

Association of Disease Definition, Comorbidity Burden, and Prognosis With Hip Fracture Probability Among Late-Life Women

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IMPORTANCE Advanced age is associated with lower use of drug treatment to prevent fractures, but concerns about comorbidities and prognosis increase the complexity of managing osteoporosis in this age group.

OBJECTIVE To determine the association of disease definition, number of comorbidities, and prognosis with 5-year hip fracture probabilities among women who are 80 years and older.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study (4 US sites) included 1528 community-dwelling women identified as potential candidates for initiation of osteoporosis drug treatment.

MAIN OUTCOMES AND MEASURES Women were contacted every 4 months to ascertain vital status and hip fracture. Five-year hip fracture probability was calculated accounting for competing mortality risk. Participants were classified into 2 distinct groups based on disease definition criteria proposed by the National Bone Health Alliance: with osteoporosis (n = 761) and without osteoporosis but at high fracture risk (n = 767). Comorbid conditions were assessed by self-report. Prognosis was estimated using a mortality prediction index. All analysis was performed between March 2018 and January 2019.

RESULTS The study had 1528 participants, all of whom were women, with a mean (SD) age of 84.1 (3.4) years. During follow-up, 125 (8.0%) women experienced a hip fracture and 287 (18.8%) died before experiencing this event. Five-year mortality probability was 24.9% (95% CI, 21.8-28.1) among women with osteoporosis and 19.4% (95% CI, 16.6-22.3) among women without osteoporosis but at high fracture risk. In both groups, mortality probability similarly increased with more comorbidities and poorer prognosis. In contrast, 5-year hip fracture probability was 13.0% (95% CI, 10.7-15.5) among women with osteoporosis and 4.0% (95% CI, 2.8-5.6) among women without osteoporosis but at high fracture risk. The difference was most pronounced among women with more comorbidities or worse prognosis. For example, among women with 3 or more comorbid conditions, hip fracture probability was 18.1% (95% CI, 12.3-24.9) among women with osteoporosis vs 2.5% (95% CI, 1.3-4.2) among women without osteoporosis but at high fracture risk.

CONCLUSIONS AND RELEVANCE Women 80 years and older who have osteoporosis, including those with more comorbidities or poorer prognosis, have a high 5-year probability of hip fracture despite accounting for competing mortality risk. In contrast, among women without osteoporosis but at high fracture risk, competing mortality risk far outweighs hip fracture probability, especially among those with more comorbidities or worse prognosis.

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While advanced age is associated with lower rates of drug treatment to prevent fracture,¹⁻⁶ the estimated 5-year hip fracture risk is high among women 80 years and older, with probabilities ranging from 7.1% among those 80 to 84 years up to 20.9% among those 90 years and older.⁷ Approximately 33% of women who survive to age 90 years will experience a hip fracture by that age, but the estimated lifetime risk of hip fracture among postmenopausal women is much lower at 17% because most women die of other causes unrelated to hip fracture prior to reaching age 90.^{7,8} Older age, low bone mineral density (BMD), and poorer health status are risk factors for hip fracture, but they also increase the risk of competing mortality. Thus, clinicians have difficulty identifying late-life women most likely to benefit from drug treatment to prevent hip fracture.

Randomized clinical trials have demonstrated the benefit of drug treatment in preventing clinical fractures within 3 to 5 years among healthy postmenopausal women with a BMD T-score of -2.5 or less or vertebral fractures⁹ and among patients with recent hip fracture. Based on this evidence, guidelines from professional organizations¹⁰ universally recommend initiation of drug treatment among women and men 50 years and older with clinically recognized osteoporosis defined by a BMD T-score of -2.5 or less, vertebral fracture, or hip fracture. However, women over 80 years of age as well as those with multiple comorbidities or poorer prognosis (ie, higher estimated mortality risk) have been excluded or underrepresented in nearly all previous trials. Consequently, concerns about comorbidity burden and prognosis not addressed in clinical trials increase the complexity of managing osteoporosis in women late in life.

In addition, there has been a shift in treatment approach in the last decade with several professional societies¹¹⁻¹³ advocating expanding indications for drug treatment based on thresholds of estimated absolute fracture risk. In 2008, the National Osteoporosis Foundation (NOF)¹⁴ proposed using thresholds of 10-year estimated fracture probabilities in patients 50 years and older with osteopenia (BMD T-score between -2.5 and -1.0) to identify high-risk candidates for drug treatment to prevent fracture. In 2014, the National Bone Health Alliance (NBHA),¹³ a consortium of musculoskeletal societies and industry partners, advocated expanding the diagnostic criteria for osteoporosis in the United States based on the rationale that many adults 50 years and older with BMD T-scores above -2.5 will subsequently experience clinical fracture events. Because of its inclusion of intervention thresholds of fracture probabilities recommended by the NOF in the diagnostic criteria, the expanded NBHA definition greatly increases the proportion of older US adults labeled as having a diagnosis of osteoporosis. If widely implemented, use of NBHA criteria will result in the majority of women 80 years and older being identified as candidates for drug treatment to prevent fracture.¹⁵

To evaluate the association of disease definition, number of comorbidities, and prognosis with hip fracture probability among women 80 years and older who might be considered candidates for initiation of drug treatment to prevent hip fracture, we studied 1528 community-dwelling, treatment-naïve

Key Points

Question What is the association of disease definition, comorbidity burden, and prognosis with 5-year hip fracture probabilities among women 80 years and older?

Findings This prospective cohort study found that the 5-year hip fracture probability, taking into account the competing risk of death, was over 3-fold higher among women with osteoporosis compared with women without osteoporosis but at high fracture risk. The difference between groups in hip fracture probabilities was even more pronounced in women with a greater number of comorbidities or poorer prognosis.

Meaning Women 80 years and older with osteoporosis, including those with more comorbidities or poorer prognosis, have a high hip fracture probability despite accounting for competing mortality risk and may be the group most likely to be candidates for drug treatment to prevent hip fractures.

women (mean age, 84.1 years) with clinically recognized osteoporosis or without osteoporosis but at high fracture risk. We determined the 5-year cumulative incidence of hip fracture with consideration of competing risk of mortality and examined whether hip fracture and mortality probabilities varied across categories based on disease definition, number of comorbid conditions, and prognosis.

Methods

Study Population

We studied participants enrolled in the Study of Osteoporotic Fractures (SOF), a prospective cohort study of community-dwelling women. From 1986 to 1988, 9704 white women 65 years and older who were able to walk unassisted were recruited for participation in SOF from 4 geographic areas of the United States.¹⁶

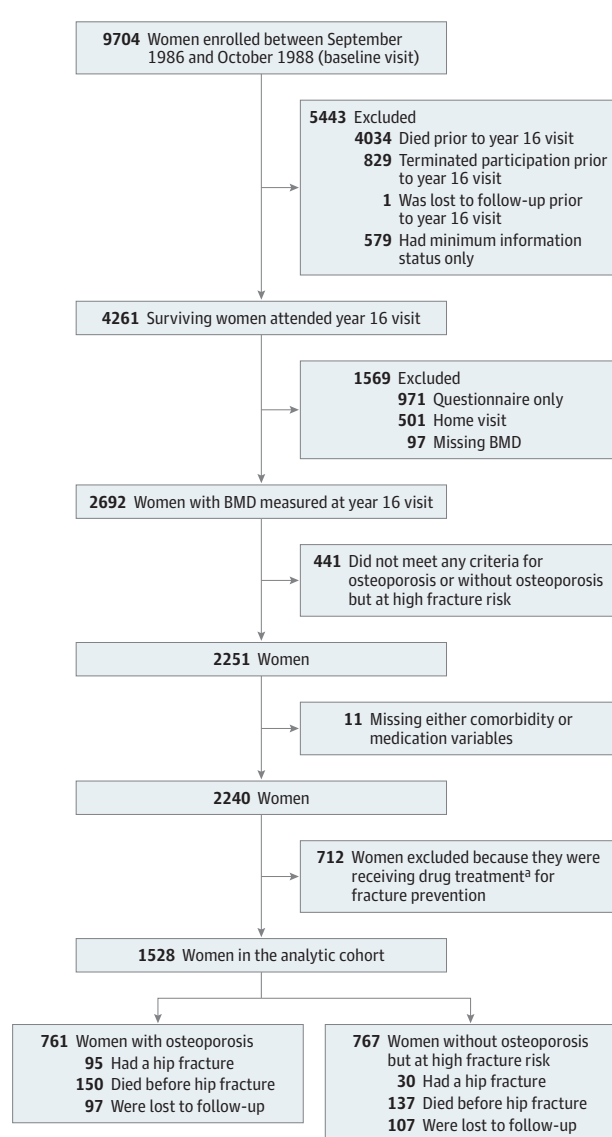
From 2002 to 2004, all active surviving women were invited to participate in the year 16 (Y16) visit; 4261 women in the original cohort (88% of active surviving participants) had at least questionnaire data collected at Y16. Of these, 2692 completed an in-clinic examination including measurement of hip BMD. The analytical cohort for this study consisted of 1528 treatment-naïve women who met study criteria for either osteoporosis ($n = 761$) or without osteoporosis but at high fracture risk ($n = 767$) (**Figure**). All analysis was performed between March 2018 and January 2019.

Human subjects review committees at each participating institution reviewed and approved the study. Each participant provided written informed consent.

Ascertainment of Clinical Fractures and Mortality

Participants or their proxies were contacted every 4 months after SOF baseline examination to ascertain vital status and ask about clinical fractures; over 95% of these contacts among active surviving participants in the SOF cohort were completed during a maximum of 29.9 years of follow-up. Self-reported fracture events were confirmed with radiographic reports. Deaths were verified with death certificates. Participants in this

Figure. Participant Enrollment Flow Diagram



BMD indicates bone mineral density.

^a Women taking estrogen, bisphosphonates, or raloxifene were excluded (no women were taking an anabolic agent).

analysis were followed up for a maximum of 5 years after the Y16 examination (mean [SD] follow-up time to event or censoring, 4.4 [1.1] years) to ascertain the incident outcomes of confirmed hip fractures and deaths. A 5-year follow-up period was used because randomized trials in postmenopausal women with clinically recognized osteoporosis have demonstrated a benefit of drug treatment in reducing hip fracture risk during this time frame, and data suggest that among 80-year-old women, the first hip fracture will occur, on average, within the next 5 years.⁸

Measurements

At the Y16 examination, participants were asked about lifestyle behaviors, health status, previous falls, selected medi-

cal conditions diagnosed by a physician, and difficulty performing basic and instrumental activities of daily living. Participants were asked to bring all drug containers used within the preceding 30 days with them to the clinic visit. Drugs were identified and recorded by clinic staff and an electronic drugs inventory database.¹⁷ Body weight and height were measured. The BMD of the total hip including femoral neck sub-region was measured using dual energy x-ray absorptiometry. The BMD T-scores at these sites were calculated on the basis of the mean and SD obtained from the NHANES III white female reference population aged 20 to 29 years.^{18,19} Information about race/ethnicity, parental history of hip fracture and fractures since age 50 was obtained at the baseline examination. To calculate the US predicted 10-year probabilities of hip and major osteoporotic fracture at Y16, data on clinical risk factors and femoral neck BMD for each participant were transmitted in a confidential manner in 2017 to the Centre for Metabolic Bone Diseases, University of Sheffield, England, where the probabilities were computed using the Fracture Risk Assessment²⁰ (FRAX) tool with BMD (version 3.12). The FRAX tool is a computer-based algorithm that uses selected clinical risk factors and country specific data with or without femoral neck BMD to estimate 10-year probability of fracture.

Determination of prevalent radiographic vertebral fractures on lateral thoracic and lumbar spine radiographs performed at the SOF baseline examination was made using vertebral morphometry; a woman was classified as having a prevalent radiographic vertebral fracture if any 1 of the ratios of morphometric vertebral heights was more than 4 standard deviations below the mean population norm for that vertebral level.²¹

Participant Strata

The definition of osteoporosis used in this study was a femoral neck or total hip bone BMD T-score of -2.5 or lower at the Y16 examination, presence of 1 or more prevalent radiographic vertebral fractures at the original SOF baseline examination, or an incident confirmed hip or clinical vertebral fracture between the SOF baseline and Y16 examinations. These criteria were used to indicate the presence of osteoporosis because guidelines¹⁰⁻¹³ universally recommend initiation of drug treatment among adults 50 years and older with clinically recognized osteoporosis defined by a BMD T-score of -2.5 or lower, vertebral fracture, or hip fracture.²²

Using expanded NBHA diagnostic criteria,¹³ women who did not meet the definition of osteoporosis were classified as being without osteoporosis but at high fracture risk if (1) they had osteopenia (femoral neck or total hip bone BMD T-score between -2.5 and -1.0) at the Y16 examination and predicted 10-year probability of hip or major osteoporotic fracture calculated using FRAX²⁰ tool at or above the NOF intervention threshold ($\geq 3\%$ for hip fracture or $\geq 20\%$ for major osteoporotic fracture),¹⁴ or (2) if they experienced a confirmed distal forearm, proximal humerus, or pelvis fracture between the SOF baseline and Y16 examinations. The FRAX intervention thresholds endorsed by NOF and NBHA were determined from the results of 1 cost-effectiveness analysis²³ that assumed that treatment effectiveness does not depend on BMD. While the FRAX

Table 1. Baseline Characteristics of Women With Osteoporosis and Women Without Osteoporosis But at High Fracture Risk

Characteristic	Participants, No. (%)			P Value
	All Women (n = 1528)	Women With Osteoporosis (n = 761)	Women Without Osteoporosis but at High Fracture Risk (n = 767) ^a	
Age, mean (SD), y	84.1 (3.39)	84.8 (3.74)	83.3 (2.82)	<.001
Self-reported health, fair/poor/very poor	327 (21.4)	177 (23.3)	150 (19.6)	.08
Current tobacco use	38 (2.5)	21 (2.8)	17 (2.2)	.52
≥2 Falls in past year	275 (18.1)	132 (17.4)	143 (18.7)	.52
Polypharmacy ^b	230 (15.1)	108 (14.2)	122 (15.9)	.35
No. of comorbidities ^c				.25
None	441 (28.9)	222 (29.2)	219 (28.6)	
1	530 (34.7)	247 (32.5)	283 (36.9)	
2	283 (18.5)	145 (19.1)	138 (18.0)	
≥3	274 (17.9)	147 (19.3)	127 (16.6)	
Prognostic index				<.001
4-5	251 (16.4)	88 (11.6)	163 (21.3)	
6-7	439 (28.7)	192 (25.2)	247 (32.2)	
8-9	434 (28.4)	235 (30.9)	199 (25.9)	
10-13	338 (22.1)	200 (26.3)	138 (18.0)	
≥14	66 (4.3)	46 (6.0)	20 (2.6)	
Difficulty				
Walking ≥2 blocks	475 (31.3)	267 (35.3)	208 (27.3)	<.001
Preparing meals	75 (4.9)	50 (6.6)	25 (3.3)	.003
Doing household chores	302 (19.9)	174 (23.0)	128 (16.7)	.002
Bathing	93 (6.1)	54 (7.1)	39 (5.1)	.10
BMI, mean (SD)	26.6 (4.7)	25.4 (4.5)	27.7 (4.5)	<.001
Gait speed, mean (SD), m/s	0.85 (0.22)	0.84 (0.22)	0.87 (0.21)	<.001
Femoral neck BMD T-score, mean (SD)	-2.24 (0.74)	-2.69 (0.65)	-1.79 (0.51)	<.001

Abbreviations: BMD, bone mineral density; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; NOF, National Osteoporosis Foundation.

^aAmong the 767 women without osteoporosis at high fracture risk, 748 (97.5%) had osteopenia and an estimated 10-year fracture probability at or above FRAX (Fracture Risk Assessment) intervention thresholds proposed by NOF.

^bRegularly taking 7 or more medications.

^cComorbid medical conditions included congestive heart failure, myocardial infarction, ischemic heart disease (angina), stroke, diabetes, chronic obstructive pulmonary disease/asthma, breast cancer, colorectal cancer, lung cancer, osteoarthritis, rheumatoid arthritis, depression, Alzheimer disease/other dementia, and parkinsonism.

tool is most commonly endorsed in the United States for clinical decision making, a systematic review of studies in postmenopausal women²⁴ concluded that no available fracture risk assessment tool is optimal and that simple tools perform as well as more complex ones such as FRAX.

Assessment of Comorbid Conditions and Prognosis

The number of comorbid conditions at Y16 was defined by a count of 14 selected self-reported conditions (footnote, **Table 1**).

Prognosis at Y16 was estimated by calculating an index using components identical or very similar to those of a validated mortality prediction index designed for use by clinicians advising older community-dwelling patients and relying on easily obtained measures.²⁵ Components included age, sex, specific comorbid conditions, body mass index, and difficulty performing basic and instrumental activities of daily living. The index (range, 0-21 points) has shown excellent discrimination for prediction of 4-year mortality in community-dwelling adults 50 years or older with a score of 14 or more points predicting a 64% probability of death during this time period.

Statistical Analysis

Characteristics of the 1528 women were compared between women with osteoporosis and women without osteoporosis

but at high fracture risk and across subgroups defined by comorbidity count or prognostic index. These analyses used analysis of variance for normally distributed continuous variables; the χ^2 test or Fisher exact test was used for categorical data. Similarly, we compared characteristics of the 1528 women by type of event (hip fracture, death prior to experiencing hip fracture, end of 5-year follow-up period).

The absolute probabilities of hip fracture during follow-up were estimated for women with osteoporosis and women without osteoporosis but at high fracture risk using the cumulative incidence function that considers mortality as a competing risk.²⁶ In addition, within each of these 2 mutually exclusive participant strata, we calculated hip fracture probability by category of comorbidity count and prognostic index.

Results

Among the 2692 women attending the Y16 examination with measurement of hip BMD (mean femoral neck T-score -1.9), 2251 (83.6%) were identified as potential candidates for drug treatment for fracture prevention according to criteria proposed by the NBHA (1121 with osteoporosis and 1130 without osteoporosis but at high fracture risk) (Figure). Of these, 1528

Table 2. Characteristics of Study Participants by Type of Event

Characteristic	Participants, No. (%)				P Value
	Event				
	All Women (n = 1528)	Hip Fracture (n = 125)	Death Prior to Experiencing Hip Fracture (n = 287)	Survived Free of Hip Fracture (n = 1116)	
Age, mean (SD)	84.1 (3.4)	85.5 (3.7)	85.3 (3.8)	83.6 (3.1)	<.001
Self-reported health, fair/poor/very poor	327 (21.4)	31 (24.8)	85 (29.6)	211 (18.9)	<.001
Current tobacco use	38 (2.5)	4 (3.2)	14 (4.9)	20 (1.8)	.01
≥2 Falls in past year	275 (18.1)	34 (27.4)	68 (23.8)	173 (15.5)	<.001
Polypharmacy ^a	230 (15.1)	22 (17.6)	61 (21.3)	147 (13.2)	.002
No. of comorbidities					<.001
None	441 (28.9)	32 (25.6)	62 (21.6)	347 (31.1)	
1	530 (34.7)	44 (35.2)	84 (29.3)	402 (36.0)	
2	283 (18.5)	20 (16.0)	67 (23.3)	196 (17.6)	
≥3	274 (17.9)	29 (23.2)	74 (25.8)	171 (15.3)	
Prognostic index					<.001
4-5	251 (16.4)	10 (8.0)	21 (7.3)	220 (19.7)	
6-7	439 (28.7)	24 (19.2)	58 (20.2)	357 (32.0)	
8-9	434 (28.4)	38 (30.4)	88 (30.7)	308 (27.6)	
10-13	338 (22.1)	41 (32.8)	99 (34.5)	198 (17.7)	
≥14	66 (4.3)	12 (9.6)	21 (7.3)	33 (3.0)	
Difficulty					
Walking ≥2 blocks	475 (31.3)	53 (42.4)	130 (45.9)	292 (26.3)	<.001
Preparing meals	75 (4.9)	9 (7.2)	25 (8.8)	41 (3.7)	<.001
Doing household chores	302 (19.9)	31 (25.0)	79 (27.9)	192 (17.3)	<.001
Bathing	93 (6.1)	14 (11.2)	26 (9.2)	53 (4.8)	.001
BMI, mean (SD)	26.6 (4.7)	24.9 (4.1)	26.2 (4.9)	26.9 (4.6)	<.001
Gait speed, m/s, mean (SD)	0.85 (0.22)	0.81 (0.20)	0.77 (0.20)	0.88 (0.22)	<.001
Femoral neck BMD T-score, mean (SD)	-2.24 (0.74)	-2.63 (0.73)	-2.32 (0.76)	-2.18 (0.72)	<.001

Abbreviations: BMD, bone mineral density; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

^aRegularly taking 7 or more medications.

treatment-naïve women were included in the analytical cohort (761 with osteoporosis and 767 without osteoporosis at high fracture risk). Among the 761 women with osteoporosis, 545 (71.6%) had no history of confirmed hip or vertebral fracture, but qualified for this group based on a BMD-T score of -2.5 or lower. Of the 767 women without osteoporosis but at high fracture risk, 748 (97.5%) qualified for this group based on BMD T-score between -2.5 and -1.0 and a fracture probability at or above FRAX intervention thresholds proposed by NOF; 19 qualified only on the basis of a history of confirmed wrist, pelvis, or humerus fracture.

Mean (SD) age at the Y16 examination among the cohort of 1528 potential candidates for initiation of drug treatment for fracture prevention was 84.1 (3.4) years, and mean (SD) femoral neck BMD T-score was -2.24 (0.74) (Table 1). A total of 274 (17.9%) women had 3 or more comorbid medical conditions, and 66 (4.3%) had poor prognosis as indicated by a prognostic index of 14 or more points. The distribution of the number of comorbidities was similar between women with osteoporosis and women without osteoporosis but at high fracture risk, but women with osteoporosis were more likely to have a higher prognostic index indicative of poorer prognosis. As expected, several traditional risk factors for hip fracture and mortality were increasingly common among women with a greater

number of comorbid conditions (eTable 1 in the Supplement) or poorer prognosis (eTable 2 in the Supplement).

During the average follow-up of 4.4 years after the Y16 examination, 125 (8.8%) women experienced a hip fracture (95 with osteoporosis and 30 without osteoporosis but at high fracture risk), and 287 (18.8%) died prior to experiencing this outcome (150 with osteoporosis and 137 without osteoporosis but at high fracture risk). Characteristics of women with incident hip fracture, women who died prior to experiencing hip fracture, and women who survived free of hip fracture are listed in Table 2.

The 5-year absolute probability of mortality was 24.9% (95% CI, 21.8%-28.1%) among women with osteoporosis and 19.4% (95% CI, 16.6%-22.3%) among women without osteoporosis but at high fracture risk (Table 3). Mortality probability steadily increased in a graded manner with greater comorbidities and poorer prognosis in both groups of women. In contrast, the 5-year hip fracture probability taking into account the competing risk of death was over 3-fold higher among women with osteoporosis compared with women without osteoporosis but at high fracture risk (13.0% [95% CI, 10.7%-15.5%] vs 4.0% [95% CI, 2.8%-5.6%]). This difference between groups in hip fracture (but not mortality) probabilities was even more pronounced in women with a greater number

Table 3. Five-Year Probability of Mortality and Hip Fracture Among Women With Osteoporosis and Women Without Osteoporosis but at High Fracture Risk

Characteristic	All-Cause Mortality, % (95% CI)		Hip Fracture, ^a % (95% CI)	
	With Osteoporosis (n = 761) ^b	Without Osteoporosis but at High Fracture Risk (n = 767) ^c	With Osteoporosis (n = 761) ^b	Without Osteoporosis but at High Fracture Risk (n = 767) ^c
All women	24.9 (21.8-28.1)	19.4 (16.6-22.3)	13.0 (10.7-15.5)	4.0 (2.8-5.6)
No. of comorbidities				
None	19.7 (15.2-24.7)	12.6 (9.6-15.9)	13.0 (9.4-17.1)	1.9 (1.3-2.9)
1	20.4 (16.1-25.1)	16.1 (12.7-19.7)	12.7 (9.4-16.5)	5.1 (3.2-7.5)
2	29.4 (22.1-37.1)	23.7 (17.3-30.6)	8.0 (5.4-11.3)	6.7 (3.3-11.8)
≥3	36.1 (28.2-44.0)	34.4 (25.8-43.0)	18.1 (12.3-24.9)	2.5 (1.3-4.2)
Prognostic Index, points				
4-5	11.6 (7.5-16.7)	7.6 (5.6-10.0)	7.0 (4.5-10.3)	2.5 (1.7-3.7)
6-7	16.2 (12.2-20.8)	13.2 (10.3-16.5)	11.6 (8.5-15.2)	1.2 (1.0-1.6)
8-9	25.2 (20.0-30.8)	22.3 (17.2-27.9)	13.0 (9.9-16.6)	4.2 (2.8-6.1)
10-13	34.1 (27.4-41.0)	37.1 (28.8-45.4)	14.2 (10.5-18.5)	10.4 (6.0-16.3)
≥14	46.7 (31.4-60.6)	40.4 (18.9-61.1)	25.3 (13.4-39.0)	5.0 (1.1-13.9)

^aCalculated using cumulative incidence function accounting for competing risk of mortality.

^bOf the 761 women with osteoporosis, 95 (12.5%) experienced a hip fracture and 150 (19.7%) died before experiencing this event.

^cOf the 767 women without osteoporosis but at high fracture risk, 30 (3.8%) experienced a hip fracture and 137 (17.9%) died before experiencing this event.

of comorbidities or poorer prognosis. Among women with 3 or more comorbidities, hip fracture probability was 18.1% (95% CI, 12.3%-24.9%) among women with osteoporosis vs 2.5% (95% CI, 1.3%-4.2%) among women without osteoporosis but at high fracture risk, while their probabilities of mortality were similar (36.1% [95% CI, 28.2%-44.0%] among women with osteoporosis vs 34.4% [95% CI, 25.8%-43.0%] among women without osteoporosis but at high fracture risk). Among women with osteoporosis and a prognostic index of 14 or more points, the probability was 46.7% (95% CI, 31.4%-60.6%) for mortality and 25.3% (95% CI, 13.4%-39.0%) for hip fracture. In contrast, among women without osteoporosis but at high fracture risk, the mortality probability (40.4% [95% CI, 18.9%-61.1%]) far outweighed the probability of hip fracture (5.0% [95% CI, 1.1%-13.9%]) among those with a prognostic index of 14 or more points.

Discussion

In this cohort of women 80 years and older, women with osteoporosis including those with more comorbidities or poorer prognosis had a high 5-year probability of hip fracture even after accounting for the competing risk of mortality. In contrast, among women identified as high fracture risk but without osteoporosis, the 5-year hip fracture probability was substantially lower, especially among those individuals with more comorbidities or poorer prognosis for whom the probability of death vastly outweighed the probability of hip fracture.

We observed a 5-year hip fracture probability of 13% among community-dwelling women 80 years and older with osteoporosis even after considering their competing risk of mortality. This finding suggests that initiation of drug treatment in late-life women with osteoporosis may still be effective in the prevention of subsequent hip fracture; results of previous fracture prevention trials²⁷⁻³⁰ have demonstrated that the time horizon to benefit is less than 5 years. Despite accounting for their

higher competing risk of death, the cumulative probability of hip fracture at 5 years was greater among women with osteoporosis and more comorbidities or worse prognosis compared with women with osteoporosis and fewer comorbidities or better prognosis. If drug therapy is equally effective in women 80 years and older as in postmenopausal women younger than 80 years, these results suggest that the absolute benefit of treatment in preventing hip fracture in late-life women may be greatest among those women with osteoporosis and substantial comorbidity burden or limited life expectancy, because these characteristics, while predictive of mortality, are also strongly associated with hip fracture risk.

Unfortunately, there is a paucity of data in late-life women supporting efficacy of pharmacologic therapy for fracture prevention. Large randomized placebo-controlled trials of 3 to 4 years of alendronate treatment in postmenopausal women with low BMD^{27,28} excluded women older than 80 years. A 3-year randomized clinical trial³¹ of risedronate vs placebo that enrolled 3886 women 80 years and older (mean age 83 years) primarily selected on the basis of 1 or more nonskeletal risk factors for hip fracture found no effect of risedronate on hip fracture risk. In contrast, a 3-year trial²⁹ of an annual infusion of zoledronic acid vs placebo in 7765 postmenopausal women with osteoporosis aged 65 to 89 years (mean age 73 years) reported a reduction in risk of any clinical fracture including hip fracture with treatment. In this trial, the effect of zoledronic acid on risk of hip fracture (but not any clinical fracture) depended on baseline age; there was a significant interaction between treatment assignment and age with a reduction in hip fracture risk among women younger than 75 years, but not among women 75 years and older.³² A trial³³ of zoledronic acid vs placebo in 2127 adults age 50 years or older (mean age 74 years, 76% women) with recent low-trauma hip fracture reported a significant reduction in subsequent risk of any clinical (but not hip) fracture at 2 years. Similarly, a recently published trial³⁴ of zoledronic acid vs placebo in 2000 women aged 65 years or older (mean age 71 years) with osteopenia (13% with

prevalent radiographic vertebral fractures and 8% with 1 BMD T-score -2.5 or lower) reported a reduction in risk of any clinical (but not hip) fracture at 6 years with treatment. Three years of denosumab treatment compared with placebo reduced the risk of hip fracture in 7868 women with osteoporosis between the ages of 60 and 90 years (mean age 72 years).³⁰ However, none of these trials examined treatment efficacy by age group. Shorter-term placebo-controlled trials^{35,36} of anabolic agents in postmenopausal osteoporotic women with osteoporosis (mean age 69 years in both trials) did not report the effect of treatment on hip fracture risk. Importantly, late-life women with multimorbidity have been underrepresented in all previous fracture-prevention trials; no trials have reported whether treatment effect is modified by the presence of comorbidity burden. Thus, there is a critical need for a better evidence base to inform clinical decision making regarding whether to initiate drug treatment for fracture prevention in women with osteoporosis in the ninth decade of life, including among those with more comorbid conditions or poorer prognosis. While ethical concerns may preclude the conduct of randomized placebo-controlled trials, observational studies such as the present investigation that carefully apply methods to minimize inherent biases can provide insight on absolute benefits vs risks of drug treatment in this patient population.³⁷

We found a much lower 5-year hip fracture probability (4%) among late-life women without osteoporosis who were identified as high fracture risk on the basis of having osteopenia and a 10-year predicted fracture probability at or above FRAX intervention thresholds proposed by the NOF. These results suggest that the absolute benefit of drug treatment to prevent hip fracture is likely to be far less in this patient population because the probability of death greatly outweighed the probability of hip fracture, especially among those with more comorbidities or poorer prognosis. Expanding the indication from women with osteoporosis to women meeting the broadened criteria recommended by NOF and NBHA resulted in a 2-fold rise (41.6% to 83.6%) in the proportion of late life-women identified as treatment candidates. These findings are in agreement with recently reported findings in 202 US women aged 80 years and older enrolled in the 2005 to 2008 National Health and Nutrition Examination Survey (NHANES).¹⁵ Prior to expanding treatment indications, randomized clinical trials are warranted to evaluate the efficacy of treatment in reducing the absolute risk of hip and clinical fractures in this substantial patient group, including among those with more comorbid conditions or worse prognosis.

Most,^{1-6,38} but not all,³⁹⁻⁴² studies of osteoporosis management patterns that typically rely on a claims-based diagnosis of fracture to identify the presence of osteoporosis have reported that older age is associated with lower rates of use of drug treatment to prevent future fractures. Specific causes of this widening treatment gap with advancing age are uncertain, but this gap is at least in part due to the failure of osteoporosis treatment guidelines to provide evidence or guidance for osteoporosis management in older patients with multimorbidity.

Limitations

The present study has several strengths, including the well-characterized large cohort of women late in life and rigorous and nearly complete ascertainment of fractures and vital status. However, this study has limitations. The cohort included community-dwelling white women, and results may not be generalizable to women of other racial/ethnic groups, men, or those residing in institutions. However, mean femoral neck BMD of SOF women attending the year 16 examination was essentially identical to that of a nationally representative sample of community-dwelling women 80 years and older enrolled in the 2005 to 2008 NHANES.⁴³ In addition, 75% of hip fractures each year in the United States occur among women, with white women accounting for 90% of women with hip fractures.⁴⁴ Hip BMD, but not spine BMD, was measured. While the diagnosis of osteoporosis can also be made by the presence of a BMD T-score of -2.5 or lower at lumbar spine, measurement at the hip is preferred for the diagnosis, especially among the aged population.²² Our findings among women without osteoporosis but at high fracture risk are limited to the FRAX intervention thresholds proposed by NOF and do not necessarily apply to strategies proposed in other countries.

Conclusions

In conclusion, late-life women with osteoporosis, including those with comorbidities or poorer prognosis, have a high hip fracture probability despite accounting for competing mortality risk and may still be drug treatment candidates to prevent future hip fracture. The absolute treatment benefit is likely lower among women without osteoporosis but at high fracture risk because mortality probability markedly outweighs probability of hip fracture in this group, especially among those with multiple comorbidities or worse prognosis.

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