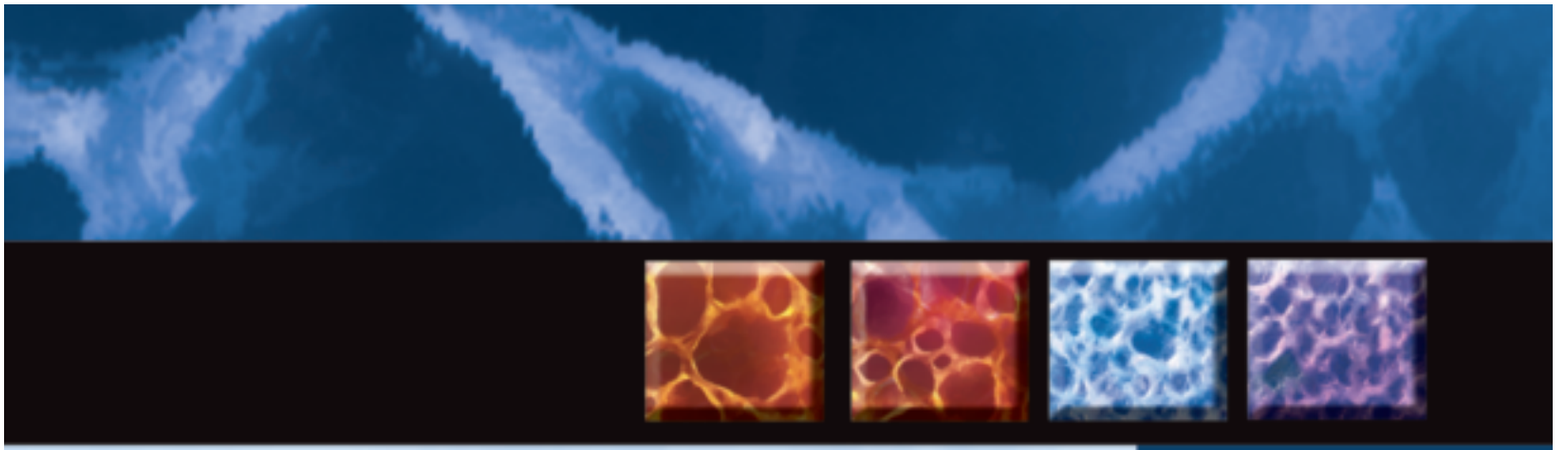

NONVERTEBRAL FRACTURE PREVENTION, TREATMENT, AND MANAGEMENT:
Critical Review of the Data

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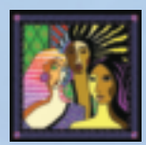

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TARGET AUDIENCE

Clinicians who manage/treat patients with osteoporosis: primary care physicians (general practitioners, family practitioners, internists), doctors of osteopathy, geriatricians, obstetricians/gynecologists, orthopedists, rheumatologists, endocrinologists, nurse practitioners, and physician assistants.

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NONVERTEBRAL FRACTURE PREVENTION, TREATMENT, AND MANAGEMENT: Critical Review of the Data

INTRODUCTION

Nonvertebral fractures are one of the most serious consequences of osteoporosis, a disease of aging that disproportionately affects women. An estimated 75 million people in Europe, Japan, and the United States have osteoporosis, causing more than 2.3 million fractures annually in the United States and Europe alone.[1] In 2002, an astounding 1 in 5 postmenopausal white women in the United States were calculated to have osteoporosis, and more than 1 in 2 were calculated to be at risk, having evidence of low bone density at the hip.[2] An even more disturbing projection is that half of all white women in the United States will experience a fracture related to osteoporosis at some time in their lives.[2] Statistics on the impact of osteoporosis and fractures due to osteoporosis are limited in African Americans and other minorities.[3] However, fractures due to osteoporosis are underdiagnosed and undertreated in all populations.[4] Bone loss increases with age in both genders, and the greater risk of osteoporosis among women is, in part, the result of longer life expectancy. As men live longer, the gender difference is expected to diminish. Currently, 1 in 5 individuals with osteoporosis is male, and 1 in 4 men >50 years of age will have a fracture due to this condition in his lifetime.[4] Additionally, the existing disparities in prevalence from country to country are expected to equalize as life expectancy improves worldwide.

Although the term "nonvertebral fracture" lacks a common definition among clinical trial reports, in a general sense it refers to any fracture not involving the spinal column. Nonvertebral fractures are more common than fractures of the vertebrae—an estimated 850,000 nonvertebral compared with 700,000 vertebral fractures occur annually in the United States. Nonvertebral fractures include more than 300,000 hip and 250,000 wrist fractures, in addition to 300,000 fractures at other nonvertebral sites.[5]

EDUCATIONAL OBJECTIVES

Upon completion of this program, the participant should be able to:

- Describe the impact of nonvertebral fracture on morbidity, mortality, economics, and quality of life
- Identify factors that put a patient at risk for nonvertebral fracture
- Assess the nonpharmacologic and pharmacologic management approaches to the prevention and treatment of nonvertebral fracture
- Critically review the currently available clinical trial data with respect to efficacy and nonvertebral fracture risk reduction, focusing on antiresorptive therapy

Hip fractures are the most debilitating and costly to treat.[1] Only 40% of individuals with hip fractures fully recover their prefracture degree of independence.[2] Hip fractures are the leading cause of admission to long-term care facilities and may be required for as many as 1 in 4 hip-fracture patients.[2] In addition, hip fractures are associated with increased risk of death.[2]

Identifying elderly individuals at greatest risk of fractures is critical to reduce the impact of osteoporosis on personal and public health. Bone mineral density (BMD) is widely used to assess fracture risk.[1] However, increasing evidence suggests that bone density is only one component of bone strength.[1] Whereas BMD measures a single, albeit important, component of risk, previous fractures are a hallmark of osteoporosis, associated with at least a doubling of the risk for subsequent fractures.[6]

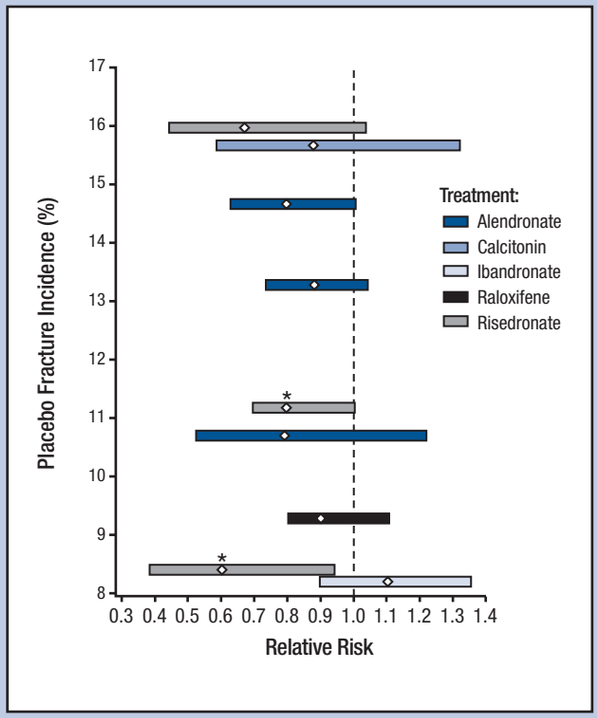
Implementation of practical and effective approaches for reducing the risk of fractures in the elderly requires a multidisciplinary effort among healthcare providers. This effort has been limited by the difficulty of integrating clinical trial data into clinical practice. The effects of nonpharmacologic, nutritional, and pharmacologic approaches on surrogate markers of fracture have not always reliably predicted clinical outcomes. The effects of pharmacologic interventions on fracture risk have been directly evaluated in several large clinical trials.[7-18] Although the Hip Intervention Prevention (HIP) trial evaluated hip fracture rate as a primary end point,[14] no trial has evaluated nonvertebral sites in aggregate as such. As a result, statistically evaluable data from individual trials are limited. Moreover, comparisons among trials are complicated by differing definitions of nonvertebral fracture. In some, but not all trials, fractures at a limited number of nonvertebral sites were tracked, whereas, in others, all reported fractures were included in subsequent analysis. Additionally, some investigators defined fractures due to osteoporosis as those that would not have occurred in a healthy person with normal BMD.[7-18]

A recent meta-analysis has addressed this gap and has shown that some pharmacologic interventions can achieve statistically significant reductions in nonvertebral fracture risks (Figure 1, page 2). Efficacy was demonstrated in populations with relatively low incidence of nonvertebral fractures in the placebo group, suggesting that treatment benefit was not related to severity of osteoporosis.[19]

This *Clinical Courier*® will discuss the importance of reducing the medical, economic, and societal impact of nonvertebral fractures. Efficacy data for antiresorptive therapy will be critically evaluated.

FIGURE 1

NONVERTEBRAL ANTIFRACTURE EFFICACY BY PLACEBO INCIDENCE[19]



*$P<.05$; statistically significant at the 5% level.

EPIDEMIOLOGY OF FRACTURES

Incidence of Nonvertebral Fractures

Nonvertebral fractures occur more frequently in women, and the incidence is strongly correlated with increasing age (Figure 2). In a 5-year prospective cohort study of low-trauma fractures due to osteoporosis, the *overall incidence* in 1000 person-years was 29.5 for women and 14.4 for men.[20] The incidence of all nonvertebral fractures increased with age in both men and women.[20] In North America, the risk of hip, spine, or forearm fracture is 40% for white women at the age of 50 years and 13% for white men.[1] Statistics for the incidence and impact of fractures due to osteoporosis in other racial and ethnic groups are limited.

Proximal femur

Hip fractures are generally the most serious fracture resulting from osteoporosis. They are usually painful and require hospitalization and rehabilitative care.[1,2] Thromboembolism and infections are associated with increased morbidity and mortality in patients with hip fracture.[21,22] In the United States, the lifetime risks for hip fracture in a 50-year-old Caucasian woman and man are 17.5% and 6.0%, respectively.[1] Each year, approximately 3% of white women aged 85 years or older will fracture a hip.[1] The annual global incidence of hip fractures is projected to be 3 million by 2025.[1]

Distal forearm

Distal forearm fractures occur approximately 4 times more frequently in women than in men and are the most common fracture occurring in perimenopausal women.[23,24] The lifetime risks for forearm fracture in a 50-year-old Caucasian woman and man in the United States are 16.0% and 2.5%, respectively.[1] The rate of wrist fracture begins to increase in women at about age 40 years, and, for reasons that are not well understood, in some countries the rate plateaus at age 65 years.[1] Because most wrist fractures result from falls, changing patterns of falling with advancing age may explain the plateau.[1]

Other fractures

The risks for proximal humeral, pelvic, and proximal tibial fractures also rise steeply with age and are higher in women than in men.[23] Similar patterns have been observed for fractures of the distal femur, rib, clavicle, and scapula.[23]

IMPACT OF NONVERTEBRAL FRACTURES

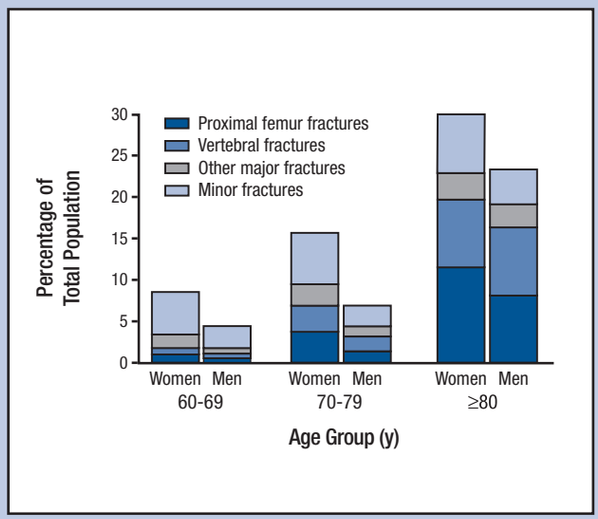
Mortality

Hip fracture has been shown to reduce life expectancy significantly, with the greatest effect in the first few months following the fracture. In the United States, the remaining life expectancy of a community-dwelling 80-year-old patient who has had a hip fracture has been shown to be reduced by about 25% (1.8 years).[25] In a prospective study involving 7512 ambulatory women aged 75 years or older, after adjusting for age and baseline health status, women with hip fracture were more than twice as likely to die during the approximately 4-year follow-up period.[26] The risk of death was greatest in the first 6 months but persisted for at least 3 years. Most post–hip-fracture deaths were caused by comorbidities such as cardiovascular disease or stroke, rather than as a direct result of the hip fracture.[26] These findings suggest that hip fracture is a harbinger of, or precipitates, accelerated progression of comorbidities.

Fracture-related mortality has been shown to be consistently greater for men than for women.[27-29] A Finnish study found that mortality in the first 4 months after hip fracture was almost twice as great for men as for women (15.5% vs 7.9%, respectively).[28] In a case-controlled study of the effects of hip fracture in elderly community-dwelling people, Fransen et al found that men with hip fracture were 7.2 times more likely to have died at 2 years than were controls without hip fracture who were matched for age, gender, and baseline health status.[29] The risk for women was only increased by a factor of 1.3 over 2 years.[29]

FIGURE 2

PERCENTAGE OF POPULATION SUSTAINING LOW-TRAUMA FRACTURES BY AGE AND GENDER



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Morbidity

A proportion of increased mortality after hip fractures may be related to the significant reduction in mobility that frequently occurs. After 1 year, between 20% and 60% of patients with hip fracture have not regained prior ambulatory status. Less than one half of patients are able to perform daily activities as independently as before the fracture.[30] In a cohort of 103 individuals older than 65 years, after 1 year, the percentage of individuals who were able to independently take food and use the bathroom decreased from 95% and 90.3%, respectively, to 85.5% and 76.4%.[31] These limitations, particularly the lack of ambulation, can worsen existing cardiovascular disease and may contribute to early death.

Long-term care is needed for individuals who have limited mobility and those who have become dependent on others for activities of daily living. As would be expected based on increased dependence, many patients are confined to long-term care facilities after hip fracture.[29] Among men and women over the age of 50 years who were admitted to a university hospital for treatment of hip fracture, 16.0% and 14.3%, respectively, required lifelong care in a residential facility 4 months after their fracture admission.[28] In addition, nearly half of all patients with forearm fractures report unsatisfactory functional outcomes at 6 months.[1]

Cost of Nonvertebral Fractures

Nonvertebral fractures exact significant costs to both individuals and society. As would be expected for a disease of the elderly, a large proportion of fracture costs is paid by Medicaid and Medicare. In a 1999 report, Medicaid covered almost one fourth of fracture costs and Medicare paid nearly half.[32] In an analysis of healthcare expenditures for patients enrolled in US healthcare plans between 1997 and 2001, patients with osteoporosis who experienced any fracture incurred more than twice the overall healthcare expenditures than did those with osteoporosis without fracture ($15,942 vs $6476, respectively).[33]

A US analysis of economic data in 1997 estimated the lifetime costs for all hip fractures to be more than $20 billion not including lost productivity.[25] The average lifetime cost for individual patients was calculated to be $81,300 in 2001 dollars, with 44% related to long-term care facilities. The cost of initial hospitalization was estimated to be $8900 in 2001 dollars. Of those lifetime costs, 33% were incurred in the first 6 months.[25]

The economic impact described in the 2004 Surgeon General's Report on Bone Health and Osteoporosis is even greater but shows a similar pattern of how the dollars were spent. The Surgeon General reported that the estimated annual cost to the US health system for all fractures ranged from $12.2 to $17.9 billion in 2002.[32] Hip fractures accounted for the largest proportion (63% or $11.3 billion) of medical care costs.[32] Hospital care represented 50% of total direct costs, and nursing home care was responsible for another large portion. The cost of initial treatment of hip fracture in 2002 was estimated to be between $30,000 and $43,000.[32] Although patients with other nonvertebral fractures do not incur the same high costs per fracture, the total direct costs are well into the billions of dollars in the United States. Moreover, indirect costs due to reduced productivity from disability or premature death are estimated to represent 26% of total fracture costs and 12% of hip-fracture costs.[32]

RISK ASSESSMENT FOR NONVERTEBRAL FRACTURES

Historically, in part for practical reasons, assessment of fracture risk has been tied to BMD. Although BMD is strongly correlated with nonvertebral fracture risk in people over the age of 55 years, a large proportion of nonvertebral fractures occur in individuals whose BMD is too high to fit the definition of osteoporosis and may even fall within the "normal" range.[34] In addition, treatment-related changes in BMD may be inadequate to explain the degree of reduction in nonvertebral fractures.[35] These observations emphasize the complexity of factors that determine bone strength.

A number of clinical risk factors have been identified that contribute to fracture risk independent of BMD (Table 1). These factors, including age, history of prior fragility fracture, parental hip fracture, cigarette smoking, use of corticosteroids, excessive alcohol consumption, and rheumatoid arthritis, may result in different assessments of fracture risk for individuals with the same BMD. Accurate risk assessment must, therefore, integrate these additional factors into clinical decision making.

The purpose of risk assessment is to identify patients for whom treatment benefits will outweigh adverse effects and will be cost-effective. Several validated screening tools have been developed to identify those individuals at risk of fracture. The Simple Calculated Osteoporosis Risk Estimation (SCORE),[36] Osteoporosis Risk Assessment Instrument (ORAI),[37] Osteoporosis Self-assessment Test (OST),[38] and FRACTURE Index[39] have demonstrated good sensitivity and moderate specificity. However, these tools are not widely used in clinical practice.

Prompted by the need to integrate multiple factors into the predictive models, investigators and clinicians have begun developing new tools that will combine BMD with other clinical risk factors and project that risk over an individual's life expectancy. Because hip fracture is the most disabling and costly fracture associated with osteoporosis, Kanis et al have suggested that an intervention threshold be based on a 10-year probability of hip fracture, using an integrated algorithm.[40]

Risk Factors Independent of BMD

Age

Age is a major risk factor for osteoporosis-related fractures for several reasons. Primary among them is the progressive and substantial loss of bone that begins around the age of 50 years in women and 65 years in men.[1] During this process, the bone cortex becomes thinner, cortical bone becomes more porous, and trabeculae are destroyed.[1] The result is changes in the microarchitecture and a decrease in BMD that can reduce bone strength.[1] In addition, age is a predictor of risk independent of BMD, presumably, in part, as a consequence of frailty and falling.

Sex

Female sex is a major risk factor. In the United States, the lifetime risk of hip fractures for women over the age of 50 years is approximately 3 times that of men of comparable age.[24] In men and women with osteoporosis, the lifetime risk of fracture for women over 50 years of age is more than twice that of men.[23] The greater risk of bone loss and other components of osteoporosis in white women compared with that in white men in many parts of the world is undoubtedly

TABLE 1

RISK FACTORS FOR OSTEOPOROSIS-RELATED FRACTURES

- Female sex
- Age
- Asian or Caucasian race
- Low BMD
- High bone turnover
- Poor visual acuity
- Neuromuscular disorders
- Excessive alcohol consumption
- Low dietary calcium intake
- Premature menopause
- Primary or secondary amenorrhea
- Primary and secondary hypogonadism in men
- Previous fragility fracture
- Glucocorticoid therapy
- Family history of hip fracture
- Low body weight
- Cigarette smoking
- Prolonged immobilization
- Vitamin D deficiency

BMD = bone mineral density.
Adapted from Kanis JA. *Lancet.* 2002;359:1929-1936 with permission from Elsevier.

the result of a complex association of factors. On average, women do not achieve the same magnitude of peak bone mass as do men, and age-related bone loss begins earlier in women as a result of the menopausal decline in estrogen levels.[1] In addition, women live longer than men do.[1] As a result of these 3 factors, a greater proportion of an average white woman's life occurs when bone loss predisposes to fracture.

Previous fracture

The risk of additional fractures increases approximately 2 times in both men and women who have had a fracture as adults and is independent of BMD.[6] The strong correlation between previous and subsequent fractures may reflect defects in bone microarchitecture not captured by BMD that decrease bone strength, or increases in nonskeletal factors such as propensity to falls.[6] The relationship between fracture risk and prior fracture at specific sites was determined by meta-analysis (Table 2). Although recurrent breaks at the same site are more probable than at other sites, any previous fracture increases the risk of a subsequent fracture at another site. For example, women who have sustained a forearm fracture are at more than 3-times greater risk of a second forearm break. At the same time, their risk of a hip fracture increases 2 times, compared with women who have no history of previous fracture.[6] Studies in children and adolescents have primarily focused on the relationship between calcium intake and skeletal health. However, researchers theorize that children with low BMD values may be at an increased risk for fractures and osteoporosis.[41,42]

TABLE 2

META-ANALYSIS OF THE RISK OF FRACTURE IN WOMEN WITH PRIOR FRACTURE AT THE SITES SHOWN COMPARED WITH WOMEN WHO HAVE NO PRIOR FRACTURE

Site of Prior Fracture	Risk of Subsequent Fracture		
	Hip	Spine	Forearm
Hip	2.3	2.5	NA
Spine	2.3	4.4	1.4
Forearm	1.9	1.7	3.3

NA = no studies available.

Klotzbuecher CM et al. *J Bone Miner Res.* 2000;15:721-739.

Increased propensity to fall

In addition to physiologic changes in bone that accompany aging, elderly people may be more likely to fall because of poor visual acuity, neuromuscular disorders, and certain medications.

Vitamin D deficiency

Nutritional deficiencies in the elderly result from a combination of insufficient dietary intake and reduced capacity to regulate calcium homeostasis, and these factors also contribute to bone loss and fracture risk. Vitamin D deficiency can result from poor nutrition, inadequate exposure to sunlight, and reduced capacity of the skin to produce vitamin D. The resulting increase in parathyroid hormone concentration is associated with increased bone turnover and bone loss.[1]

Calcium intake

Currently, average calcium intake falls substantially below recommended levels across both sexes and different ethnic groups, and calcium intake declines substantially with age.[43] Calcium insufficiency due to low intake and reduced absorption often translates into an accelerated rate of age-related bone loss in older individuals. It has also been demonstrated that the risk for hip fracture is inversely correlated with calcium intake in elderly men and women.[44]

Other risk factors

Other important risk factors for fractures due to osteoporosis include premature menopause or chemical castration as treatment for prostate cancer.[45] The use of aromatase inhibitors as adjuvant therapy for breast cancer may accelerate bone loss as well.[46] Long-term glucocorticoid therapy is a well-established cause of osteoporosis. The mechanism by which glucocorticoids induce bone loss appears to include impact of underlying disease, steroid-related changes in gonadal sex hormone production, as well as calcium absorption and excretion.[47] Genetic determinants of bone architecture and peak bone mass are thought to contribute to the risk associated with a family history of fractures due to osteoporosis. Smoking and excessive alcohol intake are modifiable risk factors for fracture.[1]

PRIMARY AND SECONDARY PREVENTION

Primary and secondary prevention of nonvertebral and vertebral fractures require a multifactorial approach that may appear daunting in light of the enormous number of trials evaluating nonpharmacologic, dietary, and pharmacologic therapies. To establish practical approaches for reducing the risk of nonvertebral fractures in the elderly, only those trials that measure fracture risk directly are truly informative. Surrogate markers including BMD and markers of bone turnover have not reliably predicted clinical benefit. Moreover, efforts to define osteoporosis-related fractures as only those occurring from low trauma may underestimate the incidence of fracture in the elderly, because osteoporosis increases the likelihood of any fracture.[1,23,24]

Nonpharmacologic Approaches

Reducing the risk of falls

Hip fractures result from a fall in about 90% of cases.[24] A range of approaches to reduce the risk of falling is shown in Table 3. The National Osteoporosis Foundation recommends that all patients should undertake regular weight-bearing, muscle-strengthening, and balance-training exercises to reduce the risk of falls and fractures.[48] The risk of falling can be reduced further by evaluating and correcting vision, hearing, and neurologic problems, reviewing prescription medications for the potential to affect balance and stability, and improving safety in the home.

TABLE 3

REDUCING THE INCIDENCE OF FALLS

- Identify high-risk activities
- Reduce use of antidepressants
- Decrease doses of diuretics
- Avoid hyponatremia
- Avoid over-the-counter sleep and allergy medicines
- Manage postural hypotension
- Manage gait and balance disorders; use gait aids if necessary
- Improve muscle strength; increase physical activity
- Improve coordination
- Improve back strength; prevent hyperkyphosis
- Emphasize proper intake of vitamin D

Adapted from Sinaki M. *Curr Osteoporos Rep.* 2004;2:131-137 with permission from Current Medicine publication.

Protective measures

Hip protectors have been suggested to reduce fracture risk in patients who do fall. More data are needed to reach a definitive conclusion regarding the use of hip protectors in high-risk individuals.[49]

Nutrition

Various nutritional deficiencies are strongly correlated with increased fracture risk in elderly patients. In contrast, studies investigating supplementation with 1 or a small number of nutrients have yielded inconsistent results. The inconsistency may reflect the complexity of bone metabolism and the need for lifelong balanced nutrition. A healthy diet is essential to any approach to fracture risk reduction. Insufficient intake of calcium and protein is associated with increased bone loss.[1] Daily intake of 1 g/kg dietary protein is recommended for elderly men and women.[1] Dietary habits that are associated with low dietary intake of calcium and vitamin D may correlate with fracture risk. Caffeinated beverages are known to increase urinary excretion of calcium. However, a subsequent compensatory reduction in calciuria later in the day may equalize the effect on calcium, suggesting that any correlation between caffeine consumption, at least in the form of carbonated beverages, is related to the substitution of these drinks for calcium-containing beverages.[50] Trace amounts of aluminum, boron, fluoride, manganese, and zinc also are thought to be important for bone health.[1] However, the Recommended Daily Allowance of many of these components has not been established.

Patients should be advised to eat a balanced diet containing milk, yogurt, cheese, and calcium-fortified products to achieve a calcium intake of 1200 to 1500 mg/d, including supplements if necessary.[48] A recent report from the Women's Health Initiative (WHI) has raised questions about current recommendations for the use of calcium and vitamin D.[51] The study results suggested that use of these supplements offered only limited protection against broken bones. Specifically, among healthy, postmenopausal women, calcium with vitamin D supplementation resulted in a small but significant improvement in hip bone density. Although use of these supplements did not significantly reduce hip fracture, in an analysis of the subgroups, researchers found that women who were most compliant taking the supplements experienced a significant 29% decrease in hip fracture and women 60 years of age or older had a significant 21% reduction in broken hips. Researchers suggested a number of factors that could account for the limited benefits provided by the supplementation trial, including higher doses of vitamin D (trial participants received 1000 mg/d of calcium and 400 IU/d of vitamin D), benefit may only exist for women who took supplements exactly as prescribed, and fewer hip fractures among the population studied than anticipated.[51] Leading researchers, however, still support the use of calcium and vitamin D but suggest that the use of these supplements alone may not be adequate for protection against osteoporosis.

Dietary sources of vitamin D include cereals, egg yolks, salt-water fish, and fortified dairy products. A range of 400 to 800 IU/d of vitamin D[48] is currently the recommended range most often quoted; however, a recently reported meta-analysis suggests that doses less than 700 to 800 IU/d are ineffective in preventing fractures.[52] In a Cochrane Review, pooled data for vitamin D plus calcium showed significant reductions in the incidence of hip fractures and new nonvertebral fractures.[53] Another study of patients over the age of 65 years also showed significant reductions in the incidence of nonvertebral fractures with daily vitamin D (700 IU cholecalciferol) and calcium (500 mg) supplementation.[54] The benefit in reduced numbers was evident by 6 months and continued throughout the 3-year follow-up. Low vitamin D levels have also been shown to correlate with inferior physical activity level, gait speed, and balance—factors that increase the risk of falls.[55]

Other vitamin deficiencies are associated with lower BMD, although data regarding fracture risk reduction are scant. Low levels of plasma vitamin B12 have been associated with increased loss of BMD at the hip.[56,57] In another study, low folate intake, but not vitamin B12 intake, was independently associated with decreased BMD.[58] Deficiencies of vitamin K (phylloquinone and menaquinone) cause reductions in BMD and increased risk of hip fractures.[59] In 2 trials, high vitamin K intake was associated with reduced risk of fractures.[59]

Pharmacologic Approaches

A major goal of therapy is to decrease fractures by increasing bone strength via decreased bone remodeling. The ideal agent would achieve this goal while still allowing adequate repair of microdamage. A number of antiresorptive agents have been evaluated for efficacy in reducing nonvertebral fractures in the elderly. Studies with 2 bisphosphonates, alendronate and risedronate, have provided the strongest evidence of efficacy to date (Table 4).[1,9,13,14]

Bisphosphonates

As bone ages, defects in the microarchitecture may accrue. Bone remodeling is an ongoing process of osteoclastic removal of aged bone and osteoblastic replacement with new healthy bone. Once osteoblasts have elaborated the proteinaceous osteoid, mineralization occurs in 2 steps. Between 50% and 60% of mineral content is laid down during the slow secondary mineralization phase.[60] Bisphosphonates act on this secondary mineralization phase. By decreasing osteoclast activity and by stimulating the normal process of osteoclast cell death, resorption of bone is reduced and more mineralization can occur.[60]

The antifracture efficacy of antiresorptive therapies is only partially explained by increases in BMD. The observations that decreases in markers of bone turnover significantly correlate with fracture risk reduction in bisphosphonate treatment suggest that effects on bone resorption may also play an important role.[61,62] Moreover, in a recent post hoc analysis of combined data from 3 pivotal fracture end point studies, changes in BMD did not predict the degree of reduction in nonvertebral fractures in individuals treated with risedronate.[35]

Alendronate

In the Fosamax International trial study (FOSIT), the cumulative incidence of nonvertebral fractures after 1 year was 2.4% in the alendronate 10-mg/d group compared with 4.4% in the placebo group (P=.021).[7]

In the Fracture Intervention Trial (FIT)-Vertebral Fracture Arm (VFA) of 2027 postmenopausal women with a history of vertebral fracture and low femoral neck BMD, the incidence of any nonvertebral fracture, a secondary end point, was reduced by a nonsignificant 20% with alendronate (5 mg for 24 months and increased to 10 mg for the remainder of the trial) compared with placebo (Figure 3, page 6).[9] Significant reductions were seen in hip fractures (51%) and wrist fractures (48%).[9]

TABLE 4

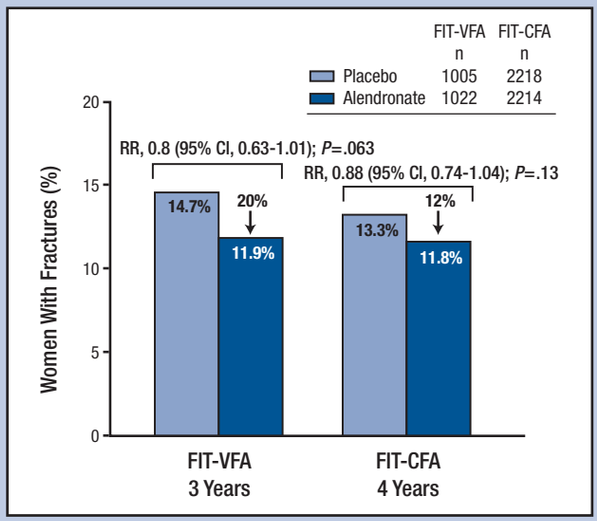
EFFECTS OF THERAPY ON HIP AND OTHER NONVERTEBRAL FRACTURES[8,9,13-15,18,70]

	Nonvertebral Fractures	Hip Fractures
Agent	**Significant Reduction in Fracture Risk**	**Significant Reduction in Fracture Risk**
Calcitonin	X	X
Raloxifene	X	X
Ibandronate	X	X
Alendronate	✔	✔
Risedronate	✔	✔
Teriparatide	✔	X

X indicates that there is no evidence of an effect.

FIGURE 3

EFFECT OF ALENDRONATE TREATMENT ON ANY NEW NONVERTEBRAL FRACTURE IN WOMEN WITH (FIT-VFA) OR WITHOUT (FIT-CFA) PRIOR VERTEBRAL FRACTURE[9,10]



FIT = Fracture Intervention Trial; VFA = Vertebral Fracture Arm; CFA = Clinical Fracture Arm; RR = relative risk; CI = confidence interval.

In the FIT–Clinical Fracture Arm (CFA), alendronate reduced the incidence of nonvertebral fracture by a nonsignificant 12% of 4432 women with low BMD but no history of vertebral fracture.[10] However, in this post hoc analysis it was noted that alendronate significantly decreased the incidence of any clinical fracture by 36% in women with baseline osteoporosis at the femoral neck.[10]

Using data from the FIT-VFA and FIT-CFA trials in women with osteoporosis, those with vertebral fracture or T-score <–2.5 were pooled to determine a secondary end point assessment of antifracture efficacy with alendronate.[11] Analysis of the pooled data determined that the relative risks for all fracture classes were significantly lower with alendronate treatment. The relative risks (RR) of any nonvertebral fracture and of those nonvertebral fractures deemed to be due to osteoporosis were 0.73 (95% confidence interval [CI], 0.61-0.87; *P*<.001) and 0.64 (95% CI, 0.51-0.80; *P*=.002), respectively.[11] Results were confirmed by meta-analysis.[63]

Risedronate

Risedronate has been demonstrated to reduce nonvertebral fracture risk in prevention trials. In the Vertebral Efficacy with Risedronate Therapy (VERT)-Multinational study of 1226 women with at least 2 prevalent vertebral fractures, compared with placebo, a 5.0-mg daily oral dose of risedronate over 3 years resulted in a nonsignificant 33% decrease in nonvertebral fractures (*P*=.06).[12] In the parallel VERT-North America trial involving 2458 women with prior vertebral fracture, compared with placebo, risedronate 5 mg/d reduced the cumulative incidence of nonvertebral fractures by 39% (*P*=.02) (Figure 4).[13]

The HIP study evaluated the incidence of hip fracture as a primary end point in 2 groups of elderly women with osteoporosis. One group was aged 70 to 79 years and had osteoporosis as determined by a nominal BMD T-score at the femoral neck of <–4 or T-score <–3 with at least 1 nonskeletal risk factor for hip fracture (eg, poor gait or propensity to fall).[14] Recalculation of T-scores using National Health and Nutrition Examination Survey (NHANES) III data yielded mean T-scores of –2.9 and –2.7 in the 2 groups of women aged 70-79 years, respectively. The second group comprised woman ≥80 years of age who had at least 1 risk factor for hip fracture (eg, difficulty standing from sitting, poor tandem gait, fall-related injury within 1 year, psychomotor score ≤5 on Clifton Modified Gibson Spiral Maze test of hand-eye coordination) or low BMD. Patients were randomized to receive either risedronate 2.5 mg/d or 5.0 mg/d or placebo. However, for analysis, data were combined for the 2 risedronate treatment groups.[14]

In the 70- to 79-year-old group with documented osteoporosis, risedronate treatment reduced the risk of hip fracture by 40% (*P*=.009) compared with placebo.[14] A post hoc analysis of these data showed that the incidence of hip fracture was reduced by 60% (*P*=.003) with risedronate in women with osteoporosis who had prior vertebral fracture. In women ≥80 years old, 58% of whom were selected primarily on the basis of risk factors, the risk of hip fracture was not significantly different with risedronate than with placebo (4.1% vs 5.1%, respectively; *P*=.35). For the combined groups, the risk of any nonvertebral fracture, a secondary end point, was reduced by 20% (*P*=.03), which was similar to the risk reduction in women with confirmed osteoporosis.[14] Analysis of pooled data from 4 large, randomized, double-blind, placebo-controlled, phase 3 studies involving a total of 1172 women with osteoporosis indicated that risedronate significantly reduced the incidence of nonvertebral fractures within 6 months compared with placebo.[64] After 1 year, nonvertebral fracture incidence was reduced by 74% compared with control (*P*=.001), and, after 3 years, the incidence was reduced by 59% (*P*=.002).

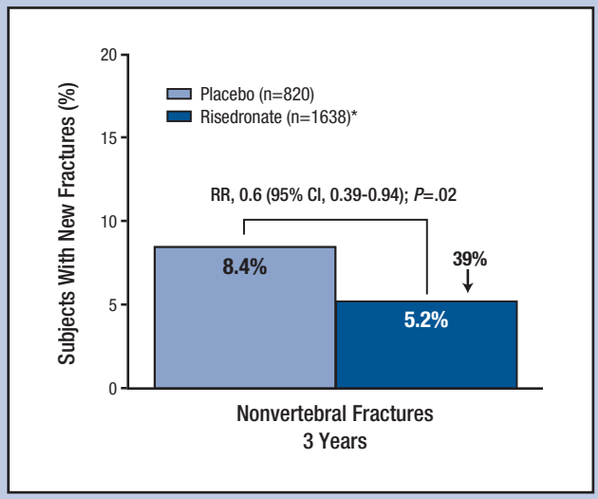
Of note, in a recent post hoc analysis by Watts et al, the incidence of fracture was equally low in patients treated with risedronate regardless of whether their BMD increased or decreased.[35] These results suggest that the effects of risedronate on BMD incompletely explain the resulting fracture risk reduction.

Ibandronate

In a single large trial, ibandronate 2.5 mg daily or intermittently (between-dose interval >2 months) delivered a similar cumulative exposure, and nonvertebral fracture rates were not significantly different from those with placebo.[15] Post hoc analysis suggested that daily ibandronate therapy reduced nonvertebral fractures by 69% (*P*=.012) in a high-risk population (femoral neck BMD T-score <–3.0), but the difference was not significant for intermittent oral ibandronate. More data are needed to establish the level of benefit with ibandronate in the treatment and prevention of nonvertebral fractures.

FIGURE 4

EFFECTS OF RISEDRONATE TREATMENT ON NONVERTEBRAL FRACTURES IN WOMEN WITH PRIOR VERTEBRAL FRACTURE[13]



*817 received 2.5 mg/d risedronate and 821 received 5.0 mg/d risedronate.

Hormone therapy and selective estrogen receptor modulators

Estrogen

Although beneficial effects of estrogen on vertebral and nonvertebral fractures were demonstrated in the WHI, the overall balance of risks and benefits is not favorable. Although estrogen appears to be beneficial in the prevention of osteoporosis, it is neither indicated nor recommended for treatment of osteoporosis.[65]

Raloxifene

Raloxifene is the only selective estrogen receptor modulator indicated for treatment of osteoporosis. This agent has not been associated with the increased risk of cardiovascular events or breast cancer observed with hormone therapy.[65] Moreover, although this agent is not indicated for prevention of breast cancer, raloxifene appears to afford some protection.[65,66]

The placebo-controlled Multiple Outcomes of Raloxifene Evaluation (MORE) trial involving 7705 postmenopausal women with osteoporosis evaluated the effects of raloxifene 60 mg/d, the Food and Drug Administration (FDA)-approved dose, or 120 mg/d on fracture risk.[8] Compared with placebo, raloxifene 60-mg/d treatment reduced the risk of new vertebral fractures by 30%, with up to 36 months of follow-up. However, no effect on the risk of nonvertebral fractures was observed (RR, 0.9; 95% CI, 0.8-1.1, for both raloxifene groups combined). In this study, the risk of thromboembolic events was increased 3 times with raloxifene.[8]

The skeletal effects of raloxifene have been evaluated in an extension of the MORE trial, the Continuing Outcomes Relevant to Evista (CORE) trial.[67] The CORE trial was designed to assess the effects of raloxifene on breast cancer for an additional 4 years beyond the 4-year MORE osteoporosis treatment trial. Women who received placebo during the MORE trial continued on placebo, and those who had taken raloxifene continued on raloxifene 60 mg/d regardless of MORE trial dose. As a secondary end point, new nonvertebral fractures were analyzed as time to first event in 4011 women. The incidence of at least 1 new nonvertebral fracture was similar in the placebo (22.9%) and raloxifene (22.8%) groups. Although CORE had limitations for fracture risk assessment, raloxifene therapy had no effect on nonvertebral fracture risk after 8 years of therapy. In contrast, BMD increases with active therapy were maintained over 7 years.[67]

Other hormonal therapies

Teriparatide

Parathyroid hormone modulates calcium and phosphate metabolism, with actions on bone and kidney, and stimulates new bone production. Teriparatide is the amino-terminal peptide of human parathyroid hormone (hPTH[1-34]). This peptide increases osteoblastic activity faster than osteoclastic activity, resulting in a net bone-forming effect.[68]

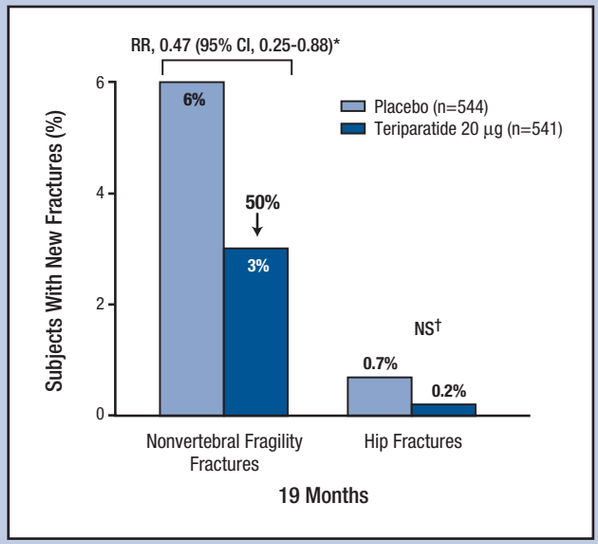
In a randomized, placebo-controlled study, 1637 postmenopausal women with at least 1 mild or 2 moderate vertebral fractures were followed for approximately 20 months.[18] Compared with placebo, the risk of any nonvertebral fracture was reduced by 35% with subcutaneous injections of teriparatide 20 μg daily. Data were further analyzed for "fragility" fractures, defined as those fractures resulting from trauma considered insufficient to cause fracture in normal bone. Compared with placebo, the relative risk of nonvertebral fragility fracture with teriparatide 20 μg daily was 0.47 (95% CI, 0.25-0.88) (Figure 5). The study was stopped early because of safety concerns raised by increased rates of osteosarcoma with long-term high-dose treatment in rats.[18]

Intact Parathyroid Hormone (iPTH[1-84])

Parathyroid hormone treatment for osteoporosis is limited to ≤2 years. A recent study found that a regimen of intact parathyroid hormone (iPTH[1-84]) for 1 year followed by alendronate for 1 year resulted in significant increases in BMD in the hip and radius compared with 1 year of teriparatide followed by 1 year of placebo.[69] These findings suggest that antiresorptive therapy can be beneficial in patients after termination of iPTH(1-84) therapy. No data regarding fracture risk have been reported.[69]

FIGURE 5

EFFECTS OF TERIPARATIDE ON NONVERTEBRAL FRACTURE IN WOMEN WITH PRIOR VERTEBRAL FRACTURE[18]



**P* value not reported.

†Incidence is too low for statistical analysis.

Calcitonin

At the FDA-approved daily doses of 200 IU and 400 IU, calcitonin has not been associated with significant reductions in nonvertebral fracture risk.[70]

ONGOING PATIENT MANAGEMENT AND ASSESSMENT

Regular monitoring of BMD by central dual x-ray absorptiometry every 1 or 2 years can be used to evaluate the response of individual patients to fracture-risk management.[48] However, BMD may not be entirely predictive of treatment efficacy, as demonstrated by Watts et al.[35] Markers of bone turnover, typically bone alkaline phosphatase and procollagen propeptides of type 1 collagen (CTX and NTX), may be useful in supplementing BMD measurements. Unfortunately, more research is needed to establish if markers such as urinary levels of CTX and NTX are clinically useful as early indicators of response to antiresorptive therapies. Moreover, treatment plans should be reevaluated as new products become available.

CONCLUSIONS

Nonvertebral fractures in the elderly are common and exact a significant toll in morbidity, mortality, and treatment costs. Although data assessing a variety of approaches to preventing osteoporosis and fractures in the elderly abound, reaching clinically meaningful conclusions is difficult, in large part because of study designs that fail to measure effects on fracture risk directly or that have limited power to detect differences in nonvertebral fracture rates. Balanced nutrition and physical activity are critical to bone health throughout life. In patients who require pharmacologic therapy, the strongest data support the use of risedronate, alendronate, or teriparatide for preventing and treating nonvertebral fractures.

REFERENCES

1. World Health Organization. WHO Tech Report 2003. Available at: http://www.osteofound.org/activities/world_health_organization.html. Accessed April 11, 2006.
2. National Osteoporosis Foundation. Impact and overview. Available at: http://www.nof.org/physguide/impact_and_overview.htm. Accessed April 12, 2006.
3. Alam NM, Archer JA, Lee E. Osteoporotic fragility fractures in African Americans: under-recognized and undertreated. *J Natl Med Assoc.* 2004;96:1640-1645.
4. National Osteoporosis Foundation. Fast facts. 2006. Available at: http://www.nof.org/osteoporosis/index.htm. Accessed April 11, 2006.
5. Riggs BL, Melton LJ III. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone.* 1995;17:505S-511S.
6. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA III, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res.* 2000;15:721-739.
7. Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Fosamax International Trial Study Group. *Osteoporos Int.* 1999;9:461-468.
8. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA.* 1999;282:637-645.
9. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet.* 1996;348:1535-1541.
10. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA.* 1998;280:2077-2082.
11. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. *J Clin Endocrinol Metab.* 2000;85:4118-4124.
12. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int.* 2000;11:83-91.
13. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *JAMA.* 1999;282:1344-1352.
14. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med.* 2001;344:333-340.
15. Chesnut IC, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res.* 2004;19:1241-1249.
16. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA.* 2003;290:1729-1738.
17. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291:1701-1712.
18. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434-1441.
19. Boonen S, Laan RF, Barton IP, Watts NB. Effect of osteoporosis treatments on risk of non-vertebral fractures: review and meta-analysis of intention-to-treat studies. *Osteoporos Int.* 2005;16:1291-1298.
20. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet.* 1999;353:878-882.
21. Rosencher N, Vielpeau C, Emmerich J, Fagnani F, Samama CM. Venous thromboembolism and mortality after hip fracture surgery: the ESCORTE study. *J Thromb Haemost.* 2005;3:2006-2014.
22. Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. *BMJ.* 2005;331:1374.
23. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ.* 2003;81:646-656.
24. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet.* 2002;359:1761-1767.
25. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. *J Am Geriatr Soc.* 2003;51:364-370.
26. Empana JP, Dargent-Molina P, Breart G. Effect of hip fracture on mortality in elderly women: the EPIDOS prospective study. *J Am Geriatr Soc.* 2004;52:685-690.
27. Endo Y, Aharonoff GB, Zuckerman JD, Egol KA, Koval KJ. Gender differences in patients with hip fracture: a greater risk of morbidity and mortality in men. *J Orthop Trauma.* 2005;19:29-35.
28. Nevalainen TH, Hiltunen LA, Jalovaara P. Functional ability after hip fracture among patients home-dwelling at the time of fracture. *Cent Eur J Public Health.* 2004;12:211-216.
29. Fransen M, Woodward M, Norton R, Robinson E, Butler M, Campbell AJ. Excess mortality or institutionalization after hip fracture: men are at greater risk than women. *J Am Geriatr Soc.* 2002;50:685-690.
30. Melton LJ III. Adverse outcomes of osteoporotic fractures in the general population. *J Bone Miner Res.* 2003;18:1139-1141.
31. Lin PC, Chang SY. Functional recovery among elderly people one year after hip fracture surgery. *J Nurs Res.* 2004;12:72-82.
32. United States Department of Health & Human Services. Bone health and osteoporosis: a report of the Surgeon General. Available at: http://www.surgeongeneral.gov/library/bonehealth. Accessed April 11, 2006.
33. Orsini LS, Rousculp MD, Long SR, Wang S. Health care utilization and expenditures in the United States: a study of osteoporosis-related fractures. *Osteoporos Int.* 2005;16:359-371.
34. Schuit SC, van der Klift M, Weel AE, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone.* 2004;34:195-202.
35. Watts NB, Geusens P, Barton IP, Felsenberg D. Relationship between changes in BMD and nonvertebral fracture incidence associated with risedronate: reduction in risk of nonvertebral fracture is not related to change in BMD. *J Bone Miner Res.* 2005;20:2097-2104.
36. Lydick E, Cook K, Turpin J, Melton M, Stine R, Byrnes C. Development and validation of a simple questionnaire to facilitate identification of women likely to have low bone density. *Am J Manag Care.* 1998;4:37-48.
37. Cadarette SM, Jaglal SB, Kreiger N, McIsaac WJ, Darlington GA, Tu JV. Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *CMAJ.* 2000;162:1289-1294.
38. Geusens P, Hochberg MC, van der Voort DJ, et al. Performance of risk indices for identifying low bone density in postmenopausal women. *Mayo Clin Proc.* 2002;77:629-637.
39. Black DM, Steinbuch M, Palermo L, et al. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos Int.* 2001;12:519-528.
40. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int.* 2005;16:581-589.
41. Bachrach LK. Assessing bone health in children: who to test and what does it mean? *Pediatr Endocrinol Rev.* 2005;2(suppl 3):332-336.
42. Cooper C, Westlake S, Harvey N, Javaid K, Dennison E, Hanson M. Review: developmental origins of osteoporotic fracture. *Osteoporos Int.* 2006;17:337-347.
43. Looker AC. Interaction of science, consumer practices and policy: calcium and bone health as a case study. *J Nutr.* 2003;133:1987S-1991S.
44. National Institutes of Health Consensus Development Conference Statement June 6-8, 1994. Available at: http://consensus.nih.gov/1994/1994OptimalCalcium097html.htm. Accessed April 11, 2006.
45. Hoff AO, Gagel RF. Osteoporosis in breast and prostate cancer survivors. *Oncology (Williston Park).* 2005;19:651-658.
46. Mackey JR, Joy AA. Skeletal health in postmenopausal survivors of early breast cancer. *Int J Cancer.* 2005;114:1010-1015.
47. Pennisi P, Trombetti A, Rizzoli R. Glucocorticoid-induced osteoporosis and its treatment. *Clin Orthop Relat Res.* 2006;443:39-47.
48. National Osteoporosis Foundation. Universal recommendations. Available at: http://www.nof.org/physguide/univeral_recommendations.htm. Accessed April 12, 2006.
49. Parker MJ, Gillespie WJ, Gillespie LD. Hip protectors for preventing hip fractures in older people. *Cochrane Database Syst Rev.* 2005:CD001255.
50. Heaney RP, Rafferty K. Carbonated beverages and urinary calcium excretion. *Am J Clin Nutr.* 2001;74:343-347.
51. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med.* 2006;354:669-683.
52. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA.* 2005;293:2257-2264.
53. Avenell A, Gillespie W, Gillespie L, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev.* 2005:CD000227.
54. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med.* 1997;337:670-676.
55. Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K. Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA Study of Elderly Women. *Osteoporos Int.* 2005;16:1425-1431.
56. Stone KL, Bauer DC, Sellmeyer D, Cummings SR. Low serum vitamin B-12 levels are associated with increased hip bone loss in older women: a prospective study. *J Clin Endocrinol Metab.* 2004;89:1217-1221.
57. Tucker KL, Hannan MT, Qiao N, et al. Low plasma vitamin B12 is associated with lower BMD: the Framingham Osteoporosis Study. *J Bone Miner Res.* 2005;20:152-158.
58. Cagnacci A, Baldassari F, Rivolta G, Arangino S, Volpe A. Relation of homocysteine, folate, and vitamin B12 to bone mineral density of postmenopausal women. *Bone.* 2003;33:956-959.
59. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health Syst Pharm.* 2005;62:1574-1581.
60. Stepan JJ, Alenfeld F, Boivin G, Feyen JH, Lakatos P. Mechanisms of action of antiresorptive therapies of postmenopausal osteoporosis. *Endocr Regul.* 2003;37:225-238.
61. Bauer DC, Black DM, Garnero P, et al. The Fracture Intervention Trial Study Group. Change in bone turnover and hip, non-spine, and vertebral fracture in alendronate-treated women: the Fracture Intervention Trial. *J Bone Miner Res.* 2004;19:1250-1258.
62. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res.* 2003;18:1051-1056.
63. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev.* 2002;23:508-516.
64. Harrington JT, Ste-Marie LG, Brandi ML, et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. *Calcif Tissue Int.* 2004;74:129-135.
65. Greenblatt D. Treatment of postmenopausal osteoporosis. *Pharmacotherapy.* 2005;25:574-584.
66. Martino S, Cauley JA, Barrett-Connor E, et al. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst.* 2004;96:1751-1761.
67. Siris ES, Harris ST, Eastell R, et al. Skeletal effects of raloxifene after 8 years: results from the Continuing Outcomes Relevant to Evista (CORE) study. *J Bone Miner Res.* 2005;20:1514-1524.
68. Teriparatide [package insert]. Indianapolis, Ind: Eli Lilly and Company; 2004.
69. Black DM, Bilezikian JP, Ensrud KE, et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. *N Engl J Med.* 2005;353:555-565.
70. Chesnut CH III, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the Prevent Recurrence of Osteoporotic Fractures study. *Am J Med.* 2000;109:267-276.

NONVERTEBRAL FRACTURE PREVENTION, TREATMENT, AND MANAGEMENT: Critical Review of the Data

CME Credit Information and Posttest Assessment

Nonvertebral Fracture Prevention, Treatment, and Management: Critical Review of the Data is a self-study newsletter designed for clinicians who manage/treat patients with osteoporosis. Continuing medical education credit will be awarded to physicians who successfully complete this activity. Participation should take approximately 1.5 hours.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the ACCME through the joint sponsorship of The University of Cincinnati College of Medicine and IMED Communications. The University of Cincinnati College of Medicine is accredited by the ACCME to sponsor continuing medical education for physicians.

The University of Cincinnati College of Medicine designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

To complete this activity and receive credit, the participant should:

- Read the educational objectives
- Read and review the newsletter
- Complete the posttest and evaluation form and mail it to:

The University of Cincinnati
Office of CME
PO Box 670567
Cincinnati, OH 45267-0567

Or fax to: 513-558-1708

Or submit via the Web at: http://webcentral.uc.edu/cme/

Participants must receive a score of 70% or better to receive credit.

Be sure to submit the posttest and evaluation form on or before May 31, 2007. After that date, the activity will no longer be designated for credit.

A CME certificate will be mailed within 4 to 6 weeks. It is recommended that participants keep a copy of their completed materials until they receive their certificate.

Posttest Assessment (Please record your answers in the space provided)

1. All of the following statements are true about nonvertebral fractures EXCEPT:
- a. The incidence in the United States is estimated to be greater than the incidence of vertebral fractures.
- b. Nonvertebral fractures are less likely to cause disability than are vertebral fractures.
- c. Nonvertebral fractures occur more frequently in women than in men.
- d. Nonvertebral fractures frequently are associated with osteoporosis in older adults.

2. One hypothesis to explain why the incidence of wrist fractures increases in patients in their 40s and plateaus once they reach age 65 is that wrist fracture:
- a. Incidence parallels age-related bone loss
- b. Occurs more often in men, and men have a shorter life expectancy than women
- c. Occurs more often in women, and women have a longer life expectancy than men
- d. Results from falling and patterns of falling change as people age

3. Among men and women over the age of 50 years who were admitted to a hospital for treatment of hip fracture, approximately how many required lifelong care in a residential faculty after 4 months?
- a. 5% to 10%
- b. 10% to 20%
- c. 20% to 30%
- d. 30% to 40%

4. Which of the following clinical risk factors have been identified as contributing to fracture risk independent of BMD?
- a. Age, history of prior fragility fracture, and parental hip fracture
- b. Smoking and excessive alcohol consumption
- c. Rheumatoid arthritis and use of corticosteroids
- d. All of the above

5. Which of the following nutritional supplements have been shown to reduce the risk of nonvertebral fractures?
- a. 400 IU vitamin D alone
- b. Vitamin D and calcium in combination
- c. Increased consumption of carbonated beverages
- d. Increased vitamin B12
- e. Increased folate

6. In the MORE trial, raloxifene treatment had:
- a. No significant effect on the risk of nonvertebral fractures
- b. No significant effect on the risk of vertebral fractures
- c. A significant effect on the risk of nonvertebral fractures
- d. A significant effect on the risk of wrist fractures

7. In patients who have 1 fracture as an adult, the risk of a subsequent fracture increases:
- a. 8 times
- b. 6 times
- c. 4 times
- d. 2 times

8. Combined data from 3 pivotal fracture–end-point studies showed that:
- a. Changes in BMD accurately predicted the degree of reduction in nonvertebral fractures in individuals treated with risedronate
- b. Changes in BMD did not predict the degree of reduction in nonvertebral fractures in individuals treated with risedronate
- c. Changes in BMD accurately predicted the degree of reduction in nonvertebral fractures in individuals treated with alendronate
- d. Changes in BMD did not predict the degree of reduction in nonvertebral fractures in individuals treated with alendronate

9. In the Fosamax International trial study (FOSIT), compared with placebo, treatment with alendronate 10 mg/d resulted in:
- a. A significant reduction in the cumulative incidence of nonvertebral fractures at the end of 1 year (4.4% vs 2.4%; *P*=.021)
- b. A nonsignificant 20% reduction in nonvertebral fracture
- c. No significant difference in nonvertebral fractures (4.4% vs 3.4%; *P*=.21)
- d. A significant reduction in vertebral fractures, but not nonvertebral fractures

10. In 1 trial of 2458 women with prior vertebral fracture, compared with placebo, risedronate 5 mg/d:
- a. Did not reduce the cumulative incidence of nonvertebral fractures
- b. Reduced the cumulative incidence of nonvertebral fractures by a nonsignificant 20%
- c. Reduced the cumulative incidence of vertebral fractures by 39% (*P*=.02)
- d. Reduced the cumulative incidence of nonvertebral fractures by 39% (*P*=.02)

Program Evaluation

Please circle the letter that best reflects your opinion of the statements below, using the following scale:

a. Strongly disagree b. Disagree c. Agree d. Strongly agree e. Does not apply

1. The program objectives were fully met.	**a**	**b**	**c**	**d**	**e**
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.	**a**	**b**	**c**	**d**	**e**
3. The educational activity has enhanced my professional effectiveness and improved my ability to:					
a. Treat/manage patients	**a**	**b**	**c**	**d**	**e**
b. Communicate with patients	**a**	**b**	**c**	**d**	**e**
c. Manage my medical practice	**a**	**b**	**c**	**d**	**e**
4. The information presented was without promotional or commercial bias.	**a**	**b**	**c**	**d**	**e**
5. The program level was appropriate.	**a**	**b**	**c**	**d**	**e**
6. I intend to change my clinical practice as a result of the information presented in this CME program.	**a**	**b**	**c**	**d**	**e**

Please explain: _____

_____

7. Suggestions regarding this material, or recommendations for future presentations:

_____

_____

_____

Posttest Answers **Expiration Date: May 31, 2007**

1.____	**2.**____	**3.**____	**4.**____	**5.**____
6.____	**7.**____	**8.**____	**9.**____	**10.**____

Registration Form

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