RESEARCH

Implications of expanding indications for drug treatment to prevent fracture in older men in United States: cross sectional and longitudinal analysis of prospective cohort study

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Kristine E Ensrud *professor*[1] *core investigator*[2], Brent C Taylor *associate professor*[1] *core investigator*[2], Katherine W Peters *statistician*[3], Margaret L Gourlay *assistant professor*[4], Meghan G Donaldson *research associate*[5], William D Leslie *professor*[6], Terri L Blackwell *statistician*[3], Howard A Fink *associate professor*[1] *core investigator*[2], Eric S Orwoll *professor*[7], John Schousboe *rheumatologist*[8] *assistant professor*[9], for the Osteoporotic Fractures in Men (MrOS) Study Group

[1]Department of Medicine and Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA; [2]Center for Chronic Disease Outcomes Research, VA Health Care System, Minneapolis, MN, USA; [3]California Pacific Medical Center Research Institute, San Francisco, CA, USA; [4]Department of Family Medicine, University of North Carolina, Chapel Hill, NC, USA; [5]Centre for Clinical Epidemiology and Evaluation, University of British Columbia, Vancouver, BC, Canada; [6]Department of Medicine, University of Manitoba, Winnipeg, MB, Canada; [7]Bone and Mineral Unit, Oregon Health and Science University, Portland, OR, USA; [8]Park Nicollet Clinic, St Louis Park, MN, USA; [9]Division of Health Policy and Management, University of Minnesota, Minneapolis, MN, USA

Abstract

Objectives To quantify incremental effects of applying different criteria to identify men who are candidates for drug treatment to prevent fracture and to examine the extent to which fracture probabilities vary across distinct categories of men defined by these criteria.

Design Cross sectional and longitudinal analysis of a prospective cohort study.

Setting Multicenter Osteoporotic Fractures in Men (MrOS) study in the United States.

Participants 5880 untreated community dwelling men aged 65 years or over classified into four distinct groups: osteoporosis by World Health Organization criteria alone; osteoporosis by National Osteoporosis Foundation (NOF) but not WHO criteria; no osteoporosis but at high fracture risk (at or above NOF derived FRAX intervention thresholds recommended for US); and no osteoporosis and at low fracture risk (below NOF derived FRAX intervention thresholds recommended for US).

Main outcome measures Proportion of men identified for drug treatment; predicted 10 year probabilities of hip and major osteoporotic fracture calculated using FRAX algorithm with femoral neck bone mineral density; observed 10 year probabilities for confirmed incident hip and major osteoporotic (hip, clinical vertebral, wrist, or humerus) fracture events calculated using cumulative incidence estimation, accounting for competing risk of mortality.

Results 130 (2.2%) men were identified as having osteoporosis by using the WHO definition, and an additional 422 were identified by applying the NOF definition (total osteoporosis prevalence 9.4%). Application of NOF derived FRAX intervention thresholds led to 936 (15.9%) additional men without osteoporosis being identified as at high fracture risk, raising the total prevalence of men potentially eligible for drug treatment to 25.3%. Observed 10 year hip fracture probabilities were 20.6% for men with osteoporosis by WHO criteria alone, 6.8% for men with osteoporosis by NOF (but not WHO) criteria, 6.4% for men without osteoporosis but classified as at high fracture risk, and 1.5% for men without osteoporosis and classified as at low fracture risk. A similar pattern was noted in observed fracture probabilities for major osteoporotic fracture. Among men with osteoporosis by WHO criteria, observed fracture probabilities were greater than FRAX predicted probabilities (20.6% *v* 9.5% for hip fracture and 30.0% *v* 17.4% for major osteoporotic fracture).

Conclusions and relevance Choice of definition of osteoporosis and use of NOF derived FRAX intervention thresholds have major effects on the proportion of older men identified as warranting drug treatment to prevent fracture. Among men identified with osteoporosis by WHO criteria, who comprised 2% of the study population, actual observed fracture probabilities during 10 years of follow-up were highest and exceeded FRAX predicted fracture probabilities. On the basis of findings from randomized trials in women, these men are most likely to benefit from treatment. Expanding indications for treatment beyond this small group has uncertain value owing to lower observed fracture probabilities

Correspondence to: K E Ensrud, One Veterans Drive (111-0), Minneapolis, MN 55417, USA ensru001@umn.edu

and uncertain benefits of treatment among men not selected on the basis of WHO criteria.

Introduction

Older men experience 29% of the fractures among adults aged 50 years and older in the United States and account for 25% of fracture related costs.[1] Many of these fractures occur at sites associated with low bone mineral density, increase in incidence after age 50 years, and are considered to be related to osteoporosis.[2 3] However, the best strategy to identify men who are candidates for drug treatment to prevent fracture is uncertain, in part because the cut-off value for bone mineral density to identify osteoporosis is less well defined in men than in women.[4] The diagnosis of osteoporosis in both men and women endorsed by the World Health Organization is based on the cut-off value of femoral neck bone mineral density used in women (T score –2.5 or lower at the femoral neck, calculated using the young white female normal reference database).[5 6] In contrast, the diagnosis of osteoporosis in men endorsed by the National Osteoporosis Foundation (NOF)[7 8] and adopted by some,[9] but not all,[10] US professional societies is defined as a T score of –2.5 or lower at the femoral neck, total hip, or lumbar spine, calculated using the young white male normal reference base. Use of the NOF's definition increases the apparent prevalence of osteoporosis in men, but controversy exists regarding whether this effect is modest or substantial.[11 12]

Randomized trials in men have shown that drug treatment increases bone mineral density,[13-17] but the efficacy of drugs in preventing clinical fracture events (that is, symptomatic fractures coming to medical attention) in men is unknown. The efficacy of drug treatment in reducing the risk of clinical fractures has been demonstrated only in postmenopausal women with osteoporosis defined by a female specific bone mineral density T score of –2.5 or lower or with existing radiographic vertebral fractures,[18] with the exception of one randomized trial of zoledronic acid in patients with recent hip fracture (75% of whom were women, 42% with osteoporosis by WHO criteria) that reported efficacy of treatment in reducing future fracture events.[19] Although osteoporosis by WHO criteria identifies postmenopausal women who benefit from drug treatment to lower the risk of clinical fractures, many postmenopausal women and older men with bone mineral density T scores above –2.5 will subsequently experience clinical fracture events.[20] This common occurrence has prompted efforts to derive estimates of the absolute risk of fracture for use in making decisions about whether to recommend starting drug treatment in men, as well as women.

The FRAX algorithm is a publicly available web based tool that uses clinical risk factors and country specific data, with or without consideration of femoral neck bone mineral density measurement, to estimate an individual patient's 10 year probabilities of hip and major osteoporotic fractures (defined by FRAX as clinical vertebral, forearm, hip, or proximal humerus fracture).[21-23] The development of the FRAX tool has been advocated by several organizations,[7-9 24] supported in part by funding from the pharmaceutical industry,[25-27] which have advocated the use of FRAX in clinical decision making to identify high risk candidates for drug treatment to prevent fracture. This has promoted a shift in treatment approach in many practice settings from one based primarily on measurement of bone mineral density to an approach based on absolute risk of fracture.

Use of FRAX in clinical practice demands a consideration of the probability of fracture at which to intervene.[28] On the basis of a cost effectiveness analysis,[29] the NOF in 2010 recommended

FRAX intervention thresholds of 3% for hip fracture and 20% for major osteoporotic fracture as cut points for starting drug treatment in US adults aged 50 years and older. However, a critical unproved assumption in this analysis is that drug treatment reduces risk of clinical fractures by 35% regardless of bone mineral density or the presence of existing vertebral fractures. Despite the controversies in identifying osteoporosis in men and lack of data on the efficacy of treatment in preventing clinical fracture events in populations other than postmenopausal women with osteoporosis as defined by WHO criteria or with existing vertebral fractures, current US treatment guidelines recommend starting drug treatment to prevent fracture in men with a history of hip or vertebral fracture, men with male specific bone mineral density T scores at or below –2.5, and men with a male specific bone mineral density T score between –1.0 and –2.5 who are at or above NOF derived FRAX intervention thresholds.

We used data collected in 5880 untreated, community dwelling US men aged 65 years or above enrolled in the prospective Osteoporotic Fractures in Men (MrOS) study to determine the incremental effects of broadening the definition of osteoporosis and use of NOF derived FRAX intervention thresholds on the proportion of older men identified as candidates for drug treatment for fracture prevention. We also compared observed and predicted 10 year fracture probabilities within distinct groups identified by osteoporosis status and fracture risk category.

Methods

Study population

From 2000 through 2002, 5994 men who were aged at least 65 years were recruited for participation in the baseline examination of the Osteoporotic Fractures in Men (MrOS) study.[30 31] The enrollment criteria were designed to recruit a cohort that represented the characteristics of community dwelling older men residing in the United States. Men were recruited from population based listings in six regions (Birmingham, Alabama; the Monongahela Valley near Pittsburgh, Pennsylvania; Minneapolis, Minnesota; Palo Alto, California; San Diego, California; and Portland, Oregon). Men with a history of bilateral hip replacement, men who were unable to walk without the assistance of another person, and men with a medical condition (in the judgment of the investigator) that would result in imminent death were excluded. The cohort for this analysis comprised the 5880 men not taking bisphosphonates at the baseline examination with hip and spine bone mineral density measurements, assessment of FRAX clinical risk factors, and incident fracture ascertainment during 10 years of follow-up.

Clinical risk factors and bone mineral density

Participants were asked at the baseline examination about race/ethnicity, history of fracture since the age of 50, diagnosis by a physician of rheumatoid arthritis, parental history of hip fracture, smoking status, and alcohol intake. 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 the clinic staff, and the information was stored in an electronic drugs inventory database.[32]

Measurements of body weight and height were used to calculate a standard body mass index. Bone mineral density of the lumbar spine and total hip including the femoral neck subregion was measured using dual energy x ray absorptiometry (QDR 4500W, Hologic, Waltham, MA).[31 33] As recommended by WHO,[6] female specific T scores at the femoral neck were calculated on the

basis of the mean and standard deviation obtained from the third National Health and Nutrition Examination Survey (NHANES III) white female reference population aged 20-29 years.[34] [35] A female specific T score at the femoral neck of –2.5 or below corresponds to an absolute value of 0.558 g/cm^2 or lower. As recommended by US professional societies including the NOF,[7-9] [36] male specific T scores at the femoral neck and total hip were calculated on the basis of means and standard deviations obtained from the NHANES III white male reference population aged 20-29 years,[35] and male specific T scores at the lumbar spine were calculated on the basis of the mean and standard deviation obtained from the densitometer manufacturer's reference database for 30 year old white men.[37] A male specific T score of –2.5 or below, as referenced in the US treatment guidelines, corresponds to an absolute value of 0.592 g/cm^2 or lower at the femoral neck, 0.681g/cm^2 or lower at the total hip, or 0.816 g/cm^2 or lower at the total lumbar spine (lumbar vertebra 1-4).

Information on bisphosphonate use (any use within the previous 30 days) was also collected during the 10 year follow-up period at the following time points: first interim questionnaire (mean 2.0 (SD 0.2) years after baseline examination), first sleep examination (3.4 (0.5) years), second examination (4.6 (0.4) years), third examination (6.9 (0.4) years), second interim questionnaire (8.9 (0.4) years), and second sleep examination (9.9 (0.8) years).

FRAX tool and 10 year predicted fracture probabilities

The FRAX web based tool is publicly available and can be used for free by providers and patients. For example, when a provider sees a patient, the provider or a designated staff member can enter the FRAX clinical risk factor values (components) into the web based tool, which instantly calculates the 10 year predicted probabilities of hip fracture and major osteoporotic fracture (defined by FRAX as hip, clinical vertebral, wrist, or proximal humerus fracture). However, the specific equations and algorithms developed by the WHO Collaborating Centre for Metabolic Bone Disease, University of Sheffield, UK that generate predicted FRAX fracture probabilities to make calculation of the FRAX probabilities for all individuals in a large population feasible have not been published. Thus, to calculate the US FRAX 10 year predicted probabilities of hip and major osteoporotic fracture for all 5800 men in this study, we transmitted data for each participant on FRAX clinical risk factors (age, sex, race/ethnicity, body mass index, history of fracture, parental history of hip fracture, smoking and alcohol consumption, use of oral glucocorticoids, and history of rheumatoid arthritis, and femoral neck bone mineral density data (absolute value in g/cm^2)) in a confidential and secure manner to the WHO center, where the probabilities were computed using FRAX models with bone mineral density (version 3.3).

If data were missing on any of the clinical characteristics (other than age, race/ethnicity, body mass index, and bone mineral density, for which none of the 5880 men had missing data), we used the default (no) value, as is recommended by the WHO center.[21] For example, if smoking status was missing for a participant, we classified the participant as a non-smoker. Data were 100% complete for all characteristics for 4285 men (73% of the cohort). By far the most common characteristic for which data were missing was "parental history of hip fracture," for which 1405 (24%) of men reported "don't know." Information on drugs used for the definition of "oral glucocorticoid use"

was missing for 238 (4%) men. Other risk factors had missing data for nine or fewer men.

Ascertainment of fractures

After the baseline examination, we contacted surviving participants every four months about fractures during the subsequent 10 year follow-up period. We selected a 10 year time point to match that specified by the FRAX tool. More than 99% of these follow-up contacts were completed. We confirmed fractures by review of radiographic reports. Incident fracture outcomes for this analysis included hip fracture and major osteoporotic fracture. Follow-up time for the analysis of a given fracture outcome ended at the date of the first fracture event, at the date of death, at the date of termination of participation in the MrOS study, or after 10 years of follow-up. Mean follow-up for the cohort was 8.6 (SD 2.5) years for hip fracture and 8.5 (2.6) years for major osteoporotic fracture. Of the 5880 men included in this study, 1634 (27.9%) died and 214 (3.6%) terminated before reaching 10 years of follow-up.

Statistical analysis

To clearly illustrate the incremental effect of both broadening the definition of osteoporosis and use of FRAX intervention thresholds on the proportion of the male population identified as candidates for treatment, we sequentially applied the WHO osteoporosis definition, the NOF osteoporosis definition, and NOF derived FRAX intervention thresholds to the 5880 men, resulting in four mutually exclusive groups: osteoporosis by WHO criteria alone; osteoporosis by NOF (but not WHO) criteria; no osteoporosis but at high risk of fracture (that is, male specific T score at femoral neck, lumbar spine, and total hip above –2.5 and predicted 10 year probability of hip fracture at least 3% or predicted 10 year probability of major osteoporotic fracture at least 20%); and no osteoporosis and at low risk of fracture (that is, male specific T score at femoral neck, lumbar spine, and total hip above –2.5, predicted 10 year probability of hip fracture less than 3%, and predicted 10 year probability of major osteoporotic fracture less than 20%).

We calculated observed 10 year probabilities of confirmed incident hip and major osteoporotic fracture events for each of the four groups by using cumulative incidence estimation, accounting for the competing risk of mortality.[38] We used FRAX models with femoral neck bone mineral density to estimate predicted 10 year probabilities for these two outcomes for each of the four groups.

In the primary analysis for calculating observed fracture probabilities, we retained men starting bisphosphonate treatment during the follow-up period in the cohort because censoring them at the time of starting treatment might lead to bias in the comparison of the observed and predicted fracture probabilities. To determine the effect of alternative approaches for handling treatment initiation, we did two sensitivity analyses. The first calculated observed fracture probabilities with censoring of men starting bisphosphonates during follow-up at the estimated time of initiation, and the second calculated observed fracture probabilities with treatment initiation considered as a competing risk. For the 426 men who started bisphosphonates during follow-up, the estimated time of initiation for a given participant was the midpoint between the last known time point when he was a non-user and the first time point when bisphosphonate use was recorded.

As the NOF guideline specifically recommends that drug treatment should be considered in men with low bone mineral density but not osteoporosis who are at or above the NOF

derived intervention threshold, we also did a secondary analysis limiting the "no osteoporosis but at high fracture risk" group (n=936) to the 859 men with a male specific bone mineral density T score between –1.01 and –2.49 and predicted 10 year probability of hip fracture of at least 3% or predicted 10 year probability of major osteoporotic fracture of at least 20%. Finally, we did sensitivity analyses limiting the cohort to the 4285 men with complete data on all clinical characteristics used in the calculation of FRAX 10 year fracture probabilities.

We used SAS version 9.2 for all analyses except those using cumulative incidence estimation, for which we used Stata version 12.1.

Results

Among the cohort of 5880 men, 130 (2.2%) were identified as having osteoporosis by using WHO criteria based on a female specific T score of –2.5 or below at the femoral neck. With subsequent application of the NOF definition, an additional 422 men were identified as having osteoporosis, resulting in a total prevalence of osteoporosis (based on male specific T score of –2.5 or below at the femoral neck, total hip, or lumbar spine) of 9.4%. Of these 422 men who met NOF (but not WHO) criteria for osteoporosis, 142 men had a male specific bone mineral density T score of –2.5 or below at the femoral neck (15 additional men were then subsequently identified owing to a male specific bone mineral density T score of –2.5 or below at the total hip, and finally 265 additional men were subsequently identified owing to a male specific T score of –2.5 or below at the lumbar spine). With subsequent application of the FRAX intervention thresholds proposed by the NOF, 936 (15.9%) additional men without osteoporosis by any criteria were identified as being at high risk of fracture, raising the total prevalence of men potentially eligible for drug treatment to 25.3%. Of these 936 men, 859 (91.8%) had a male specific bone mineral density T score between –1.01 and –2.49.

The mean age of men in the overall cohort was 73.6 (range 65-100) years. The table⇓ shows the characteristics of the cohort according to category of osteoporosis definition and fracture risk. In particular, among the 936 men without osteoporosis by WHO or NOF bone mineral density criteria but who were classified as being at high risk of fracture by virtue of their FRAX 10 year predicted fracture probabilities, the mean age and proportion with previous fracture were similar to those among the 130 men with osteoporosis by WHO criteria. Among this "no osteoporosis but at high fracture risk" group, 934 (99.8%) men had a FRAX 10 year probability of hip fracture of 3% or higher, but only 65 (6.9%) had a 10 year probability of major osteoporotic fracture of 20% or higher (63 men met both FRAX intervention thresholds, 871 men were identified on the basis of the 3% hip threshold alone, and two men were identified on the basis of the 20% major osteoporotic fracture threshold alone). Among the 130 men with osteoporosis by WHO criteria, 128 (98.5%) had a 10 year probability of hip fracture of 3% or higher and 30 (23.1%) had a 10 year probability of major osteoporotic fracture of 20% or higher (30 men met both FRAX intervention thresholds, 98 were identified on the basis of the 3% hip threshold alone, none was identified on the basis of the 20% major osteoporotic fracture threshold alone, and two met neither FRAX intervention threshold).

During the 10 year follow-up period, 177 (3.0%) men had a hip fracture. Observed hip fracture probabilities incrementally decreased across the groups defined by category of osteoporosis definition and fracture risk, ranging from 20.6% (osteoporosis by WHO criteria) to 6.8% (osteoporosis by NOF (but not WHO)

criteria), 6.4% (no osteoporosis but at high fracture risk), and 1.5% (no osteoporosis and at low fracture risk) (fig 1⇓). Among men with osteoporosis, the observed hip fracture probabilities were greater than the predicted probabilities. In men with osteoporosis by WHO criteria, the observed probability was 20.6% (95% confidence interval 14.0% to 28.0%) compared with the FRAX predicted probability of 9.5% (8.2% to 10.7%). On the other hand, the observed and predicted hip fracture probabilities were similar among men without osteoporosis, including those at high and those at low fracture risk.

A total of 429 (7.3%) men had a major osteoporotic fracture during the 10 year follow-up period. Observed fracture probabilities ranged from 30.0% (osteoporosis by WHO criteria) to 18.0% (osteoporosis by NOF (but not WHO) criteria), 12.0% (no osteoporosis but at high fracture risk), and 4.8% (no osteoporosis and at low fracture risk) (fig 2⇓). Similar to the results for hip fracture, observed probabilities of major osteoporotic fracture were greater than predicted probabilities among men with osteoporosis, especially those identified by WHO criteria for whom the observed probability was 30.0% (22.2% to 38.1%) compared with the FRAX predicted probability of 17.4% (16.0% to 18.8%). This discrepancy was again not apparent among men without osteoporosis, including those at high and those at low fracture risk.

Findings for the comparisons of observed to predicted fracture probabilities were similar in analyses in which men starting bisphosphonates during follow-up were censored at the time of initiation or when initiation of bisphosphonates was considered as a competing risk. In addition, results were not altered in analyses in which the group of men without osteoporosis but at high fracture risk was limited to the 859 men with male specific bone mineral density T scores between –1.01 and –2.49. Finally, limiting the cohort to the 4285 men with complete data on all clinical characteristics used in the calculation of FRAX 10 year fracture probabilities did not alter our findings for the proportion of men identified as candidates for drug treatment or results on observed and predicted fracture probabilities.

Discussion

In this cohort of community dwelling older men living in the United States, we found that the choice of definition of osteoporosis and use of National Osteoporosis Foundation derived FRAX intervention thresholds had major effects on the proportion of men identified as candidates for drug treatment to prevent fracture. Expanding the indication for treatment from men with osteoporosis defined by WHO criteria to men meeting criteria using FRAX intervention thresholds proposed by the NOF resulted in more than a 10-fold rise in the proportion of men identified as candidates for drug treatment. Among the 2% of men identified as having osteoporosis by WHO criteria, who constitute the group most likely to benefit from drug treatment to prevent fracture, observed 10 year fracture probabilities were highest and exceeded FRAX predicted probabilities.

Comparison with other studies

Choice of normative database and number of skeletal sites considered had a substantial effect on the estimated prevalence of osteoporosis in older men in this study; a fourfold increase in the prevalence occurred when we defined osteoporosis by using NOF (male normative database, three skeletal sites) instead of WHO (female normative database, one skeletal site) criteria. These findings are in agreement with most,[12][35][39][40] but not all,[11] previous studies. Use of a female derived bone mineral density T score threshold to define osteoporosis in men is

supported by a meta-analysis that reported similar relative risks of fracture per unit decrease in femoral neck bone mineral density in men and women and similar age adjusted hip fracture rates in men and women for any given absolute value of femoral neck bone mineral density.[41] Both the NOF and the Endocrine Society in the United States recommend use of male derived bone mineral density T score thresholds.[7-9] In contrast, the International Society of Clinical Densitometry recently reversed its earlier position advocating use of a young male normative database and recommended that T scores in men be calculated using a young female normative database.[10 36 42]

Nearly one out of every six older men in this cohort did not meet criteria for osteoporosis using even the most liberal definition but were classified as at high risk of fracture on the basis of having a 10 year probability of hip or major osteoporotic fracture at or above FRAX intervention thresholds proposed by the NOF. Of these, the vast majority (92%) had male specific bone mineral density T score between −1.01 and −2.49 and would be candidates for drug treatment according to guidelines proposed by the NOF and endorsed by other US professional societies.[7-9 36] Our finding that the application of NOF treatment guidelines markedly increased the proportion of older men identified as candidates for treatment is consistent with those reported in other studies,[43] including a previous analysis of this cohort.[44] Our results expand on these previous cross sectional reports by clearly showing the incremental effect of broadening the definition of osteoporosis and use of the FRAX intervention thresholds recommended by the NOF.

Although basing the treatment decision on a patient's absolute risk of fracture is appealing, the efficacy of currently available treatment in preventing clinical fractures in men and women without osteoporosis defined by female specific norms or existing vertebral fractures has not been demonstrated. Previous trials in men with low bone mineral density have been powered to detect a change in bone mineral density or a reduction in risk of new vertebral fractures identified on the basis of radiographs alone[13-17]; no trials in men have shown a benefit of treatment in reducing the risk of clinical fractures. With the exception of one trial in patients with recent hip fracture,[19] evidence of the efficacy of treatment in reducing clinical fractures is limited to trials in postmenopausal women with osteoporosis defined by a female specific bone mineral density T score of −2.5 or below or with existing radiographic vertebral fractures.[18] Systematic reviews of trials of bisphosphonates in postmenopausal women have not reported significant reductions in risk of non-vertebral fractures among women without osteoporosis or existing vertebral fractures.[18 45] Although one trial of clodronate reported efficacy of treatment in reducing clinical fractures (but not hip fractures) in older women not selected on the basis of bone mineral density,[46] other pivotal trials of alendronate, risedronate, and denosumab found no benefit of treatment in reducing clinical fractures among women not selected on the basis of the WHO definition of osteoporosis (that is, female specific bone mineral density T score −2.5 or below) or existing vertebral fractures.[47-49] In addition, whether higher estimated FRAX probabilities identify a subgroup of patients who benefit more from treatment is unknown. Post hoc analyses of trials in women of drugs including raloxifene and alendronate have not found evidence of an interaction between level of FRAX 10 year fracture probability and treatment assignment for prediction of risk of fracture events,[50 51] although some evidence supported an interaction in trials of denosumab and clodronate.[52 53]

Our results indicate that using criteria other than the WHO definition of osteoporosis to select older men for drug treatment substantially increases the pool of men labeled as abnormal,

with potential consequences of overdiagnosis and overtreatment. Because considerable uncertainty exists, randomized trials are clearly warranted to evaluate the efficacy of treatment in reducing clinical fractures in older adults without osteoporosis but at high fracture risk before expanding indications for drug treatment.

The performance of the FRAX tool has been the subject of multiple previous studies, including a recent study using data collected in the Osteoporotic Fractures in Men (MrOS) study that evaluated the performance of FRAX models with and without bone mineral density in the overall cohort.[54] Findings suggested that discrimination of men with and without incident fracture events was improved by addition of bone mineral density to the calculation, although even the models with bone mineral density were limited in their ability to predict fracture events, especially non-hip fractures (the area under the curve statistic for hip fracture was 0.67 without and 0.77 with bone mineral density; for major osteoporotic fracture it was 0.63 without and 0.67 with bone mineral density). Results also indicated suboptimal calibration of FRAX models with bone mineral density (underestimation of hip fracture probability and overestimation of major osteoporotic fracture probability). The observed 10 year cumulative incidence hip fracture probability was 3.0% compared with a mean 10 year FRAX predicted probability of 2.3%, and the observed 10 year cumulative incidence major osteoporotic fracture probability was 6.9% compared with a mean 10 year FRAX predicted probability of 7.6%.[54]

Our study determined observed and FRAX predicted probabilities within mutually exclusive groups of men identified by osteoporosis status and fracture risk, as US professional societies have strongly recommended that clinicians consider both bone mineral density and fracture risk defined using NOF derived FRAX intervention thresholds in making the critical decision about whether to recommend drug treatment to a patient. We found a wide range of observed 10 year probabilities of hip and major osteoporotic fracture events across these distinct groups of men. As expected, observed probabilities were highest among men with osteoporosis as defined by WHO criteria using a young female specific normative database, intermediate among men with osteoporosis defined by NOF (but not WHO) criteria using a male specific normative database, intermediate among men without osteoporosis but at high fracture risk, and lowest among men without osteoporosis and at low fracture risk. Among men with osteoporosis by WHO criteria, one out of every five had a hip fracture and three out of every 10 had a major osteoporotic fracture. On the basis of evidence from randomized trials in women, these men with osteoporosis defined using a young female specific normative database are most likely to benefit from drug treatment to prevent fracture. However, our results indicated that fracture probabilities as calculated by the FRAX tool in this group of men underestimated their actual fracture risk. Because the FRAX tool did not underestimate fracture risk among men without osteoporosis, differences in predicted fracture probabilities across groups were smaller than actual observed differences in fracture probabilities. As patients may be prepared accept a higher absolute fracture risk than providers are before considering drug treatment to be justified,[55] information about absolute fracture risk must be accurately conveyed to the patients most likely to benefit from treatment. In addition, evidence suggests that a large discrepancy may exist between NOF recommended FRAX intervention thresholds and acceptable intervention thresholds of patients.[55]

In addition to FRAX, many other tools for assessing fracture risk have been developed. A recent systematic review of these tools identified a total of 48 instruments,[56] but only six were validated more than once in a population based setting with acceptable methodological quality. None of these six tools consistently performed better than the others, and simple tools often did as well as or better than more complex tools including FRAX. No studies determined the effectiveness of tools in selecting patients for treatment or reported that a screening and/or treatment strategy based on a specific tool reduced the risk of clinical fractures. Thus, randomized trials are needed to evaluate the comparative effectiveness of strategies based on fracture risk assessment tools in reducing risk of clinical fracture events before widespread adoption of these tools into clinical decision making in the practice setting regarding whether to recommend drug treatment. In addition, decreasing the societal burden of fractures among older adults will require effective interventions beyond available skeletal treatments targeted at patients with low bone mineral density. Thus, randomized trials are also warranted to evaluate the efficacy of non-skeletal interventions (for example, community based fall prevention strategies) in reducing fracture events.

Strengths and limitations of study

This study has several strengths, including the large, well characterized cohort with nearly complete long term follow-up of fracture events. Observed fracture probabilities were adjusted for the competing risk of mortality.

However, this study has several limitations. The cohort comprised community dwelling, predominantly white men living in the United States. Characteristics including status of clinical risk factors for fracture and hip bone mineral density were in general similar to those of a population based sample of men aged 65 years and over enrolled in NHANES III,[44] but fewer men in the MrOS study were current smokers. This may in part explain the discrepancy between observed and predicted FRAX fracture probabilities among men with osteoporosis in our cohort, as smoking is a risk factor for mortality.

Our findings on the effect of using FRAX intervention thresholds on the proportion of men identified as warranting drug treatment are limited to the thresholds identified by the NOF for the United States and do not necessarily apply to strategies proposed in other countries.[57-59] For example, the National Osteoporosis Guideline Group,[58] in collaboration with other societies in the United Kingdom, recommends using the FRAX 10 year probability of major osteoporotic fracture calculated without bone mineral density to assess the need for bone mineral density testing in an adults aged 50 years and older; among patients requiring a bone mineral density test, the re-calculated FRAX 10 year probability of major osteoporotic fracture with bone mineral density is used to determine whether drug treatment is warranted. In these guidelines, FRAX intervention thresholds for bone mineral density testing and for starting drug treatment vary according to age. To our knowledge, the implications of using these guidelines on the proportion of UK adults identified as candidates for drug treatment to prevent fracture have not been examined. Our findings suggest that use of a single FRAX intervention threshold based on probability of major osteoporotic fracture of 20% would identify a much smaller proportion of older men without evidence of osteoporosis (by any definition) as warranting drug treatment, as the vast majority of men in this group in our study were identified as being eligible for treatment because they met or exceeded the hip fracture threshold of 3%. However, our findings also indicate that reliance on the FRAX 20% threshold

alone without consideration of bone mineral density would fail to identify more than 75% of men with osteoporosis by WHO criteria.

Although evidence exists showing the efficacy of several drug treatments in preventing clinical fractures among postmenopausal women with existing vertebral fractures,[60] and one randomized trial has shown efficacy of zoledronic acid in preventing symptomatic fractures among patients with recent hip fracture,[19] our study did not specifically look at the effect of selecting older men for drug treatment on the basis of these criteria. Because the equations and algorithms that generate the fracture risk probabilities have not been published for the FRAX tool, this study could not investigate the relative importance of individual FRAX clinical risk factors in fracture prediction. Finally, the absolute number of fracture events in each of the four groups of men in this study was small, and our findings should be confirmed using data collected in other long term prospective studies of older men.

Conclusions and implications

In conclusion, broadening the indication for drug treatment beyond men with osteoporosis as defined by WHO criteria resulted in a large increase in the proportion of older community dwelling men in the United States who were identified as warranting drug treatment to prevent fracture. Men with osteoporosis by WHO criteria had observed probabilities of clinical fracture events that exceeded their FRAX predicted probabilities. Based on data from trials in women, these men with osteoporosis by WHO criteria are most likely to benefit from treatment. As the goal of treatment is to prevent clinical (symptomatic) fractures, our results in the context of the available medical literature indicate that treatment should be offered to men who meet WHO criteria for osteoporosis (that is, femoral neck bone mineral density of 0.558 g/cm^2 or below), men with existing vertebral fractures, and men with a recent history of hip fracture. Expanding indications for treatment beyond this group has unknown value owing to lower observed fracture probabilities and uncertain benefits of treatment and would result in overdiagnosis and overtreatment. Randomized clinical trials are warranted to evaluate the efficacy of drug treatment in reducing clinical fractures in older men and women without osteoporosis but at high risk of fracture before a fundamental change in the strategy used to identify candidates for drug treatment is adopted.

What is already known on this topic

The efficacy of drug treatment in preventing clinical (symptomatic) fractures in men is unknown, but treatment in postmenopausal women with osteoporosis reduces the risk of clinical fractures

Several US professional societies now recommend using cut points of 10 year absolute fracture risk as estimated by the FRAX tool in making decisions about whether to start drug treatment in adults aged 50 or over

Previous studies have suggested that application of these recommended FRAX intervention thresholds increases the proportion of older adults identified as candidates for drug treatment

However, the incremental impact of both broadening the definition of osteoporosis and use of FRAX intervention thresholds on the proportion of older men identified as candidates for drug treatment is uncertain

What this study adds

Depending on the definition of osteoporosis and the FRAX absolute fracture risk cut points applied to the study population, the proportion of men labeled as abnormal and warranting treatment varied from 2% up to 25%

Among men identified as having osteoporosis according to a stringent definition, who comprised 2% of the study population, actual observed fracture probabilities during 10 years of follow-up were highest and exceeded FRAX predicted fracture probabilities

Based on results of randomized trials in women, these men are most likely to benefit from drug treatment to prevent fracture

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Table

Table 1| Characteristics of 5880 participants according to definition of osteoporosis and fracture risk category*. Values are numbers (percentages) unless stated otherwise

Characteristic	Overall cohort (n=5880)	Osteoporosis by WHO† criteria (n=130)	Osteoporosis by NOF‡ (but not WHO) criteria (n=422)	No osteoporosis by WHO or NOF criteria	
				High fracture risk§ (n=936)	Low fracture risk§ (n=4392)
Mean (SD) age, years	73.6 (5.9)	77.1 (6.4)	74.3 (6.2)	77.9 (5.0)	72.5 (5.5)
Age group, years:					
65-69	1747 (30)	19 (15)	116 (27)	42 (4)	1570 (36)
70-74	1678 (29)	25 (19)	105 (25)	184 (20)	1364 (31)
75-79	1419 (24)	37 (28)	112 (27)	339 (36)	931 (21)
≥80	1036 (18)	49 (38)	89 (21)	371 (40)	527 (12)
White ethnicity	5257 (89)	118 (91)	377 (89)	908 (97)	3854 (88)
Mean (SD) bone mineral density, g/cm^2:					
Lumbar spine	1.17 (0.25)	0.94 (0.19)	0.88 (0.13)	1.12 (0.19)	1.22 (0.24)
Femoral neck	0.79 (0.13)	0.52 (0.04)	0.65 (0.08)	0.69 (0.07)	0.83 (0.11)
Total hip	0.96 (0.14)	0.68 (0.08)	0.80 (0.09)	0.87 (0.09)	1.00 (0.12)
Mean (SD) body mass index, kg/m^2	27.4 (3.8)	24.6 (3.2)	26.1 (4.3)	26.2 (3.1)	27.9 (3.8)
Current smoker	205 (3)	9 (7)	16 (4)	34 (4)	146 (3)
≥3 alcoholic drinks/day	237 (4)	3 (2)	14 (3)	58 (6)	162 (4)
Any fracture since age 50	1299 (22)	52 (40)	121 (29)	381 (41)	745 (17)
Oral corticosteroid use	477 (8)	13 (10)	57 (14)	110 (12)	297 (7)
Rheumatoid arthritis	304 (5)	8 (6)	21 (5)	82 (9)	193 (4)
Parental history of hip fracture	743 (13)	21 (16)	62 (15)	355 (38)	305 (7)
FRAX 10 year probability of hip fracture ≥3%	1299 (22)	128 (98)	237 (56)	934 (~100)	0 (0)
FRAX 10 year probability of major osteoporotic fracture ≥20%	122 (2)	30 (23)	27 (6)	65 (7)	0 (0)
Started bisphosphonate treatment during follow-up	426 (7)	40 (31)	134 (32)	91 (10)	161 (4)
Incident hip fracture	177 (3)	26 (20)	28 (7)	59 (6)	64 (1)
Incident major osteoporotic fracture	429 (7)	38 (29)	74 (18)	111 (12)	206 (5)
Died during follow-up	1883 (32)	55 (42)	151 (36)	430 (46)	1247 (28)

All characteristics assessed at baseline except for incident hip fracture, incident major osteoporotic fracture, and death.

*Fracture risk calculated using models with femoral neck bone mineral density (BMD).

†World Health Organization definition of osteoporosis based on use of female specific T score of −2.5 or below at femoral neck (that is, femoral neck BMD ≤0.558 g/cm^2).

‡National Osteoporosis Foundation definition of osteoporosis based on use of male specific T score of −2.5 or below at femoral neck, total hip, or lumbar spine; this group (osteoporosis by NOF but not WHO criteria) includes men with femoral neck BMD 0.558-0.592 g/cm^2, total hip BMD ≤0.681 g/cm^2, or total lumbar spine BMD ≤0.816 g/cm^2.

§High fracture risk as defined by FRAX (with BMD) 10 year probabilities of hip fracture ≥3% or major osteoporotic fracture ≥20%; low fracture risk as defined by FRAX (with BMD) 10 year probabilities of hip fracture <3% and major osteoporotic fracture <20%.
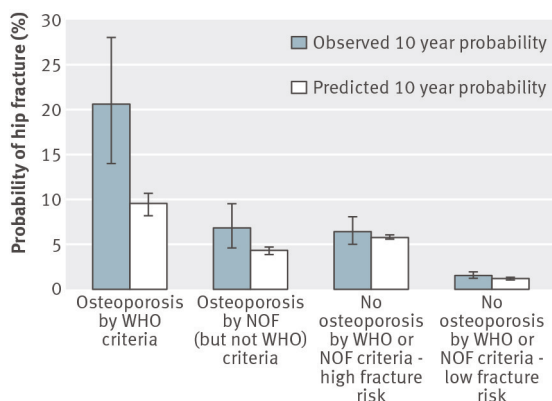
Figures

Fig 1 Observed versus predicted 10 year probability of hip fracture according to definition and fracture risk. 26 hip fractures occurred among 130 men with osteoporosis by WHO criteria alone, 28 among 422 men with osteoporosis by National Osteoporosis Foundation (NOF) (but not WHO) criteria, 59 among 936 men without osteoporosis but at high risk of fracture, and 64 among 4392 men without osteoporosis and at low risk of fracture
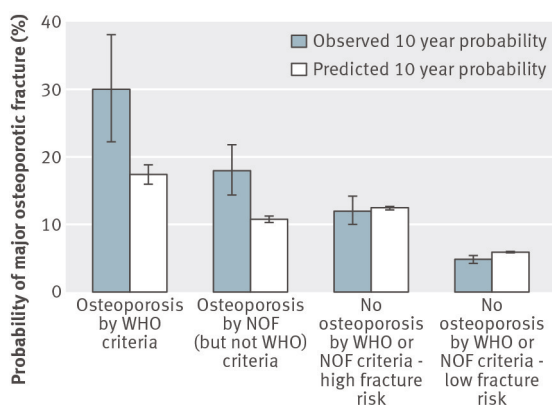

Fig 2 Observed versus predicted 10 year probability of major osteoporotic fracture according to definition and fracture risk. 38 major osteoporotic fractures occurred among 130 men with osteoporosis by WHO criteria alone, 74 among 422 men with osteoporosis by National Osteoporosis Foundation (NOF) (but not WHO) criteria, 111 among 936 men without osteoporosis but at high risk of fracture, and 206 among 4392 men without osteoporosis but at low risk of fracture