0)	4.3 (0.9–21.2)	
Early menopause	51 (30.4)	42 (29.6)	1.0 (0.6–1.6)	
Aromatase inhibitor	10 (6.0)	4 (2.8)	0.5 (0.1–1.5)	
Current estrogen use	25 (14.9)	25(17.6)	1.2 (0.7–2.2)	
Fall in previous 12 months	67 (40.1)	44 (31.7)	0.7 (0.4–1.1)	
Self-perceived fracture risk				
Osteoporosis concern				
Very concerned	70 (42.2)	39 (27.7)	0.3 (0.1–0.8)	
Somewhat concerned	86 (51.8)	85 (60.3)	0.6 (0.3–1.3)	
Not at all concerned	10 (6.0)	17 (12.1)	Reference	
Self-rated risk of osteoporosis compared with women of same age				
Much higher	27 (16.6)	7 (5.1)	0.1 (0–0.2)	0.1 (0–0.3)
A little higher	53 (32.5)	22 (16.1)	0.1 (0–0.3)	0.1 (0–0.3)
About the same	55 (33.7)	51 (37.2)	0.2 (0.1–0.6)	0.2 (0.1–0.6)
A little lower	22 (13.5)	31 (22.6)	0.3 (0.1–0.9)	0.3 (0.1–1.0)
Much lower	6 (3.7)	26 (19.0)	Reference	Reference

[a] Reduced model using backward elimination to retain covariates with a threshold p value of 0.05

[b] Fracture at a site other than hip or spine

guidelines from the American Association of Clinical Endocrinologist endorsed the NOF 2008 guidelines which recommended pharmacologic treatment in osteopenic individuals if their 10-year probability of fracture is ≥3 % at hip and ≥20 % for a major osteoporotic fracture. However, the guidelines of the American College of Physicians recommend treating osteopenic individuals at increased risk of developing osteoporosis and that a single factor sometimes may be sufficient to warrant treatment with a pharmacologic agent. As a result, the women in our study who were treated in a manner that is not concordant with the NOF guidelines may be in concordance with clinical guidelines from other national groups.

In addition to lack of and conflicting clinical evidence and inconsistent guidelines, we speculate that the poor adherence to clinical guidelines reported in our study is consistent with treatment patterns in other disease states and may in part reflect physicians' attitudes toward clinical practice guidelines in general. Many physicians believe that practice guidelines were developed to constrain costs and that they restrict individualized care. These and other concerns may lead to low rates of adherence to clinical practice guidelines [10–13].

The objective of our study was to assess adherence to the NOF guidelines, not the "appropriateness" of treatment, quality of care, or reasons for the observed discordance, although we speculate that lack of clinical evidence and a low physician acceptance toward clinical guidelines in general may be two possible explanations. Given uncertainties regarding the benefits and risks associated with treatment of osteopenia, the decision to treat or not to treat should depend on physicians' clinical judgment and patients' preference and understanding of the potential risks and benefits. This may be particularly true in our study because women with a prior history of hip or spine fracture were excluded to allow us to examine osteoporosis medication use only as a primary preventive measure. Thus, our study population represents a lower risk subgroup of all women with osteopenia. Many factors that may have prompted osteoporosis treatment were not evaluated in our study, including chronic use of oral glucocorticoids, a significant interval decline in bone density, biochemical measures of bone remodeling indicating high rate of bone turnover, and strong individual preference for or against using osteoporosis medications. Among those recommended for therapy, 25 received estrogen therapy. Because estrogen therapy prevents the development of osteoporosis, there is a rationale to consider these women as "treated" and thus increasing the proportion of women treated in concordance with the NOF guidelines from 168 (54 %) to 193 (62 %) among women recommended for therapy.

Despite the strengths of our study that included 597 older women with osteopenia recruited from the community, a limitation is that all data were self-reported except for bone density. We relied heavily on the self-reported information to assess exposure to osteoporosis medications and concordance with NOF guidelines. If such information was not self-reported correctly, subjects would have been misclassified, and self-reported weight, as an example, has been shown to be systemically under-reported [14]. Another limitation of the study was that all subjects were from Alabama or surrounding areas, and all had at least one DXA test performed at UAB. Thus, they do not represent the general population of postmenopausal women 55 years of age or older. In addition, we were unable to distinguish between those who were never prescribed with osteoporosis medications and those for whom medications were prescribed but never used. Finally, the cross sectional design of the study makes it possible that participants currently receiving treatment had lower bone density at the time of treatment initiation than when measured in our study. Antiresorptive medications are highly efficacious in increasing bone mineral density.

In conclusion, we found that women with osteopenia often were not treated in adherence to the NOF guidelines. Instead of fracture risk factors, women's self-assessment of their osteoporosis risk compared to their peers was one of the strongest determinants of the receipt of osteoporosis medication for the primary prevention of osteoporosis. Given the possible increased long-term risk associated with certain antiresorptive medications [15, 16], our findings highlight the urgent need to identify clearly defined subgroups of women with low bone mass (osteopenia) in whom the benefits of anti-osteoporosis treatment outweigh the risks.

Conflicts of interest JZ has received research support from Amgen and Genentech; ED has received research support from Amgen; JRC has received research grants and honoraria, and consulted for Merck, Eli Lilly, Amgen; KGS has received research grants from Amgen and Merck and consulted for Merck and Lily.

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