Long-term Use of Oral Anticoagulants and the Risk of Fracture

Pedro J. Caraballo, MD; John A. Heit, MD; Elizabeth J. Atkinson, MS; Marc D. Silverstein, MD; W. Michael O'Fallon, PhD; M. Regina Castro, MD; L. Joseph Melton III, MD

Background: Vitamin K participates in bone metabolism and, since oral anticoagulants antagonize vitamin K, their use may increase the risk of osteoporosis.

Objective: To evaluate fracture risk at all skeletal sites following exposure to oral anticoagulants.

Methods: In a population-based retrospective cohort study, 572 Olmsted County, Minnesota, women 35 years or older at their first lifetime venous thromboembolism event between 1966 and 1990 were followed up for fractures. Risk was assessed by comparing new fractures with the number expected from sex- and age-specific fracture incidence rates for the general population (standardized incidence ratio [SIR]).

Results: Altogether, 480 fractures occurred during 6314 person-years of follow-up. Increasing exposure to oral anticoagulation was associated with an increased SIR for vertebral fractures: at less than 3 months of exposure, 2.4 (95% confidence interval [CI], 1.6-3.4); 3 to less than 12 months, 3.6 (95% CI, 2.5-4.9); and 12 months or more, 5.3 (95% CI, 3.4-8.0); and for rib fractures: at less than 3 months, 1.6 (95% CI, 0.9-2.7); 3 to less than 12 months, 1.6 (95% CI, 0.9-2.6); and 12 months or more, 3.4 (95% CI, 1.8-5.7). The data revealed no increased risk for other types of fractures. Oral anticoagulation for 12 months or more was an independent predictor of vertebral fractures (P = .009) and rib fractures (P = .02), but not other fractures.

Conclusions: Long-term exposure to oral anticoagulation is associated with an increased risk of vertebral and rib fractures. The mechanism by which this occurs is still unclear and needs further investigation.

Arch Intern Med. 1999;159:1750-1756

OSTEOPOROSIS is a growing problem in postmenopausal women and elderly men. This same population has frequent indications for long-term anticoagulation, and warfarin sodium use is purportedly a strong risk factor for osteoporosis. The coumarins antagonize vitamin K through inhibition of the enzyme, vitamin K epoxide reductase. Vitamin K functions as a cofactor in the posttranslational -carboxylation of glutamic acid and, as a result of oral anticoagulant therapy, there is production of nonfunctional, undercarboxylated proteins, including osteocalcin and matrix Gla protein. Osteocalcin is considered an indicator of bone formation, while absence of matrix Gla protein is associated with severe osteopenia and fractures in a mouse model. The adverse effects of vitamin K deficiency and oral anticoagulants on young, rapidly growing bone have been well described both in animal models and in humans, but their effects on adult bone are uncertain. In postmenopausal women, low serum vitamin K and high levels of undercarboxylated osteocalcin correlate with low bone density. Likewise, 6 of 11 studies found decreased bone density in subjects exposed to long-term oral anticoagulants. However, a meta-analysis showed that oral anticoagulation was associated with a reduction of about 0.4 SD in bone density of the radius but no significant change in bone density of the hip or spine. High levels of undercarboxylated osteocalcin were shown to increase hip fracture risk almost 2-fold even after adjustment for femoral bone density. The most recent report found no increase in the risk of nontraumatic, nonvertebral fractures when self-reported warfarin users were compared with nonusers. However, the estimate was based on 15 fractures among 149 warfarin users, so statistical power was quite limited. To address this potentially important issue in more detail with longer follow-up of a larger sample of women, we performed a population-based...
SUBJECTS AND METHODS

STUDY SETTING AND SUBJECTS

Population-based epidemiologic research can be conducted in Olmsted County, Minnesota, because medical care is virtually self-contained within the community and there are relatively few providers. The majority of care is provided by the Mayo Clinic, Rochester, Minn, which maintains a common medical record system with its 2 large affiliated hospitals in the community (St Mary’s and Rochester Methodist) for more than 90 years. The diagnoses and surgical procedures in these records are indexed, as are the medical records of the other providers who serve the local population, most notably the Olmsted Medical Center.27 Following approval by Mayo’s Institutional Review Board, we used this unique database (the Rochester Epidemiology Project) to identify all Olmsted County residents with a first lifetime event of venous thromboembolism (VTE) from January 1, 1966, through December 31, 1990, as described in detail elsewhere.28 Altogether, 2218 Olmsted County residents had their initial event of VTE during the study period, and 1244 patients (56%) were women. For this analysis, we included only women. However, we excluded 234 women who were younger than 35 years at the time of the initial event and 438 others because they died (n = 419) or were lost to follow-up (n = 14) within the first year, or did not have medical records available for review (n = 5). The remaining 572 women constitute the subjects of this report.

DATA COLLECTION AND FOLLOW-UP

Following additional approval by Mayo’s Institutional Review Board and respecting Minnesota law regarding access to medical records for research,29 we reviewed each subject’s complete (inpatient and outpatient) medical record in the community. Mayo Clinic records, for example, contain the details of every inpatient hospitalization at its 2 hospitals, every outpatient office or clinic visit, all emergency department and nursing home care, as well as all radiographic reports and pathology reports, including autopsies.30 For oral anticoagulation therapy, the first and last dates of each course of treatment received for any indication through last follow-up were recorded. We also collected a large number of baseline clinical characteristics. These included (1) patient data: age, race, weight, and height (most recent prior to VTE), body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) and obesity (BMI > 27.3), smoking status (none, former, or current), alcohol use (any prior to VTE), age at menopause (≥1 year without menstruation), and type of menopause (natural or artificial); (2) type of VTE event and treatment; (3) medical history: physician’s diagnosis of pregnancy or postpartum period, active malignancy (excluding nonmelanoma skin cancer), neurologic disease (parkinsonism, dementia, stroke, or other disease with paresis), congestive heart failure, chronic lung disease (emphysema, chronic bronchitis, bronchiectasis, and interstitial lung disease), gastrectomy, liver disease (hepatitis and cirrhosis), inflammatory bowel disease, chronic renal disease (physician’s diagnosis with creatinine > 176.8 μmol/L [≥2 mg/dL] for 3 months), myeloproliferative disease, alcoholism, endocrine disease (hyperthyroidism, hypoparathyroidism, Cushing syndrome, and hyperprolactinemia), osteoporosis (physician’s or radiographic diagnosis), and rheumatoid arthritis; and (4) medications: chemotherapy (cytotoxic or immunosuppressive therapy for malignancy), tamoxifen citrate and oral contraceptives if used within 3 months prior to VTE, and glucocorticoids (excluding inhalers), levothyroxine sodium, anticonvulsants (phenytoin or phenobarbital), and hormone replacement therapy (estrogen and/or progestin) if used for 1 month or more anytime prior to VTE.

Patients were then followed forward in time through their records at any local provider of medical care until death or the last medical record entry in order to identify all new fractures. The records contained the clinical history and the radiologist’s report of each fracture, but the original roentgenograms were not available for review. Thus, the diagnosis of vertebral fracture was accepted on the basis of a radiologist’s report of compression or collapse of 1 or more thoracic or lumbar vertebrae. All fractures were classified according to the circumstances of the injury: by convention, falls from standing height or lower were considered “moderate trauma,” while motor vehicle crashes and falls from heights were deemed “severe trauma.” Ascertainment of fractures is believed to be complete except for vertebral fractures, some of which are never diagnosed.31 A restricted definition of an “osteoporotic” fracture was also used, ie, a nonpathologic, nonviolent (fall from standing height or lower, spontaneous, or incidental clinical finding) fracture of thoracic or lumbar vertebrae, distal forearm, or proximal femur at 35 years or older.

STATISTICAL ANALYSIS

Several methods were used to evaluate the influence of oral anticoagulation on fracture risk. First, person-years of follow-up for each individual were categorized according to the person’s warfarin exposure and age. Because we excluded subjects with less than 1 year of follow-up, the index date was taken to be 1 year after the initial VTE event. All person-years from the entire cohort that had similar categorizations were combined (eg, 0 to <3, 3-12, and ≥12 months of oral anticoagulation). The number of incident fractures by type that were observed in each of these groups was compared with the number expected for community residents in general (standardized incidence ratio [SIR]). Expected numbers of fractures were derived by applying sex- and age-specific incidence rates from the local population for these fractures31-36 to the age-specific person-years of follow-up in the previously described groups. Ninety-five percent confidence intervals (CIs) for the SIRs were calculated assuming that the expected rates were fixed and the observed fractures follow a Poisson distribution.37

In a second analysis, the cumulative incidence of new fractures (1 - the probability of surviving free of fracture) was projected for up to 20 years following the index date using product-limit life-table methods.38 Log-rank tests were used to compare observed and expected cumulative incidence curves.39

Finally, the influence of the duration of warfarin exposure and other characteristics on fracture risk was assessed using the Cox model.40 Warfarin exposure was evaluated as a time-dependent variable and, as in the person-year analysis, was categorized as “zero to less than 3 months,” “3 to more than 12 months,” and “12 months or more.” A stepwise variable selection method was used to choose independent variables for the final models. The calculations were performed using SAS software (SAS Institute, Inc, Cary, NC).
Altogether 1244 Olmsted County women had their first lifetime event of VTE between 1966 and 1990. Of these, 572 women were 35 years or older at the time of the VTE event and had at least 1 year of follow-up thereafter. At baseline, their mean ± SD age was 63.9 ± 15.8 years, with a range from 35 to 95 years. Ninety-nine percent were white, reflecting the racial composition of the community (96% white in 1990). Altogether, 491 women (86%) were postmenopausal, with a mean age at menopause of 46.8 ± 6.1 years. The first VTE event was deep vein thrombosis in 312 (55%) and pulmonary embolism with or without deep vein thrombosis in 259 (45%). Four hundred ninety-three women (87%) were exposed to heparin within a year after the VTE event, with a mean ± SD duration of 6.1 ± 4.1 days. Exposure to any oral anticoagulant was present in 545 women (95%) with a mean lifetime exposure of 16.1 ± 36.8 months, ranging from 0 to 27.4 years. Only 2 oral anticoagulants were used, dicumarol and warfarin. Dicumarol was prescribed in a small number of patients and, since it has exactly the same mechanism of action as warfarin, both were considered together in the analysis.

For the purpose of this analysis, clinical conditions thought to be related to fracture risk were arbitrarily compiled into groups: (1) those related to an increased risk of falling, (2) those metabolic conditions predisposing to secondary osteoporosis, and (3) those associated with a decreased risk for secondary osteoporosis (protective factors). Table 1 shows the frequency of these conditions individually and by group. Although the large number of conditions evaluated were relatively infrequent individually, they were common in aggregate. Altogether, 66% of the women had a history of 1 or more of the conditions associated with increased fracture risk and 85% had at least 1 of the conditions evaluated.

The cohort of 572 women was followed up for 6314 person-years, and 257 women (45%) were still alive at last follow-up. A total of 480 fractures occurred after the index date, of which 86 (18%) were caused by severe trauma and 21 (4%) were due to some specific pathological process; the remaining 78% resulted from only minimal or moderate trauma, including the majority of fractures of the vertebrae (90%), proximal femur (91%), and distal forearm (73%). As delineated in Table 2, the 243 women with at least 1 new fracture (considering all skeletal sites) were comparable to the 218.7 expected on the basis of overall community fracture rates (SIR, 1.1; 95% CI, 0.98-1.3). However, a 30% increase (SIR, 1.3; 95% CI, 1.1-1.5) in the risk of 1 or more osteoporotic fractures (defined in “Methods” section) was almost entirely due to a 3.3-fold increase in new vertebral fractures (95% CI, 2.7-4.1). There was almost a 2-fold increase in the risk of rib fractures (SIR, 1.9; 95% CI, 1.4-2.6) and almost a 3-fold increase in fractures of the pelvis (SIR, 2.9; 95% CI, 1.9-4.3). However, the risk of limb fractures in general was not increased (SIR, 1.0; 95% CI, 0.8-1.2). A 10% increase in the risk of all nonosteoporotic fractures together was not statistically significant (SIR, 1.1; 95% CI, 0.97-1.3). The cumulative incidence of any fracture at 20 years was 66% compared with an expected 62% (P = .10). There was an increase in osteoporotic fractures at 20 years (43% observed vs 37% expected; P = .001), but the increase was greater for vertebral fractures (32% vs 12%; P < .001) and rib fractures (16% vs 9%; P < .001). The latter data are illustrated in Figure 1.

When fracture risk was assessed by duration of exposure to oral anticoagulants, vertebral and rib fractures were the only ones that showed an increasing risk with greater exposure (Table 2). For vertebral fractures, the risk increased from 2.4 (95% CI, 1.6-3.4) with less than 3 months of exposure, to 3.6 (95% CI, 2.5-4.9) with 3 to less than 12 months, and to 5.3 (95% CI, 3.4-8.0) with therapy for 12 months or more. For rib fractures, the risk was 1.6 (95% CI, 0.9-2.7) with less than 3 months and 1.6 (95% CI, 0.9-2.6) with 3 to less than 12 months of therapy, increasing to 3.4 (95% CI, 1.8-5.7) with 12 months or more of exposure (Figure 2).

Among the other variables assessed at baseline, age was positively associated with fracture risk (Table 3).
Each 10-year increase in age was associated with a 33% increase in the risk of any fracture (95% CI, 1.2-1.4) independent of other risk factors. Other independent predictors of overall fracture risk in a multivariate analysis included a history of osteoporosis (hazard ratio [HR], 1.5; 95% CI, 1.1-2.0), malignancy (HR, 2.2; 95% CI, 1.2-4.2), or liver disease (HR, 4.7; 95% CI, 1.5-15). Increasing height and weight were protective for all osteopo-

---

### Table 2. Observed (Obs) Fractures After the Index Date in Comparison With Expected Numbers (Exp) and Standardized Incidence Ratios (SIRs) by Length of Exposure to Oral Anticoagulation Among Olmsted County, Minnesota, Women Following Their First Lifetime Event of Venous Thromboembolism, 1966-1990

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>Entire Cohort</th>
<th>&lt;3 mo</th>
<th>3 to &lt;12 mo</th>
<th>≥12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
<td>SIR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Skull/face</td>
<td>8</td>
<td>4.5</td>
<td>1.8</td>
<td>0.8-3.5</td>
</tr>
<tr>
<td>Cervical spine/posterior elements</td>
<td>5</td>
<td>1.8</td>
<td>2.7</td>
<td>0.9-6.4</td>
</tr>
<tr>
<td>Vertebrae (thoracic/lumbar)</td>
<td>94</td>
<td>28.1</td>
<td>3.3</td>
<td>2.7-4.1</td>
</tr>
<tr>
<td>Ribs</td>
<td>46</td>
<td>23.8</td>
<td>1.9</td>
<td>1.4-2.6</td>
</tr>
<tr>
<td>Sternum/clavicle/scapula</td>
<td>13</td>
<td>6.8</td>
<td>1.9</td>
<td>1.0-3.3</td>
</tr>
<tr>
<td>Proximal humerus</td>
<td>22</td>
<td>14.7</td>
<td>1.5</td>
<td>0.9-2.3</td>
</tr>
<tr>
<td>Shaft/distal humerus</td>
<td>9</td>
<td>4.0</td>
<td>2.3</td>
<td>1.0-4.3</td>
</tr>
<tr>
<td>Shaft/proximal forearm</td>
<td>7</td>
<td>7.5</td>
<td>0.9</td>
<td>0.4-1.9</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>30</td>
<td>27.8</td>
<td>1.1</td>
<td>0.7-1.5</td>
</tr>
<tr>
<td>Hand/fingers</td>
<td>20</td>
<td>14.4</td>
<td>1.4</td>
<td>0.9-2.1</td>
</tr>
<tr>
<td>Pelvis</td>
<td>26</td>
<td>8.9</td>
<td>2.9</td>
<td>1.9-4.3</td>
</tr>
<tr>
<td>Proximal femur</td>
<td>43</td>
<td>32.2</td>
<td>1.3</td>
<td>0.9-1.8</td>
</tr>
<tr>
<td>Shaft/distal femur</td>
<td>12</td>
<td>6.8</td>
<td>1.8</td>
<td>0.9-3.1</td>
</tr>
<tr>
<td>Patella</td>
<td>1</td>
<td>5.1</td>
<td>0.2</td>
<td>0.0-1.1</td>
</tr>
<tr>
<td>Tibia/foot/ankle</td>
<td>27</td>
<td>25.3</td>
<td>1.1</td>
<td>0.7-1.6</td>
</tr>
<tr>
<td>Foot/toes</td>
<td>20</td>
<td>24.4</td>
<td>0.8</td>
<td>0.5-1.3</td>
</tr>
<tr>
<td>Any fracture</td>
<td>243</td>
<td>218.7</td>
<td>1.1</td>
<td>0.9-1.3</td>
</tr>
<tr>
<td>Any osteoporotic fracture†</td>
<td>148</td>
<td>113.9</td>
<td>1.3</td>
<td>1.1-1.5</td>
</tr>
<tr>
<td>Any nonosteooporotic fracture</td>
<td>161</td>
<td>142.0</td>
<td>1.1</td>
<td>0.9-1.3</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†Nonpathologic, nonviolent fracture of thoracic or lumbar vertebrae, distal forearm, or proximal femur at 35 years or older.

---

**Figure 1.** Observed and expected cumulative incidence (1 − the probability of surviving free of fracture) of any rib fracture and any vertebral fracture among 572 Olmsted County, Minnesota, women following their first lifetime event of venous thromboembolism from January 1, 1966, through December 31, 1990.
rotic fractures combined and for vertebral fractures in univariate analyses, as was BMI. Since these are so closely related, only BMI was considered in the final analysis and was an independent predictor of decreased osteoporotic (HR, 0.97; 95% CI, 0.94-0.99) and vertebral (HR, 0.96; 95% CI, 0.93-0.99) fracture risk. Alcohol use and cigarette smoking were also associated with a reduced risk of fracture in univariate analyses. However, cigarette smoking was positively associated with alcohol use and, when adjusted for age, neither was significant. Other risk factors that were independently associated with vertebral or rib fractures in multivariate analyses included glucocorticoid use (HR, 2.8; 95% CI, 1.4-5.7) and neurologic disease (HR, 2.0; 95% CI, 1.1-3.6) for vertebral fractures and malignancy (HR, 4.9; 95% CI, 1.9-13) for rib fractures. Hormone replacement therapy was not protective for fractures in this analysis and other potential treatments for osteoporosis were not evaluated.

Because 95% of the women were exposed to oral anticoagulants at some point, any exposure (vs none) was not a significant predictor of subsequent fracture risk in univariate analyses or in multivariate analyses controlling for other risk factors. However, when length of exposure was divided into groups, we found that oral anticoagulation for 12 months or more was associated with an increased risk of vertebral fractures ($P<.001$), rib fractures ($P=.003$), and all osteoporotic fractures combined ($P<.001$) in univariate analyses. In multivariate analyses, treatment for this duration was an independent predictor of vertebral fractures ($P=.009$), rib fractures ($P=.02$), and all osteoporotic fractures together ($P=.02$) after controlling for other factors.

This investigation, of a large population-based cohort of women exposed to oral anticoagulants and followed up after their first lifetime VTE event, found an association between exposure to oral anticoagulation and the risk of vertebral and rib fractures but not other fractures. After adjusting for other risk factors, anticoagulant therapy for 12 months or more was associated with a 2-fold in-

![Table 3. Univariate Analyses of Potential Risk Factors for Fracture Among Olmsted County, Minnesota, Women Following Their First Lifetime Event of Venous Thromboembolism, 1966-1990*](image)
crease in vertebral fractures and a 2.1-fold increase in rib fractures.

A study of hemodialysis patients found significantly decreased (3-fold) serum vitamin K1 levels among 9 patients with fractures compared with 41 patients without a fracture. Likewise, vitamin K deficiency, as manifested by undercarboxylated osteocalcin, has been shown to be an independent predictor of hip fracture, increasing the risk by 90%.” Since oral anticoagulants increase undercarboxylated osteocalcin, we might have anticipated an increase in hip fracture risk in this cohort. However, we found no such increase, even in the group with long-term exposure (≥12 months) to warfarin, and we had greater than 95% power to detect a doubling of hip fracture risk in our cohort. We also did not find an increase in the risk of distal forearm fractures, as might have been expected from several studies that showed a decrease in bone density of the distal and ulnaward radius after exposure to oral anticoagulation. However, fracture risk is sometimes overestimated by bone density changes and sometimes underestimated. Thus, we did observe an increase in vertebral fracture risk despite indications that spinal bone density is not influenced by vitamin K status or oral anticoagulation. To our knowledge, there is little additional published information about fracture risk after exposure to oral anticoagulants. Data from the Study of Osteoporotic Fractures did not show any difference in overall fracture rates between warfarin users and nonusers after 3.5 years of follow-up, but only 15 fractures were observed among the warfarin users, and vertebral fractures were not assessed.

The specific role of vitamin K in bone metabolism is still not well defined, and therefore the consequences of oral anticoagulant use on bone quality are also unclear. As noted in the introduction, vitamin K is involved in bone metabolism through the γ-carboxylation of proteins (ie, osteocalcin, matrix Gla protein), which is inhibited by oral anticoagulants. However, there are other effects of vitamin K on bone physiology that do not seem to be affected by oral anticoagulation, ie, inhibition of dinoprostone, interleukin 6, and of osteocalcalf like multinucleated cell formation. These findings suggest that vitamin K deficiency might augment bone resorption through other pathways, and we have shown that elevated bone resorption is an independent risk factor for fracture. This might explain in part differences in fracture risk between subjects with vitamin K deficiency, as reported by others, and the patients exposed to oral anticoagulation who are described herein. Our data do not allow direct assessment of any pathophysiologic mechanism responsible for the association of vertebral and rib fractures with long-term anticoagulation, but future research should look for other differences in bone response between anticoagulation and vitamin K deficiency.

The present study has a number of strengths. This large population-based inception cohort represents the complete spectrum of VTE survivors in the community. The clinical characteristics and oral anticoagulation treatments were recorded prior to any knowledge of resultant fractures, and the medical records contained detailed documentation of the fractures that occurred during each subject’s residency in the community, the vast majority of which come to medical attention. Incidence should, therefore, be nearly complete, and we have no reason to believe that ascertainment would systematically differ between our study cohort and the general population from which the expected fracture rates were obtained, with the possible exception of vertebral fractures. The incidence rates used in these calculations were based on clinically recognized vertebral fractures, and they provide a low estimate of vertebral fracture frequency in the population. If women with VTE were followed up more closely for vertebral fractures than community women generally, the overall increase in vertebral fractures that we observed (SIR, 3.3; 95% CI, 2.7-4.1) might be an overestimate, and something similar might happen with rib fractures. An alternative approach is to use incidence rates derived from prevalence data, but they are too high since many vertebral deformities do not represent actual clinical fractures. If the latter rates are substituted in the analysis, however, the overall vertebral fracture risk is no longer elevated (SIR, 1.1; 95% CI, 0.9-1.4), although the increase associated with oral anticoagulation for 12 months or more (SIR, 1.7; 95% CI, 1.1-2.6) is still statistically significant. Thus, an overall SIR of only 1.1 is almost certainly an underestimate, but our reported SIR of 3.3 may be an overestimate; the truth should lie somewhere in between.

There are also limitations to this retrospective approach. Risk factors for falls could not be thoroughly assessed and special measurements, such as vitamin K status, osteocalcin levels, or bone density, were not performed. These could be evaluated in a prospective study aimed at elucidating the pathophysiologic basis for the excess vertebral and rib fractures. Also, our results are not generalizable to nonwhites since the Olmsted County population is largely white and slightly younger than US whites in general. However, age-adjusted hip fracture incidence rates from Rochester are quite comparable with those for US whites. These considerations had little effect on our overall conclusion that the risk of fractures was not markedly increased among women who were exposed to oral anticoagulation except for vertebral and rib fractures. Perhaps exposure to oral anticoagulation should not be considered an important risk factor for generalized osteoporosis, but its effects on the axial skeleton need to be better understood.

Accepted for publication December 21, 1998.

This work was supported in part by National Institutes of Health, Bethesda, Md, research grants AG04875, HL46974, and AR30582.

The authors thank Mary Roberts for assistance in preparing the manuscript.

Reprints: L. Joseph Melton III, MD, Department of Health Sciences Research, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

REFERENCES


42. Riggs BL, Melton LJ III, O’Fallon WM. Drug therapy for vertebral fractures in osteoporosis: evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. Bone. 1996;18:197S-205S.


