Annals of Internal Medicine

ORIGINAL RESEARCH

# Change in Bone Mineral Density Is an Indicator of Treatment-Related Antifracture Effect in Routine Clinical Practice

## A Registry-Based Cohort Study

**William D. Leslie, MD, MSc; Sumit R. Majumdar, MD, MPH; Suzanne N. Morin, MD, MSc; and Lisa M. Lix, PhD**

**Background:** Whether change in bone mineral density (BMD) is an accurate indicator of antifracture effect in clinical practice is unknown.

**Objective:** To evaluate repeated BMD testing as an indicator of treatment-related fracture risk reduction.

**Design:** Registry-based cohort study.

**Setting:** Manitoba, Canada.

**Patients:** 6629 women aged 40 years or older initiating osteoporosis treatment with 2 consecutive dual-energy x-ray absorptiometry scans (mean interval, 4.5 years).

**Measurements:** Change in BMD between the first and second dual-energy x-ray absorptiometry scans categorized as stable, detectable decrease, or detectable increase. Incident fractures were ascertained from health services data.

**Results:** During a mean of 9.2 years, 910 (13.7%) women developed incident fractures, including 198 with hip fractures. After adjustment for baseline fracture probability, women with a detectable decrease in total hip BMD compared with stable BMD had an absolute increase of 2.9% (95% CI, 1.5% to 4.4%) and 5.5% (CI, 2.8% to 8.1%) in the 5- and 10-year cumulative incidence of any fracture, respectively. In contrast, risk for any fracture in women with a detectable increase in total hip BMD was 1.3% (CI, 0.4% to 2.2%) and 2.6% (CI, 0.7% to 4.5%) lower after 5 and 10 years, respectively. Consistent results were seen for change in femoral neck and lumbar spine BMD and across a range of subgroup analyses.

**Limitation:** Lack of standardization in the BMD testing interval.

**Conclusion:** Treatment-related increases in total hip BMD are associated with reduced fracture risk compared with stable BMD, whereas decreases in BMD are associated with greater risk for fractures. Monitoring BMD in clinical practice may help to identify women with a suboptimal response to osteoporosis treatment.

**Primary Funding Source:** None.

*Ann Intern Med.* doi:10.7326/M15-2937 www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 19 July 2016.

Osteoporosis-related fractures are common and impose a large societal burden in terms of human and economic costs (1). In the absence of a typical low-trauma fracture (for example, vertebral compression fracture) (2), the diagnosis of osteoporosis is usually based on finding low bone mineral density (BMD) from dual-energy x-ray absorptiometry (DXA) (3, 4). Screening with DXA is recommended for women aged 65 years or older and in younger women with elevated fracture risk (5). In appropriately selected women, approved treatments can reduce fracture risk in primary and secondary prevention settings (6, 7).

The role for repeated BMD testing after initial evaluation is uncertain because prospective studies have not shown that repeated BMD measurements or changes in BMD were more predictive of subsequent fractures than the baseline measurement (5, 8). The practice of repeated BMD testing during pharmacotherapy also remains controversial (9, 10). Group-level clinical trial data suggest that greater increases in BMD are associated with greater fracture risk reduction (11, 12), but this may be more difficult to show in individuals as measurement error is typically 3% to 5% (13–15). In clinical trials in which "good" patients are selected for participation and their adherence is closely monitored, "treatment failure"—defined as detectable BMD loss—is uncommon, particularly when the patients are receiving bisphosphonates, which is the most widely used class of drugs for osteoporosis (16).

Results from clinical trials are not always applicable to clinical practice in which patients are lost to follow-up, adherence and persistence with medications are difficult to monitor, and patients often have underlying conditions that would exclude many from trial participation. We used population-based registries from Manitoba, Canada, to assess the effectiveness of repeated BMD testing in routine clinical practice as a predictor of treatment-related fracture risk reduction in women initiating treatment.

## METHODS

### Patient Population

In Manitoba, Canada (population, 1.2 million persons), health services are provided to virtually all residents through a public health care system. Since 1997, DXA testing has been managed as an integrated program (the Manitoba Bone Density Program); criteria for baseline testing include screening women at age 65 years and younger women with additional risk factors (17). Consistent with national guidelines, the program's recommended interval for initial follow-up is 3 years for most patients, 1 year for those receiving systemic glucocorticoid therapy or aromatase inhibitors, and at least 5 years for those previously reported as low-risk (18). The program maintains a database of all DXA re-

sults that can be linked with other population-based computerized health databases through an anonymous personal identifier. The DXA database has completeness and accuracy in excess of 99% (19). From this database, we identified all women aged 40 years or older with baseline DXA measurements of the hip or lumbar spine obtained from 1 of the program's cross-calibrated primary DXA instruments (Prodigy; GE Healthcare Lunar) after 1 April 1998. We then identified those with a follow-up DXA examination before 31 March 2013 (minimum interval of 1 year) for assessment of change in BMD in at least 1 measurement site (total hip, femoral neck, or lumbar spine). Using linkage to the province-wide retail pharmacy network (20), we identified women not receiving osteoporosis treatment during the year before baseline DXA testing (defined as no pharmacy-dispensed bisphosphonate, calcitonin, systemic estrogen product, raloxifene, or teriparatide) who initiated 1 of these same osteoporosis treatments between the first and second DXA scans (defined as 1 or more prescription dispensations). Analyses did not consider subsequent medication switching. The study was approved by the Health Research Ethics Board of the University of Manitoba.

### BMD Measurements

Lumbar spine and hip DXA scans were performed and analyzed in accordance with manufacturer recommendations. Femoral neck and total hip T-scores (number of SDs above or below the mean BMD for young adults) were calculated from NHANES III (Third National Health and Nutrition Examination Survey) reference values for white women (21); lumbar spine (L1 to L4) T-scores were based on the manufacturer's reference values for white women (22). The program's quality assurance is under strict supervision by a medical physicist (17). The instruments used for this study exhibited stable long-term performance (coefficient of variation, <0.5%). All reporting physicians and supervising technologists are required to maintain DXA certification with the International Society for Clinical Densitometry.

The absolute BMD difference (measured in $g/cm^2$) between the 2 DXA tests was compared with 95% least-significant change (LSC) values for assessment of change using accepted methods, where LSC is the least amount of change in BMD that can be considered statistically significant (23–25). The BMD measurement error of the Manitoba Bone Density Program used for computing the LSC is derived from more than 400 DXA scan pairs (most performed on different days but within 28 days by different technologists). We have previously reported that this approach (rather than same-day repositioning with the same technologist) is more representative of measurement error encountered during clinical monitoring (26). From these scan pairs, we obtained the following 95% LSC values, which are within acceptable ranges (25): total hip, 0.030 $g/cm^2$; lumbar spine, 0.050 $g/cm^2$; and femoral neck, 0.055 $g/cm^2$. An observed absolute difference less than these values would be considered to be within the range of measurement error (stable), whereas an increase or decrease exceeding these values would be outside the range of measurement error (detectable increase or decrease in BMD, respectively). The use of the absolute difference for BMD monitoring follows International Society for Clinical Densitometry recommendations and avoids errors that can arise when change is expressed as a percentage (27, 28).

### Baseline Fracture Probability Calculations

The 10-year probability of the risk for major osteoporotic fracture was calculated by using the Canadian version of the World Health Organization Fracture Risk Assessment Tool (FRAX), version 3.7 (FRAX Desktop Multi-Patient Entry) (29, 30). Age, body mass index, femoral neck BMD, and other data required for calculating fracture probability with FRAX were assessed through a combination of hospital discharge abstracts (diagnoses and procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification, before 2004 and International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada thereafter), physician billing claims (coded using International Classification of Diseases, Ninth Revision, Clinical Modification), and information collected directly from patients at the time of DXA scanning as previously described (Appendix Table, available at www.annals.org) (31). The Canadian FRAX was calibrated by using nationwide hip fracture data (30). Predictions agreed closely with observed fracture risk in our population (31, 32).

### Fractures Outcomes

Records from Manitoba Health were assessed for the presence of incident nontraumatic hip, clinical vertebral, forearm, and humerus fracture diagnostic codes (collectively designated as major osteoporotic fractures) using previously validated algorithms (33, 34). Fractures that were not associated with trauma codes were assessed through a combination of hospital discharge abstracts and physician billing claims. We required that hip and forearm fracture codes be associated with site-specific fracture reduction, fixation, or casting codes to enhance specificity for an acute fracture event. To minimize potential misclassification of prior incident fractures, we conservatively required that there be no hospitalization or physician visit for the same fracture type in the 6 months preceding an incident fracture diagnosis.

### Statistical Analysis

Cumulative fracture incidence after the first DXA scan (index date) was studied using survival analysis. Observations were censored for death, migration out of province, or end of follow-up (31 March 2013). Our primary analysis examined change in total hip BMD between DXA scans, which was the site with the smallest measurement error; these scans were categorized as stable (referent), detectable decrease, or detectable increase. Cumulative incidence curves, along with point estimates and 95% CIs at 5 and 10 years, were directly adjusted for baseline fracture probability (35). Average absolute differences in cumulative fracture risk were

*Table 1.* Baseline Characteristics of the Study Population, Overall and by Incident Fracture Status*

| Characteristic | Overall (*n* = 6629) | No Fracture (*n* = 5719) | Fracture (*n* = 910) | *P* Value |
|---|---|---|---|---|
| Mean age (SD), *y* | 64.3 (10.1) | 63.9 (10.0) | 66.9 (10.3) | <0.001 |
| Age, *n* (%) | | | | |
| 40-64 y | 3359 (50.7) | 2998 (52.4) | 361 (39.7) | <0.001 |
| 65-74 y | 2188 (33.0) | 1857 (32.5) | 331 (36.4) | |
| ≥75 y | 1082 (16.3) | 864 (15.1) | 218 (24.0) | |
| Mean 10-y fracture probability (SD), %† | 11.7 (7.3) | 11.2 (6.9) | 14.7 (8.7) | <0.001 |
| Osteoporosis diagnosis (T-score ≤−2.5), *n* (%) | 3789 (57.2) | 3190 (55.8) | 599 (65.8) | <0.001 |
| Mean T-score among patients with osteoporosis (SD) | | | | |
| Total hip | −1.6 (1.0) | −1.5 (1.0) | −1.9 (1.0) | <0.001 |
| Femoral neck | −1.9 (0.8) | −1.8 (0.8) | −2.1 (0.8) | <0.001 |
| Lumbar spine | −2.2 (1.2) | −2.2 (1.2) | −2.5 (1.2) | <0.001 |
| Mean BMD interval (SD), *y* | 4.5 (2.2) | 4.5 (2.2) | 4.8 (2.4) | <0.001 |
| BMD interval, *n* (%) | | | | |
| 1-3 y | 1604 (24.2) | 1392 (24.3) | 212 (23.3) | <0.001 |
| 3-5 y | 3013 (45.5) | 2642 (46.2) | 371 (40.8) | |
| >5 y | 2012 (30.4) | 1685 (29.5) | 327 (35.9) | |

BMD = bone mineral density; FRAX = Fracture Risk Assessment Tool.
* Percentages may not sum to 100 due to rounding.
† FRAX major osteoporotic fractures were computed with BMD.

compared based on change in BMD (detectable decrease or increase vs. stable BMD), and 95% CIs were estimated. Analyses were conducted using SAS, version 9.3 (SAS Institute).

We did a series of secondary sensitivity analyses to test the robustness of our findings and explore potential interactions. First, we examined hip fractures as the outcome of interest given their large implications on morbidity, mortality, and cost compared with other fractures. Second, we constructed separate models for change in femoral neck and lumbar spine BMD. Finally, we explored potential interactions in multiplicative Cox proportional hazards models stratified according to age (40 to 64, 65 to 74, and ≥75 years); baseline BMD (osteoporotic vs. nonosteoporotic T-scores); BMD testing interval (1 to 2.9, 3 to 5, and >5 years); and medication possession ratio (<0.5, 0.50 to 0.79, and ≥0.80), which is an adherence measure calculated as the total days of medication supplied between the BMD tests divided by the testing interval. In the Cox regression models, we examined 3 continuous measures of change in BMD: absolute change (measured in g/cm$^2$), percent change, and annual percent change. Hazard ratios (HRs) were adjusted for baseline fracture probability. The proportional hazards assumption was confirmed by testing the correlation between scaled Schoenfeld residuals versus time.

### Role of the Funding Source

This study received no funding.

## RESULTS

The potentially eligible population consisted of 6799 women (Appendix Figure 1, available at www.annals.org). After 170 ineligible women were excluded, the final study population contained 6629 women initiating treatment in which change in BMD could be assessed at 1 or more skeletal sites (total hip, 6563 women; femoral neck, 6572 women; lumbar spine, 5690 women; and all 3 sites, 5656 women). The smaller number of lumbar spine measurements reflects scans that could not be reported due to structural artifacts, chiefly age-related degenerative changes. Mean age at baseline was 64.3 years (SD, 10.1) (Table 1). Most women (57.2%) met the BMD criterion for osteoporosis at 1 or more skeletal sites. Additional risk factors for fracture were used in computing baseline probability (Appendix Table). Of the 2840 women who were not osteoporotic on baseline DXA measurements, 43% had a T-score between −2 and −2.5, 12% had a prior major osteoporotic fracture, and 13.9% had a high FRAX score (major osteoporotic fracture ≥20% or hip fracture ≥3%). Bisphosphonates were initially prescribed in 84.9% of women; 87.9% were receiving bisphosphonates after 4 years.

### Changes in BMD Over Time

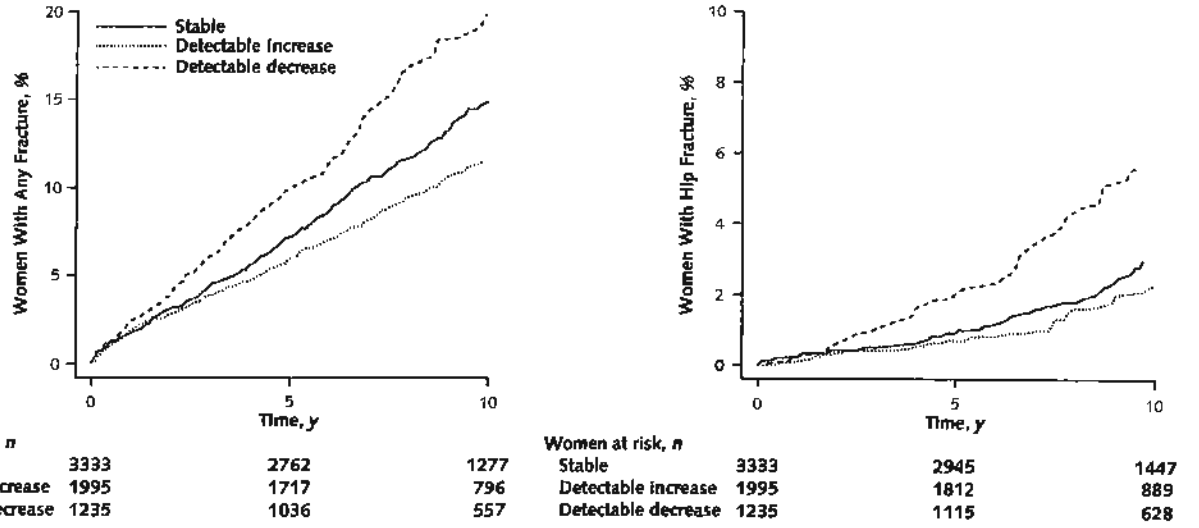
The mean interval between the first and second BMD tests was 4.5 years (SD, 2.2). A detectable increase was more common than a detectable decrease (Table 2). For the total hip, a detectable increase was seen in 30.4% of women and a detectable decrease was seen in 18.8% (stable in 50.8%). Detectable change was less common at the femoral neck (increase, 9.8%;

*Table 2.* Detectable Change in BMD Between the First and Second DXA Scans*

| Measurement Site | Stable | Detectable Decrease | Detectable Increase |
|---|---|---|---|
| Total hip | 3333 (50.8) | 1235 (18.8) | 1998 (30.4) |
| Femoral neck | 5284 (80.4) | 642 (9.8) | 647 (9.8) |
| Lumbar spine | 2861 (50.3) | 585 (10.3) | 2245 (39.4) |

BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry.
* Values are numbers (percentages). Classification of change is based on the absolute difference in BMD between the 2 DXA scans (in g/cm$^2$) compared with the 95% least significant change (total hip, 0.030 g/cm$^2$; lumbar spine, 0.050 g/cm$^2$; and femoral neck, 0.055 g/cm$^2$).

*Figure 1.* Cumulative fracture risk, by change in total hip BMD.




Cumulative incidence functions are directly adjusted for baseline fracture probability. BMD = bone mineral density. Left. For any fractures, the detectable decrease vs. stable BMD ($P < 0.001$) and detectable increase vs. stable BMD ($P = 0.004$) are depicted. Right. For hip fractures only, the detectable decrease vs. stable BMD ($P < 0.001$) and detectable increase vs. stable BMD ($P = 0.167$) are depicted.

decrease, 9.8%; and stable, 80.4%) than the lumbar spine (increase, 39.4%; decrease, 10.3%; and stable, 50.3%). A detectable decrease in BMD affecting 1 or more measurement sites was seen in 1526 (23.0%) women who initiated osteoporosis therapy, representing almost 1 in 4 women.

### Association Between Detectable Change in BMD and Fracture

During 61 088 person-years of follow-up (median, 9.2 years; range, 1.0 to 14.8 years), 910 (13.7%) women sustained 1 or more fractures (hip, 198 women; vertebral, 242 women; humerus, 163 women; and forearm, 401 women). Cumulative fracture incidence showed differences according to detectable change in total hip BMD (Figure 1). Compared with stable total hip BMD, a detectable decrease in total hip BMD was associated with a greater risk for fracture ($P < 0.001$), whereas a detectable increase was associated with lower risk for fracture ($P = 0.004$). When analysis was limited to hip fractures, a detectable decrease in total hip BMD was again associated with greater risk for fracture ($P < 0.001$) but a significant difference was not seen for a detectable increase ($P = 0.167$).

Cumulative fracture risk after 5 and 10 years was greater in women with a detectable decrease in total hip BMD than those with stable BMD; in contrast, risk was lower in those with a detectable increase in total hip BMD (Table 3). Women with a detectable decrease in total hip BMD compared with those with stable BMD had an absolute increase in the risk for any fracture (2.9% [95% CI, 1.5% to 4.4%] after 5 years and 5.5% [CI, 2.8% to 8.1%] after 10 years) and hip fracture (0.9% [CI, 0.4% to 1.5%] after 5 years and 2.8% [CI, 1.2% to 4.3%] after 10 years). In contrast, the risk for any fracture in women with a detectable increase in total hip BMD was 1.3% (CI, 0.4% to 2.2%) lower after 5 years and 2.6% (CI, 0.7% to 4.5%) lower after 10 years. Fracture risk after 5 and 10 years based on change in femoral neck and lumbar spine BMD was generally consistent with the results for total hip BMD. Subgroup analyses for change in total hip BMD showed consistent results according to baseline age, whether baseline BMD measurement was osteoporotic, BMD testing interval, or medication possession ratio (Figure 2).

### Sensitivity Analysis

When change in BMD was analyzed as a continuous measure, findings paralleled those based on the categorical analysis. Every SD increase in total hip BMD during treatment was associated with a 19% relative reduction in the fracture hazard rate (HR, 0.81 [CI, 0.76 to 0.86]); we also found a significant reduction for change in femoral neck BMD (HR, 0.83 [CI, 0.77 to 0.88]). In contrast, association between lumbar spine BMD and incident fracture risk was modest and of borderline statistical significance (HR, 0.94 [CI, 0.88 to 1.02]). Similar results were seen when change was expressed as a percent change or annual percent change (Appendix Figure 2, available at www.annals.org). No significant interactions were identified.

## DISCUSSION

Using a population-based BMD registry linked with comprehensive administrative databases for Manitoba, Canada, we were able to examine fracture outcomes in women initiating osteoporosis therapy in relation to changes in BMD measurements. The major finding was that change in total hip BMD after initiation of osteoporosis treatment was an indicator of fracture risk reduction. Most important, the greater the increase in total

*Table 3.* Cumulative Fracture Risk After 5 and 10 Years, by Change in BMD*

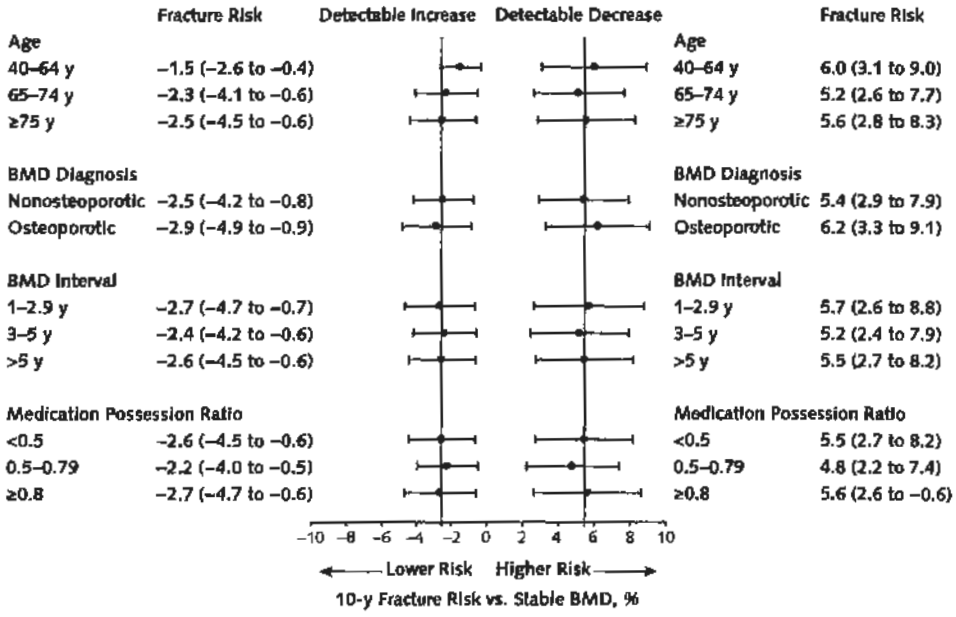
| BMD Change Category | Risk for Any Fracture (95% CI), % | | Risk for Hip Fracture (95% CI), % | |
|---|---|---|---|---|
| | 5 y | 10 y | 5 y | 10 y |
| **Total hip** | | | | |
| Detectable decrease | 10.1 (8.7 to 11.5) | 20.1 (17.7 to 22.5) | 1.9 (1.3 to 2.5) | 5.8 (4.3 to 7.3) |
| Stable | 7.2 (6.5 to 8.0) | 14.7 (13.3 to 15.9) | 1.0 (0.7 to 1.2) | 3.0 (2.4 to 3.6) |
| Detectable increase | 5.9 (5.1 to 6.7) | 12.1 (10.6 to 13.5) | 0.7 (0.5 to 1.0) | 2.3 (1.6 to 3.0) |
| Detectable decrease vs. stable | 2.9 (1.5 to 4.4) | 5.5 (2.8 to 8.1) | 0.9 (0.4 to 1.5) | 2.8 (1.2 to 4.3) |
| Detectable increase vs. stable | −1.3 (−2.2 to −0.4) | −2.6 (−4.5 to −0.7) | −0.2 (−0.5 to −0.1) | −0.7 (−1.6 to 0.2) |
| **Femoral neck** | | | | |
| Detectable decrease | 11.2 (9.1 to 13.2) | 22.0 (18.4 to 25.6) | 2.4 (1.4 to 3.3) | 7.2 (4.7 to 9.6) |
| Stable | 7.1 (6.5 to 7.8) | 14.5 (13.5 to 15.6) | 0.9 (0.7 to 1.2) | 2.9 (2.4 to 3.5) |
| Detectable increase | 5.8 (4.5 to 7.0) | 11.8 (9.3 to 14.2) | 0.9 (0.5 to 1.4) | 3.0 (1.7 to 4.2) |
| Detectable decrease vs. stable | 4.0 (2.0 to 6.1) | 7.5 (3.8 to 11.2) | 1.4 (0.6 to 2.3) | 4.3 (1.8 to 6.7) |
| Detectable increase vs. stable | −1.4 (−2.7 to −0.1) | −2.7 (−5.3 to −0.1) | 0 (−0.5 to 0.5) | 0 (−1.3 to 1.4) |
| **Lumbar spine** | | | | |
| Detectable decrease | 8.9 (6.9 to 10.9) | 17.9 (14.1 to 21.4) | 1.9 (0.9 to 2.8) | 6.0 (3.4 to 8.6) |
| Stable | 6.7 (5.9 to 7.5) | 13.60 (12.30 to 14.97) | 1.00 (0.70 to 1.30) | 3.2 (2.5 to 3.9) |
| Detectable increase | 6.5 (5.6 to 7.3) | 13.2 (11.8 to 14.6) | 0.6 (0.4 to 0.8) | 1.9 (1.3 to 2.4) |
| Detectable decrease vs. stable | 2.2 (0.2 to 4.3) | 4.2 (0.4 to 8.1) | 0.9 (0 to 1.8) | 2.9 (0.2 to 5.5) |
| Detectable increase vs. stable | −0.2 (−1.2 to 0.8) | 0.4 (−2.3 to 1.5) | −0.4 (−0.7 to −0.1) | −1.3 (−2.2 to −0.5) |

* All estimates are directly adjusted for baseline fracture probability.

hip BMD, the lower the fracture risk. In contrast, a decrease in total hip BMD during treatment was not uncommon and occurred in almost 1 in 5 women. This was associated with a substantially increased fracture risk (absolute increase of 5.5% after 10 years for total hip BMD) compared with stable BMD.

Our findings have face validity given the strong association between BMD and fracture risk, as well as the clinical trial evidence that change in BMD contributes to (but does not fully explain) antifracture benefits (11, 12, 36). Consistent results were seen across a range of subgroup analyses. Although changes in femoral neck BMD mirrored the findings at the total hip, changes in lumbar spine BMD were not a consistent indicator of treatment-related fracture risk reduction. Age-related spinal degenerative disease can confound the assessment of BMD in the lumbar spine and can produce erroneous results in older adults during follow-up (37).

*Figure 2.* Subgroup analyses for absolute difference in fracture risk (95% CI) after 10 y, by change in total hip BMD.




Solid reference line is for the overall population. BMD = bone mineral density.
* All results are directly adjusted for baseline fracture probability (log transformed).

Our study complements previous reports that have looked at BMD monitoring in women not receiving osteoporosis therapy. Gourlay and colleagues (38) found that the likelihood of transition to a diagnosis of osteoporosis was strongly dependent on baseline BMD T-score in women aged 67 years or older. Whereas a testing interval as short as 1 year was recommended for women with advanced osteopenia (T-score, −2.00 to −2.49), a testing interval as long as 15 years might be appropriate for women with BMD in the normal or mildly osteopenic range (T-score ≥−1.49). A subsequent report from the Women's Health Initiative BMD cohort study (39) concluded that postmenopausal women aged 50 to 64 years without osteoporosis on their first BMD test were unlikely to benefit from frequent rescreening before age 65 years. The change in BMD in the absence of treatment or high-risk medications (such as glucocorticoids or aromatase inhibitors) is typically small—0.5% to 1.5% per year (13–15). Although longer testing intervals could be considered for women who are not receiving therapy, this does not address the equally important issue of BMD monitoring in those starting osteoporosis treatment.

Osteoporosis therapies, particularly those involving bisphosphonates, produce early increases in BMD, and group effects can be seen in less than 1 year (40, 41). Bell and colleagues (16) reported that treatment failure (detectable decrease in BMD) was uncommon in women participating in a clinical trial of oral alendronate, which has been interpreted as evidence against routine BMD monitoring during treatment (9). Unlike clinical trials in which participants are selected because they have a high likelihood of good adherence and a low likelihood of adverse effects, trying to assess a patient's adherence and persistence with therapy in clinical practice is notoriously difficult (42). In a pooled analysis from 3 pivotal risedronate trials (active treatment in 2047 women), Watts and colleagues (43) reported that patients whose BMD showed any decrease were at a significantly greater risk for radiographic vertebral fracture than those whose BMD showed any increase. However, fracture risk was similar in patients with a smaller (<5%) versus larger (≥5%) increase in BMD. This study did not assess the total hip site, clinical vertebral fractures, or nonvertebral fractures and also did not differentiate reductions in BMD that exceeded the LSC from those in a range consistent with measurement error. Although not the focus of the current study, we observed that change in BMD was equally predictive of fracture in both osteoporotic and nonosteoporotic women, which may help to inform discussion about the effectiveness of osteoporosis therapy in those whose BMD is not in the osteoporotic range (44).

Our data suggest that in clinical practice, treatment response is much less consistent than in the clinical trial setting examined by Bell and colleagues (16). Monitoring BMD provides useful information about whether an antifracture benefit has occurred. If confirmed, our results could help inform a goal-directed (or treat-to-target) paradigm for osteoporosis therapy (45). Although theoretically attractive, this approach has not been implemented to date because suitably responsive indicators of antifracture benefits have not been identified (46, 47). Monitoring for change in BMD may contribute to this strategy. Such organizations as the U.S. Preventive Services Task Force have provided strong guidance about initial BMD testing for screening purposes, but they have not formulated similarly strong recommendations about repeated BMD testing given the limitations of the available evidence (5).

Strengths of our study include broad inclusion criteria, which are representative of women treated in routine clinical practice, and access to a DXA registry that has rigorous data collection and linkage to administrative health care databases (17, 19). Our results are therefore likely to be more applicable to clinical practice than those of prospective research cohorts (38) or clinical trials (16).

Our study also has limitations. First, the threat of "confounding by indication" exists in all observational studies; however, that all women in this study initiated treatment largely mitigates this concern. In addition, women with strong contraindications to therapy or those who are primarily nonadherent (that is, they do not fill an initial prescription) were excluded, but this also reflects a common clinical reality. Second, we lacked a standardized BMD testing interval. Although a fixed interval would be seen in a clinical trial or a research cohort, in clinical practice it cannot be strictly enforced. However, our findings did not change in analyses stratified by testing interval (from 1 to 3 years to >5 years) and alternative measures of change (including annual percent change), suggesting that the lack of a fixed testing interval is not an important limitation. Unfortunately, our study cannot provide specific guidance on the optimal testing interval, where a relatively short testing interval is often recommended (for example, 1 to 2 years after initiating therapy) (9, 10, 48), or the value of additional tests after a second BMD assessment. Third, we did not consider change in clinical management that might occur based on the results from the second BMD measurement. It is possible that when confronted with a detectable decrease in BMD, patients might improve their adherence to therapy or physicians might consider a change in therapy. Alternatively, patients with a detectable increase in BMD might be considered for a "drug holiday." Any of these actions would be expected to bias our results toward the null, and therefore our findings are likely to be conservative. Fourth, our estimation of baseline fracture probability with FRAX was limited by incomplete information on parental hip fracture and reliance on proxies for smoking and high alcohol intake; however, we have previously shown that FRAX probability computed in this way still accurately reflects fracture risk in patients receiving osteoporosis treatment (49). Finally, we could not assess whether falls were a risk modifier because they are incompletely recorded in administrative data and are not considered in the FRAX algorithm (50).

In conclusion, our data support the use of serial BMD monitoring in routine clinical practice as an indicator of treatment-related antifracture effect for women

initiating osteoporosis therapy. Treatment-related detectable increases in total hip BMD are associated with lower risk for fracture than stable BMD, whereas detectable decreases are associated with greater risk for fracture. Almost one quarter of women in our sample had detectable decreases in BMD and a commensurate increased risk for fracture. Monitoring BMD in routine clinical practice may identify women with a suboptimal response to osteoporosis treatment who would benefit from closer follow-up, attention to secondary causes of osteoporosis, and directed inquiries about medication adherence and persistence.

From University of Manitoba, Winnipeg; University of Alberta, Edmonton; and McGill University, Montreal, Canada.

**Note:** This article has been reviewed and approved by the members of the Manitoba Bone Density Program Committee.

**Disclaimer:** The results and conclusions are those of the authors, and no official endorsement by the Manitoba Centre for Health Policy at the University of Manitoba, Manitoba Health, or other data providers is intended or should be inferred.

**Acknowledgment:** The authors thank the Manitoba Centre for Health Policy for use of data contained in the Population Health Research Data Repository (Health Information Privacy Committee Project Number 2012/2013-18) and Dr. Shuman Yang for assisting with SAS programming and figure preparation.

**Financial Support:** Dr. Majumdar is supported by his role as the Endowed Chair in Patient Health Management (Faculties of Medicine and Dentistry and Pharmacy and Pharmaceutical Sciences, University of Alberta). Dr. Morin is supported by her role as Scholar through Research Funds of Quebec Health. Dr. Lix is supported by her role as a Research Manitoba Chair.

**Disclosures:** Dr. Leslie reports grants from Amgen (paid to facility) and speaker fees (paid to facility) from Eli Lilly and Novartis outside the submitted work. Dr. Morin reports grants from Amgen and Merck (paid to institution) and personal fees from Amgen outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-2937.

**Reproducible Research Statement:** *Study protocol and data set:* Not available. *Statistical code:* SAS code for producing directly adjusted risk estimates is available from Dr. Leslie (e-mail, bleslie@sbgh.mb.ca).

**Requests for Single Reprints:** William D. Leslie, MD, MSc, Department of Medicine (C5121), University of Manitoba, Winnipeg, 409 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada; e-mail, bleslie@sbgh.mb.ca.

Current author addresses and author contributions are available at www.annals.org.

## References

1. **NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy.** Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285:785-95. [PMID: 11176917]
2. **Ensrud KE, Schousboe JT.** Clinical practice. Vertebral fractures. N Engl J Med. 2011;364:1634-42. [PMID: 21524214] doi:10.1056/NEJMcp1009697
3. **Raisz LG.** Clinical practice. Screening for osteoporosis. N Engl J Med. 2005;353:164-71. [PMID: 16014886]
4. **Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N.** A reference standard for the description of osteoporosis. Bone. 2008;42:467-75. [PMID: 18180210] doi:10.1016/j.bone.2007.11.001
5. **U.S. Preventive Services Task Force.** Screening for osteoporosis: U.S. preventive services task force recommendation statement. Ann Intern Med. 2011;154:356-64. [PMID: 21242341] doi:10.7326/0003-4819-154-5-201103010-00307
6. **MacLean C, Newberry S, Maglione M, McMahon M, Ranganath V, Suttorp M, et al.** Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Ann Intern Med. 2008;148:197-213. [PMID: 18087050]
7. **Hopkins RB, Goeree R, Pullenayegum E, Adachi JD, Papaioannou A, Xie F, et al.** The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women. BMC Musculoskelet Disord. 2011;12:209. [PMID: 21943363] doi:10.1186/1471-2474-12-209
8. **Hillier TA, Stone KL, Bauer DC, Rizzo JH, Pedula KL, Cauley JA, et al.** Evaluating the value of repeat bone mineral density measurement and prediction of fractures in older women: the study of osteoporotic fractures. Arch Intern Med. 2007;167:155-60. [PMID: 17242316]
9. **Compston J.** Monitoring osteoporosis treatment. Best Pract Res Clin Rheumatol. 2009;23:781-8. [PMID: 19945689] doi:10.1016/j.berh.2009.09.007
10. **Bruyère O, Reginster JY.** Monitoring of osteoporosis therapy. Best Pract Res Clin Endocrinol Metab. 2014;28:835-41. [PMID: 25432355] doi:10.1016/j.beem.2014.07.001
11. **Hochberg MC, Greenspan S, Wasnich RD, Miller P, Thompson DE, Ross PD.** Changes in bone density and turnover explain the reductions in incidence of nonvertebral fractures that occur during treatment with antiresorptive agents. J Clin Endocrinol Metab. 2002;87:1586-92. [PMID: 11932287]
12. **Wasnich RD, Miller PD.** Antifracture efficacy of antiresorptive agents are related to changes in bone density. J Clin Endocrinol Metab. 2000;85:231-6. [PMID: 10634392]
13. **Cummings SR, Bates D, Black DM.** Clinical use of bone densitometry: scientific review. JAMA. 2002;288:1889-97. [PMID: 12377088]
14. **Cummings SR, Palermo L, Browner W, Marcus R, Wallace R, Pearson J, et al.** Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. Fracture Intervention Trial Research Group. JAMA. 2000;283:1318-21. [PMID: 10714731]
15. **Berger C, Langsetmo L, Joseph L, Hanley DA, Davison KS, Josse R, et al; Canadian Multicentre Osteoporosis Study Research Group.** Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. CMAJ. 2008;178:1660-8. [PMID: 18559803] doi:10.1503/cmaj.071416
16. **Bell KJ, Hayen A, Macaskill P, Irwig L, Craig JC, Ensrud K, et al.** Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. BMJ. 2009;338:b2266. [PMID: 19549996] doi:10.1136/bmj.b2266
17. **Leslie WD, MacWilliam L, Lix L, Caetano P, Finlayson GS.** A population-based study of osteoporosis testing and treatment following introduction of a new bone densitometry service. Osteoporos Int. 2005;16:773-82. [PMID: 15580480]
18. **Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, et al; Scientific Advisory Council of Osteoporosis Canada.** 2010 clinical practice guidelines for the diagnosis and manage-

ment of osteoporosis in Canada: summary. CMAJ. 2010;182:1864-73. [PMID: 20940232] doi:10.1503/cmaj.100771
19. Leslie WD, Caetano PA, Macwilliam LR, Finlayson GS. Construction and validation of a population-based bone densitometry database. J Clin Densitom. 2005;8:25-30. [PMID: 15722584]
20. Kozyrskyj AL, Mustard CA. Validation of an electronic, population-based prescription database. Ann Pharmacother. 1998; 32:1152-7. [PMID: 9825079]
21. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, et al. Updated data on proximal femur bone mineral levels of US adults. Osteoporos Int. 1998;8:468-89. [PMID: 9850356]
22. Schousboe JT, Shepherd JA, Bilezikian JP, Baim S. Executive summary of the 2013 International Society for Clinical Densitometry Position Development Conference on bone densitometry. J Clin Densitom. 2013;16:455-66. [PMID: 24183638] doi:10.1016/j.jocd.2013.08.004
23. Glüer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genant HK. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. Osteoporos Int. 1995;5:262-70. [PMID: 7492865]
24. Glüer CC. Monitoring skeletal changes by radiological techniques. J Bone Miner Res. 1999;14:1952-62. [PMID: 10571696]
25. Shepherd JA, Lu Y, Wilson K, Fuerst T, Genant H, Hangartner TN, et al; International Society for Clinical Densitometry Committee on Standards of Bone Measurement. Cross-calibration and minimum precision standards for dual-energy X-ray absorptiometry: the 2005 ISCD Official Positions. J Clin Densitom. 2006;9:31-6. [PMID: 16731429]
26. Leslie WD. Factors affecting short-term bone density precision assessment and the effect on patient monitoring. J Bone Miner Res. 2008;23:199-204. [PMID: 17937536]
27. Baim S, Wilson CR, Lewiecki EM, Luckey MM, Downs RW Jr, Lentle BC. Precision assessment and radiation safety for dual-energy X-ray absorptiometry: position paper of the International Society for Clinical Densitometry. J Clin Densitom. 2005;8:371-8. [PMID: 16311420]
28. Leslie WD; Manitoba Bone Density Program. The importance of spectrum bias on bone density monitoring in clinical practice. Bone. 2006;39:361-8. [PMID: 16537116]
29. Kanis JA, Oden A, Johansson H, Borgström F, Ström O, McCloskey E. FRAX and its applications to clinical practice. Bone. 2009;44: 734-43. [PMID: 19195497] doi:10.1016/j.bone.2009.01.373
30. Leslie WD, Lix LM, Langsetmo L, Berger C, Goltzman D, Hanley DA, et al. Construction of a FRAX® model for the assessment of fracture probability in Canada and implications for treatment. Osteoporos Int. 2011;22:817-27. [PMID: 21161509] doi:10.1007/s00198-010-1464-2
31. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA; Manitoba Bone Density Program. Independent clinical validation of a Canadian FRAX tool: fracture prediction and model calibration. J Bone Miner Res. 2010;25:2350-8. [PMID: 20499367] doi:10.1002/jbmr.123
32. Fraser LA, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, et al; CaMos Research Group. Fracture prediction and calibration of a Canadian FRAX® tool: a population-based report from CaMos. Osteoporos Int. 2011;22:829-37. [PMID: 21161508] doi:10.1007/s00198-010-1465-1
33. Leslie WD, Tsang JF, Caetano PA, Lix LM; Manitoba Bone Density Program. Effectiveness of bone density measurement for predicting osteoporotic fractures in clinical practice. J Clin Endocrinol Metab. 2007;92:77-81. [PMID: 17032716]
34. Lix LM, Azimaee M, Osman BA, Caetano P, Morin S, Metge C, et al. Osteoporosis-related fracture case definitions for population-based administrative data. BMC Public Health. 2012;12:301. [PMID: 22537071] doi:10.1186/1471-2458-12-301
35. Storer BE, Gooley TA, Jones MP. Adjusted estimates for time-to-event endpoints. Lifetime Data Anal. 2008;14:484-95. [PMID: 18791867] doi:10.1007/s10985-008-9098-9
36. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312:1254-9. [PMID: 8634613]
37. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Eisman JA. A longitudinal study of the effect of spinal degenerative disease on bone density in the elderly. J Rheumatol. 1995;22:932-6. [PMID: 8587085]
38. Gourlay ML, Fine JP, Preisser JS, May RC, Li C, Lui LY, et al; Study of Osteoporotic Fractures Research Group. Bone-density testing interval and transition to osteoporosis in older women. N Engl J Med. 2012;366:225-33. [PMID: 22256806] doi:10.1056/NEJMoa1107142
39. Gourlay ML, Overman RA, Fine JP, Ensrud KE, Crandall CJ, Gass ML, et al; Women's Health Initiative Investigators. Baseline age and time to major fracture in younger postmenopausal women. Menopause. 2015;22:589-97. [PMID: 25349960] doi:10.1097/GME.0000000000000356
40. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev. 2002;23:570-8. [PMID: 12202472]
41. Watts NB, Josse RG, Hamdy RC, Hughes RA, Manhart MD, Barton I, et al. Risedronate prevents new vertebral fractures in postmenopausal women at high risk. J Clin Endocrinol Metab. 2003;88: 542-9. [PMID: 12574177]
42. Silverman S. Adherence to medications for the treatment of osteoporosis. Rheum Dis Clin North Am. 2006;32:721-31. [PMID: 17288974]
43. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. J Clin Densitom. 2004;7:255-61. [PMID: 15319494]
44. Crandall CJ, Newberry SJ, Diamant A, Lim YW, Gellad WF, Suttorp MJ, et al. Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis: Update of a 2007 Report. AHRQ Comparative Effectiveness Reviews. Report no. 12-EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
45. Cummings SR, Cosman F, Eastell R, Reid IR, Mehta M, Lewiecki EM. Goal-directed treatment of osteoporosis. J Bone Miner Res. 2013;28:433-8. [PMID: 23300146] doi:10.1002/jbmr.1854
46. Kanis JA, McCloskey E, Branco J, Brandi ML, Dennison E, Devogelaer JP, et al. Goal-directed treatment of osteoporosis in Europe. Osteoporos Int. 2014;25:2533-43. [PMID: 25199574] doi:10.1007/s00198-014-2787-1
47. Leslie WD, Majumdar SR, Lix LM, Morin SN, Johansson H, Odén A, et al. Can change in FRAX score be used to "treat to target"? A population-based cohort study. J Bone Miner Res. 2014;29:1074-80. [PMID: 24877235]
48. Lenchik L, Kiebzak GM, Blunt BA; International Society for Clinical Densitometry Position Development Panel and Scientific Advisory Committee. What is the role of serial bone mineral density measurements in patient management? J Clin Densitom. 2002;5 Suppl: 529-38. [PMID: 12464709]
49. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA; Manitoba Bone Density Program. Does osteoporosis therapy invalidate FRAX for fracture prediction? J Bone Miner Res. 2012;27:1243-51. [PMID: 22392538] doi:10.1002/jbmr.1582
50. Kanis JA, Hans D, Cooper C, Baim S, Bilezikian JP, Binkley N, et al; Task Force of the FRAX Initiative. Interpretation and use of FRAX in clinical practice. Osteoporos Int. 2011;22:2395-411. [PMID: 21779818] doi:10.1007/s00198-011-1713-z

**Current Author Addresses:** Dr. Leslie: Department of Medicine (C5121), University of Manitoba, 409 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada.
Dr. Majumdar: General Internal Medicine, University of Alberta, 5-134B Clinical Sciences Building, 11350-83rd Avenue, Edmonton, Alberta T6G 2G3, Canada.
Dr. Morin: General Internal Medicine, McGill University Health Centre, Montreal General Hospital, 1650 Cedar Avenue, Room B2-118, Montréal, Québec H3G 1A4, Canada.
Dr. Lix: Department of Community Health Sciences, University of Manitoba, S113-750 Bannatyne Avenue, Winnipeg, Manitoba R3P 2H5, Canada.

**Author Contributions:** Conception and design: W.D. Leslie, S.R. Majumdar, L.M. Lix.
Analysis and interpretation of the data: W.D. Leslie, S.R. Majumdar, L.M. Lix.
Drafting of the article: W.D. Leslie, L.M. Lix.
Critical revision of the article for important intellectual content: W.D. Leslie, S.R. Majumdar, S.N. Morin, L.M. Lix.
Final approval of the article: W.D. Leslie, S.R. Majumdar, S.N. Morin, L.M. Lix.
Provision of study materials or patients: W.D. Leslie.
Statistical expertise: W.D. Leslie, L.M. Lix.
Obtaining of funding: W.D. Leslie.
Administrative, technical, or logistic support: W.D. Leslie.
Collection and assembly of data: W.D. Leslie.

**Web-Only References**

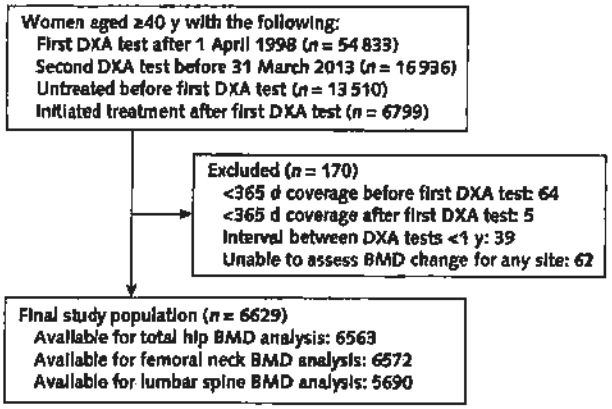
51. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC Classification and DDD Assignment. Oslo, Norway: World Health Organization; 2005.

***Appendix Table.*** Study Population Baseline Characteristics, by Variables Used in Fracture Probability Assessment and Incident Fracture Outcomes*

| Characteristic | Overall | No Fracture | Incident Fracture | *P* Value |
|---|---|---|---|---|
| Patients, *n* | 6629 | 5719 | 910 | |
| Mean age (SD), *y* | 64.3 (10.1) | 63.9 (10.0) | 66.9 (10.3) | <0.001 |
| Mean body mass index (SD), $kg/m^2$† | 25.6 (4.7) | 25.6 (4.7) | 25.5 (4.8) | 0.65 |
| Prior fracture, *n (%)* | 1140 (17.2) | 889 (15.5) | 251 (27.6) | <0.001 |
| Parental hip fracture, *n (%)*‡ | 276 (4.2) | 248 (4.3) | 28 (3.1) | 0.077 |
| Chronic obstructive pulmonary disease, *n (%)*§ | 511 (7.7) | 420 (7.3) | 91 (10.0) | 0.005 |
| Glucocorticoid use, *n (%)*‖ | 306 (4.6) | 256 (4.5) | 50 (5.5) | 0.174 |
| Rheumatoid arthritis, *n (%)* | 229 (3.5) | 190 (3.3) | 39 (4.3) | 0.139 |
| Alcohol abuse, *n (%)*§ | 174 (2.6) | 136 (2.4) | 38 (4.2) | 0.002 |
| Mean femoral neck T-score (SD) | −1.9 (0.8) | −1.8 (0.8) | −2.1 (0.8) | <0.001 |
| Mean fracture probability (SD), %¶ | 11.7 (7.3) | 11.2 (6.9) | 14.7 (8.7) | <0.001 |

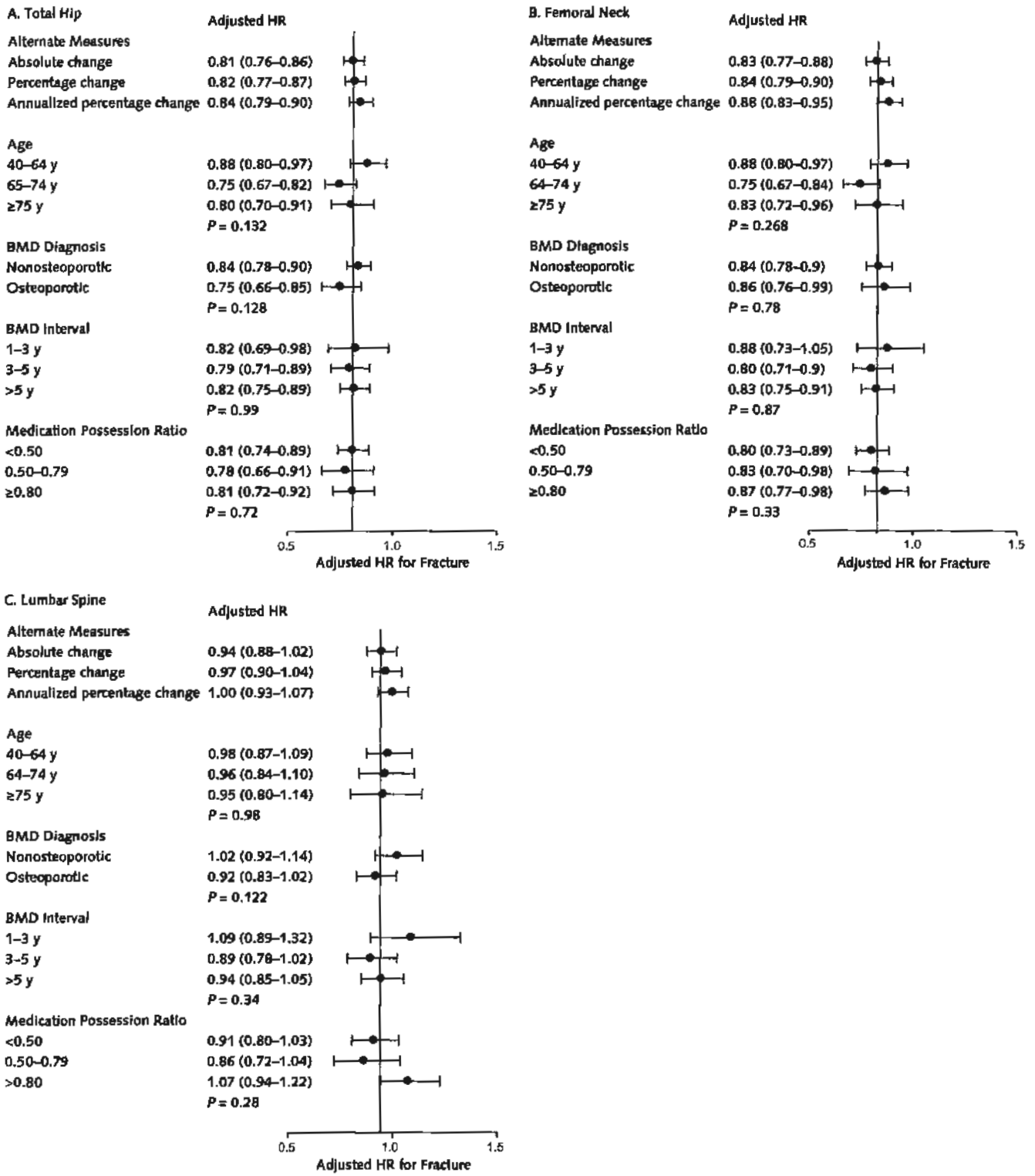
BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry; FRAX = Fracture Risk Assessment Tool.
* Prior fracture and other conditions required for calculating fracture probability with FRAX were assessed through a combination of hospital discharge abstracts (diagnoses and procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification, before 2004 and International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada, thereafter) and physician billing claims (coded using the International Classification of Diseases, Ninth Revision, Clinical Modification) and information collected at the time of DXA scanning as previously described (31).
† Height was measured at the time of the DXA examination with a wall-mounted stadiometer, and weight was assessed without shoes using a standard floor scale (before 2000, height and weight were obtained by self-report). Body mass index (in kilograms/meters squared) was calculated as weight (in kilograms) divided by height (in meters) squared and divided into quintiles.
‡ Obtained by self-report in 1904 women scanned from 2005 onward. It was not available for earlier years.
§ Proxies were used for smoking (chronic obstructive pulmonary disease diagnosis) and high alcohol intake (alcohol or substance abuse diagnosis) over the same time frame; these show prevalence similar to that of population-based data (31, 32).
‖ Prolonged glucocorticoid use (a >90-d supply dispensed in the year before DXA testing) was obtained from the provincial pharmacy system (51).
¶ FRAX major osteoporotic fractures computed with BMD.

***Appendix Figure 1.*** Study population eligibility and ineligibility criteria.




BMD = bone mineral density; DXA = dual-energy x-ray absorptiometry.

***Appendix Figure 2.*** Adjusted HRs (95% CIs) for incident fracture per SD increase in BMD using continuous measures of change.




Solid reference line is for absolute change in the overall population. *P* values are for interactions. All results are adjusted for baseline fracture probability. BMD = bone mineral density; HR = hazard ratio. A. Total hip: absolute change (for subgroups), 1 SD = 0.048 g/cm$^2$; percent change, 1 SD = 5.95%; and annual percent change, 1 SD = 1.56% per year. B. Femoral neck: absolute change (for subgroups), 1 SD = 0.048 g/cm$^2$; percent change, 1 SD = 6.10%; and annual percent change, 1 SD = 1.60% per year. C. Lumbar spine: absolute change (for subgroups), 1 SD = 0.067 g/cm$^2$; percent change, 1 SD = 7.48%; and annual percent change, 1 SD = 2.04% per year.