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Regional differences in treatment for osteoporosis. The Global Longitudinal Study of Osteoporosis in Women (GLOW)

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Abstract

Purpose—To determine if important geographic differences exist in treatment rates for osteoporosis and whether this variation can be explained by regional variation in risk factors.

Methods—The Global Longitudinal Study of Osteoporosis in Women is an observational study of women ≥55 years sampled from primary care practices in 10 countries. Self-administered questionnaires were used to collect data on patient characteristics, risk factors for fracture, previous fractures, anti-osteoporosis medication, and health status.

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Results—Among 58,009 women, current anti-osteoporosis medication use was lowest in Northern Europe (16%) and highest in USA and Australia (32%). Between 48% (USA, Southern Europe) and 68% (Northern Europe) of women aged ≥65 years with a history of spine or hip fracture since age 45 were untreated. Among women with osteoporosis, the percentage of treated cases was lowest in Europe (45– 52% versus 62–65% elsewhere). Women with osteopenia and no other risk factors were treated with anti-osteoporosis medication most frequently in USA (31%) and Canada (31%), and least frequently in Southern Europe (12%), Northern Europe (13%), and Australia (16%). After adjusting for risk factors, US women were threefold as likely to be treated with anti-osteoporosis medication as Northern European women (odds ratio 2.8; 95% confidence interval 2.5–3.1) and 1.5 times as likely to be treated as Southern European women (1.5, 1.4–1.6). Up to half of women reporting previous hip or spine fracture did not receive treatment.

Conclusions—The likelihood of being treated for osteoporosis differed between regions, and cannot be explained by variation in risk factors. Many women at risk of fracture do not receive prophylaxis.

Keywords

Fracture; Regional variation; Women; Risk factor; Preventive treatment

1. Introduction

Fractures in older women reduce quality of life and contribute to increases in morbidity and mortality [1]. Optimal reduction of fractures requires that treatment decisions be based on treating those at greatest risk of fracture, who are likely to benefit from anti-osteoporosis medication (AOM).

Wide variation exists in the application of treatment, with a low overall prevalence of treatment for women at risk of fracture [2]. The recognition that clear, consistent, and widely accepted guidance for treatment has been lacking, has resulted in the development of tools for identifying those most at risk of fracture [3, 4], although these tools have become widely available only recently.

The assessment of regional variation in rates of specific medical treatments and procedures has been used to identify inconsistency in the application of medical and surgical interventions [5], and to identify the need for more consistent application of treatment guidelines. To the extent that regional and national variations exist in the frequency of treatment to reduce fracture risk, these differences could be driven by dissimilar patterns of risk or practice. It is important therefore to account for differences in the distribution of fracture risk between regions if the goal is to assess variation in treatment practices. The prevalence of risk factors for fragility fracture has been documented in national and regional reports, but studies have varied in their methods, so that appropriate comparisons across regions have been difficult [6-9]. Estimates of prevalence for a number of risk factors have varied by as much as fivefold to ninefold [10]. For these reasons, it is important that data on risk factors and treatment in different regions are collected using a uniform method from a large number of women from different countries. In this study, data on treatment and risk factors were collected in the same way in five regions, to determine if important differences

exist in rates of treatment between areas and whether this variation can be explained by differences in risk factors.

2. Methods

A detailed description of the methods used in the Global Longitudinal Study of Osteoporosis in Women (GLOW) study has been published [11]. In brief, GLOW is an observational cohort study conducted by 723 physicians in 17 local investigation centers in 10 countries (Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, UK, and USA).

Practices typical of each region were recruited through primary care networks organized for administrative, research or educational purposes, or by identifying all physicians within a geographic area. Physician networks included regional health-system-owned or managed practices, health maintenance organizations, independent practice associations, and other primary care practice networks. Networks established for the purpose of general medical research were used only if they were not established exclusively for osteoporosis research and did not consist primarily of physicians whose primary focus was academic. Primary care physicians were defined as those who spent the majority of their time providing primary healthcare to patients, and included internists, family practitioners, and general practitioners. A random sample of physicians was invited in areas that had more eligible physicians than were necessary to recruit a sufficient number of women.

Each practice provided names and addresses of women aged 55 years and older who had been seen by their physician in the past 24 months. Sampling was stratified by age to ensure that two thirds comprised women aged 65 years and older. Women were excluded if they were unable to complete the study survey because of cognitive impairment or language barriers, institutionalization, or illness.

2.1 Assessment by questionnaire

Questionnaires were designed to be self-administered and covered domains including: demographic characteristics and risk factors; perception about fracture risk and osteoporosis; medication use (currently taking or ever taken); medical diagnoses; healthcare use and access; physical activity; and physical and emotional health status. Where possible, questions from published validated instruments were used, including the National Health and Nutrition Examination Survey (NHANES) [12], European Quality of Life 5 Dimensions Index (EQ-5D) [13], and the Medical Outcomes Study 36-item short form (SF-36; physical function and vitality components) [14].

2.2 Risk factor assessment

Personal risk factors included those demonstrated in previous studies to be independent predictors of future fractures [15–17], and those employed in multivariable predictive models [18, 19]. The risk factors with the greatest prevalence and impact on fracture risk were chosen for this study, and include: age; current weight and height; maternal hip fracture; falls in the past 12 months; previous fracture since age 45 years; current cigarette smoking; premature menopause; the need to use arms to rise from a chair; and current use of corticosteroids.

2.3 Treatment assessment

Use of an AOM was defined as self-reported current use of any of the following: alendronate, risedronate, etidronate, ibandronate, pamidronate, raloxifene, teriparatide, tibolone, calcitonin, strontium ranelate, and zoledronic acid or estrogen-replacement therapy. Analysis of treatment of women at lower risk for fracture, and of women with osteopenia (low bone mass) and no other major risk factors, was conducted using two treatment definitions, one including and one excluding estrogen, to account for the use of estrogen for the treatment of menopausal symptoms in younger women, and not as an explicit treatment for osteoporosis. “Major risk factors” were defined in the case of the osteopenia category as age >75 years, prior fracture, and maternal hip fracture. These major risk factors were chosen because they were hypothesized to be well understood by physicians and are reasonably easy to ascertain from the patient.

2.4 Ethics approval and follow-up

Each study site obtained ethics committee approval to conduct the study in that location. Invitations to participate in the study and baseline questionnaires were mailed to all potential subjects. Women who did not respond initially were followed-up with sequential postcard reminders, second questionnaires, and telephone interviews.

2.5 Statistical analysis

The three major regions were defined as Northern Europe (Amsterdam, Essen, Leuven, and Southampton), Southern Europe (Barcelona, Lyon, Paris, and Verona), and the USA (Birmingham, Cincinnati, Los Angeles, New York, Pittsburgh, Seattle, and Worcester). Australia (Sydney) and Canada (Hamilton) were left as distinct regions, and were omitted from adjusted analyses because of the relatively low number of subjects in each of these regions versus the other regions.

Medians and interquartile ranges are reported for continuous variables (age, body mass index [BMI]) and percentages for dichotomous variables. The fitting of the model was done using generalized estimating equations where physician practice was modeled as a random effect nested within geographic site. Odds ratios (ORs) for regions were computed by averaging the effects of the corresponding sites. Factors adjusted for in the multivariable model included: age; any fracture since age 45 years; maternal history of hip fracture; and BMI.

3. Results

A total of 60,393 women participated in the baseline survey, representing a median response rate of 62% across all study sites [11]. There were 58,009 subjects with complete data for current use of AOM. Among all study sites, the lowest proportion of current use of an AOM was 16% in Northern Europe, and the highest was 32% in the USA and in Australia (Table 1). When treatment prevalence was stratified according to age ≥65 years with a prior hip or spine fracture, the highest proportions of women treated were in Australia (73%) and Canada (64%), although the number of subjects in this category in these regions was low. In both the USA and Southern Europe, 52% of subjects with prior fracture of the hip or spine

were treated with AOM. Treatment of this group was least frequent in Northern Europe (42%).

Among women who reported a diagnosis of osteoporosis, a similar prevalence of treatment was found in Australia, Canada, and the USA (65%, 64%, and 62%, respectively); the lowest percentages treated were in Northern Europe (45%) and Southern Europe (52%). Removing estrogen replacement from the definition of AOM had only a small effect on the report of treatment with AOM for those aged ≥65 years, the greatest difference being a reduction in treatment prevalence of 3% in the USA and Northern Europe. Similarly, the effect of removing estrogen from the treatment definition for the group reporting an osteoporosis diagnosis was no greater than 5% (Australia).

Women who reported a diagnosis of osteopenia and no other major risk factors for fracture were treated least frequently in both European regions (20%) and most frequently in the USA (39%) and Canada (42%). When estrogen was removed from the definition of treatment, more than twice the proportion remained treated in the USA and Canada (31%) compared with in Northern Europe (13%), Southern Europe (12%), and Australia (16%).

The distribution of risk factors by geographic region for the 60,393 women is shown in Table 2. The risk factors self-reported most frequently were previous fracture after age 45 years (24%), a fall in the past 12 months (38%), the need to use arms to rise from a chair (34%), and fair or poor general health (23%). The frequencies of these risk factors varied across geographic regions and, due primarily to the large sample size, were all statistically significant at $P<.001$. The magnitude of these differences, however, was notable for certain risk factors in certain regions. Southern Europeans reported the highest frequency of previous fracture (28% versus a GLOW average of 24%), and almost twice the percentage of Southern European women reported fair or poor health (45%) compared with the GLOW average of 23%. Northern Europeans were more frequently current smokers (12%), but the prevalences of maternal hip fracture (9.6%) and weight <125 lb/<57 kg (12%) in this region were low compared with other regions. Women from the USA and Canada needed to use their arms to rise from a chair most frequently (38%), and had the highest prevalence of menopause before age 45 years (18%).

The unadjusted OR for treatment with AOM in the USA versus Northern Europe was 2.6 (95% confidence interval [CI] 2.3–2.9), and in the USA versus Southern Europe was 1.3 (95% CI 1.2–1.4) (Table 3). In Southern Europe, women were twice as likely to be treated as in Northern Europe in this unadjusted analysis (OR 2.0; 95% CI 1.8–2.3). In the adjusted comparison, the OR for treatment with AOM in the USA versus Northern Europe was 2.8 (95% CI 2.5–3.1), and in the USA versus Southern Europe was 1.5 (95% CI 1.4–1.6). Southern European women were almost twice as likely to be treated as Northern European women (OR 1.9; 95% CI 1.6–2.1).

Analysis of treatment according to key selected major risk factors for fracture (Table 3) indicated that the OR for treatment of women with versus those without a past fracture was 1.8 (95% CI 1.7–1.9), and that the OR for treatment of women whose mothers did versus did

not fracture their hip was 1.2 (95% CI 1.2–1.3). The effects of BMI and age (per 10-year increase) were also significant.

4. Discussion

After adjusting for differences in risk factors for fracture in a large cohort of women in Europe and the USA, women in the US sites were almost three times as likely to be treated as women in the Northern European sites, and 1.5 times as likely to be treated as women in the Southern European sites. Women in Southern Europe were almost twice as likely to be treated as women in Northern Europe. Because the multivariable analyses adjust for the most significant risk factors for fracture, differences in the distribution of these risk factors do not explain the differences detected in treatment frequency based on the region in which subjects live. Additionally, the small changes in ORs between the adjusted and unadjusted analyses provide evidence that regional variation in risk factors explains only a small portion of the variation in treatment by region. Region also had the strongest relationship with treatment for osteoporosis when compared with established risk factors for fracture, such as past fracture, maternal fracture, and BMI.

The reduction of morbidity and mortality associated with fractures in women involves identification of those at risk and taking preventive measures, which can include using efficacious treatment, and/or reducing risk factors within the control of the patient and her physician, such as exercise to improve balance, reducing the risk of falls by eliminating sedating medications, or reducing fall hazards in the home. In the case of fracture prevention, treatment is available that has been proven to reduce fractures associated with osteoporosis. Our results underline the need for improvement in the identification and treatment of the population who are most at risk of fracture.

In all regions, high proportions of women at risk of fracture remain untreated. However, there appear to be important differences in the populations most likely to receive treatment, particularly when comparing the USA, Northern Europe and Southern Europe. Between 48% (USA, Southern Europe) and 68% (Northern Europe) of women aged ≥65 years who reported a history of spine or hip fracture since age 45 years were untreated. The low proportion of older women with previous hip or spine fractures who are treated in Northern Europe compared with all other regions suggest that women at higher risk of fracture are receiving treatment less often in Northern Europe than in other regions.

On the other hand, approximately twice the proportion of women with osteopenia and no other risk factors are treated in the USA and Canada compared with other regions. This higher frequency of treatment of women at lower risk of fracture in the USA than in Europe may indicate that many women who may not be likely to benefit from treatment are receiving it in the USA. However, treatment of low-risk women in Southern Europe is unlikely to account for the greater likelihood of being treated in Southern Europe than in Northern Europe, as Southern Europe has the lowest percentage of women with osteopenia and no other risk factors who report treatment (20% including estrogen, 12% without estrogen). This fact, combined with a proportion of women aged ≥65 years with a history of

hip or spine fractures who are treated that is identical to that in the USA (52%), may indicate that physicians are targeting treatment.

Therefore, while it appears that women likely to benefit from treatment in the USA, Canada, Australia, and Southern Europe are receiving treatment more often than in Northern Europe, there may also be over-treatment of women who are at low risk of future fracture in the USA and Canada, although osteopenia was self-reported and not validated by bone mineral density results.

Several studies conducted in the late 1990s and early 2000s identified a substantial gap in anti-fracture treatment among women after a fragility fracture [2]. The studies reviewed by Elliot-Gibson et al. found low rates of treatment in this high-risk population; however, definitions of treatment in the studies reviewed and in the methods of data collection varied, and in many cases were not consistent with the definition used in the present study. A large cross-sectional study by Gehlbach et al. [20] examined use of antiresorptive prescription medication in women aged 65 years and older using NHANES data from 1999 to 2000 and 2001 to 2002, and found that only 17% of older women who sustained any fracture since age 50 were receiving treatment with antiresorptive medications. In our international sample, 51% of women 65 years and older who had a hip or spine fracture after age 45 reported treatment with an antiresorptive medication, and this varied from 42% in Northern Europe to 73% in Australia. It is possible that the data on treatment presented here represent an increase in treatment for this high-risk group. Another potential explanation for the higher prevalence of treatment in our study is, however, that we restricted the prior fracture subgroup to women who had hip and spine fractures, and these fractures may be more likely to attract the attention of the treating physician.

This is the first study, to the best of our knowledge, to document both the under-treatment of women who are among those most likely to benefit from treatment, as well as the potential over-treatment of women with osteopenia (low bone mass). National Osteoporosis Foundation treatment guidelines recommend treatment for women with moderately low bone mass when accompanied by other major risk factors, but in this study, we examined treatment of women who reported osteopenia with no prior fracture history and who did not report having a mother who had sustained a hip fracture [21]. While an equal number of fractures occurs in women with osteopenia as among women with osteoporosis, the incidence of fracture for women with osteopenia and no other major risk factors for fracture is low compared with for women with osteoporosis [22]. Additionally, treating these women with prescription AOM is unlikely to be cost-effective [23]. It is possible that some of the women in this category have other major risk factors (such as current use of corticosteroids), but the numbers are likely to be small, and inclusion of other risk factors would be unlikely to explain the magnitude of the difference in treatment of this population in the USA versus Europe.

One potential source of variation is the absence, in the past, of clear guidelines enabling physicians to target treatment appropriately to those most at risk. The poor ability of the classifications of osteoporosis and osteopenia alone to predict who will fracture has compromised the ability of physicians to target treatment properly towards those who would

benefit the most, which in turn may also have made it difficult for national health plans and insurers to justify paying for preventive treatment. Skepticism about the need to treat osteoporosis and the serious consequences of fracture, as well as lack of patient understanding of their risk of fracture [24], may also be barriers to treatment to prevent fractures.

Initiatives are now underway to move from bone mineral density-based treatment criteria to treatment criteria that employ risk factors alone, or in combination with bone mineral density, to predict an absolute risk of fracture over time [19]. Such efforts, if successful, could result in more consistency in the use of best practices for the assessment of risk and prevention of fractures. Additional research into the source of variation in treatment according to where a woman lives could also help guide how best to reduce this variation and ensure that women who need treatment to reduce fracture risk are receiving it.

Our study has both limitations and strengths with respect to our ability to assess regional differences in the use of AOM in older women. Although GLOW was designed to identify subjects and elicit information from them in a uniform way, differences in participation rates and interpretation of questionnaire items may have contributed to regional differences in the observed risk factor and treatment prevalence. However, we believe that variation between regions due to such factors is likely to be far less than when comparing regional data from separate studies. While we attempted to enroll representative groups of subjects in each region, we recognize that individuals who choose to participate in studies of this kind may be a select group with characteristics that differ from those of the broader population. The prevalence of osteoporosis and related fractures may have been underestimated as this information is self-reported and women with decreases in bone density or with subclinical fractures, in particular vertebral fractures, may have been missed, placing our assessments of under-treatment on the conservative side. A comparison of USA GLOW data with the NHANES III cohort [11], however, showed that the mean ages, and the prevalences of low weight, osteoporosis diagnosis, fracture of the spine or hip, maternal fracture, and common comorbid conditions (hypertension, high cholesterol, and asthma) were similar in the two groups, which supports the representativeness of the whole population. However, women in the GLOW sample had a higher level of education, were more often white, and had better self-reported health than women in the NHANES study. While the validity of self-reported risk factors may be questioned, a recent systematic review of self report of risk factors for osteoporosis showed a suitable degree of accuracy [25]. The particular sites included in the GLOW study may also not have treatment patterns that are representative of the wider geographic regions used in this analysis. However, the reported rates of treatment in this study are similar to those reported in other samples from countries in GLOW [26]. This study was also limited to specific regions, and no Asian or African countries were included. Our results might not, therefore, be translatable to these regions of the world.

5. Conclusions

These data on fracture risk factors and treatment in older women demonstrate that a substantial number of older women who may be at risk of future fractures are not receiving treatment to reduce that risk. In addition, important differences exist between the regions

studied in the targeting of treatment towards women most at risk of fracture. Finally, the region in which a woman lives appears to be a stronger predictor of treatment than well-established risk factors. The reasons for such regional variation should be explored in future studies to help guide efforts to improve consistency and effectiveness of care for osteoporosis.

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Abbreviations

AOM	Anti-osteoporosis
BMI	Body mass index
CI	Confidence interval
GLOW	Global Longitudinal Study of Osteoporosis in Women
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio

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Table 1

Percentage of women receiving anti-osteoporosis medication, by study region and risk characteristic.

	All	Australia	Canada	Northern Europe	Southern Europe	USA
Number of sites	17	1	1	4	4	7
Number of women	58,009[a]	2807	3802	13,368	10,881	27,151
Treatment with AOM[b] (%)						
Estrogen included in AOM	27	32	31	16	26	32
≥65 years, past spine or hip fracture (*n*=1966)	51	73	64	42	52	52
Osteoporosis (*n*=12,357)	57	65	64	45	52	62
Osteopenia, <75 years, no prior fracture, no maternal hip fracture or osteoporosis (*n*=2140)	34	30	42	20	20	39
Estrogen excluded from AOM	20	21	26	9.5	21	23
≥65 years, past spine or hip fracture (*n*=1971)	49	72	62	39	51	49
Osteoporosis (*n*=12,364)	54	60	62	41	50	58
Osteopenia, <75 years, no prior fracture, no maternal hip fracture or osteoporosis (*n*=2141)	25	16	31	13	12	31

AOM, anti-osteoporosis medication.

[a]Of the original sample of 60,393, data on AOM use was incomplete or missing for 2384, resulting in a sample of 58,009 with complete data on AOM use.

[b]Within each category for AOM use, regional differences between actual and expected values are statistically significant using the chi-square test at $P<.001$.

Table 2

Percentage of women with fracture risk factors, by study region.

	All	Australia	Canada	Northern Europe	Southern Europe	USA
Number of study sites	17	1	1	4	4	7
Number of women	60,393	2904	3985	14,092	11,242	28,170
Median age (IQR) (years)	68 (61–75)	65 (60–73)	68 (62–76)	67 (61–74)	67 (61–74)	68 (61–76)
Median BMI (IQR) (kg/m^2)	26 (23–30)	25 (22–28)	27 (24–31)	26 (23–29)	25 (22–28)	26 (23–31)
Fracture since age 45 years (%)	24	25	22	23	28	23
Maternal hip fracture (%)	13	14	13	9.6	15	14
Current smoking (%)	9.2	4.8	11	12	9.9	7.7
Menopause age ≤45 years (%)	15	9.7	18	12	9.7	18
Fall in past 12 months (%)	38	38	38	35	35	40
Needs arms to rise from chair (%)	34	28	38	32	30	38
Self-rated health fair/poor (%)	23	14	17	25	45	16
Told had osteopenia (%)	16	18	17	8.3	12	22
Told had osteoporosis (%)	22	21	27	16	32	21
Current use of cortisone/prednisone (%)	3.1	4.6	3.6	2.7	2.7	3.2

BMI, body mass index; IQR, interquartile range.

Note: 6% missing information on osteoporosis or osteopenia, 5% missing bone density exam and BMI, <5% missing other variables.

Table 3

Multivariable models predicting anti-osteoporosis medication use by region

	Adjusted for physician practice only (n = 58,009)	**Adjusted for physician practice and factors shown below (n = 51,124)**
	Odds ratio (95% confidence interval)	Odds ratio (95% confidence interval)
USA vs. Northern Europe	2.6 (2.3–2.9)	2.8 (2.5–3.1)
USA vs. Southern Europe	1.3 (1.2–1.4)	1.5 (1.4–1.6)
Southern Europe vs. Northern Europe	2.0 (1.8–2.3)	1.9 (1.6–2.1)
Age (per 10–year increase)		1.04 (1.01–1.07)
Past fracture		1.8 (1.7–1.9)
Maternal fracture		1.2 (1.2–1.3)
BMI (per 1 kg/m^2 increase)		0.93 (0.92–0.94)