AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS 2001 MEDICAL GUIDELINES FOR CLINICAL PRACTICE FOR THE PREVENTION AND MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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INTRODUCTION

A critical need exists for efficient, measurable systems of disease management that reconcile conflicts between socioeconomic responsibility and patient welfare. Clinical guidelines have become an important component of these systems because they address elements of care that are effective and that reduce the variability in our approach to patient management.

The American Association of Clinical Endocrinologists (AACE) 2001 Medical Guidelines for Clinical Practice for the Prevention and Management of Postmenopausal Osteoporosis address the prevention, diagnosis, and management of postmenopausal osteoporosis, a disorder that is recognized as a major public health problem because of its physical and socioeconomic consequences. They are intended to simplify medical decision making and to help physicians and their patients make good decisions about skeletal health and postmenopausal osteoporosis.

The specific goals of these guidelines are to reduce the incidence of fractures related to osteoporosis and to achieve the highest quality of life for individual patients by using the most effective and efficient methods of diagnosis and management.

In the preparation of this 2001 edition, reports in the peer-reviewed literature dealing with prevention, diagnosis, and treatment of postmenopausal osteoporosis, which were published and indexed between 1996 (the publication date of the previous edition of these guidelines) and January 2001, were identified by computer search, reviewed, and graded for clinical relevance and scientific merit. Although cost-effectiveness was carefully considered, variabilities in actual costs could not be accurately determined. Therefore, cost-effectiveness modeling was not undertaken.

Whenever possible, recommendations were based on randomized, prospective, double-blind studies of well-defined patient populations. Studies that used the most relevant clinical endpoint, fracturing, were considered "level 1" evidence. When level 1 evidence was not available, recommendations were based on cross-sectional studies, investigations that tested smaller or nonrandomized patient populations, or studies that tested secondary or surrogate clinical endpoints for fracture, such as bone mineral density (BMD) or bone turnover markers, in treated populations (level 2 evidence). When stronger evidence was not available, reviews, editorials, and expert opinions were used (level 3 evidence).

We recognize that the process of developing clinical guidelines necessarily results in a narrowing and codification of clinical choices, which can be inappropriate in some clinical situations. Because the application of objective information to the specific needs of patients is the ultimate responsibility of the practicing physician, clinical practice guidelines are not intended to be rigid or restrictive, nor should they be used for the formation of public policy.

As a basic principle of medical decision making, AACE also recognizes a physician's prerogative to refer the patient for consultation to qualified experts. Osteoporosis is a complex endocrinologic disorder of bone and mineral metabolism. Formal training in the science and clinical management of metabolic bone disease is a basic element of the endocrinologist's academic preparation. Therefore, the clinical endocrinologist is a reliable resource for primary physicians who seek consultation for their patients with osteoporosis and other metabolic bone diseases and for patients who desire subspecialty care.

Referral to an osteoporosis specialist is appropriate when the patient is in any of the following circumstances:

1. Has osteoporosis that is unexpectedly severe or has unusual features at the time of initial assessment
   - Has very low BMD (a T-score below -3.0 or a Z-score below -2.0)
   - Has osteoporosis despite young age (premenopausal)
   - Has fractures despite borderline or normal BMD
2. Has a suspected or known condition that may underlie the osteoporosis (for example, hyperthyroidism, hyperparathyroidism, hypercalciuria, Cushing's syndrome, or hypogonadism)
3. Is a candidate for combination therapy
4. Is intolerant of approved therapies
5. Fails to respond to treatment
   - Takes estrogen yet has low baseline BMD
   - Is undergoing treatment yet shows an apparent loss of BMD on serial studies
   - Has fractures despite treatment

POSTMENOPAUSAL OSTEOPOROSIS: DEFINITION

Postmenopausal osteoporosis is a condition characterized by the following features:

- Low bone mass
- Microarchitectural deterioration of bone tissue, leading to bone fragility
- A consequent susceptibility to fracture

Osteoporosis-related fractures may lead to diminished quality of life, disability, and even death.

The World Health Organization (WHO) has established an operational definition of osteoporosis based on BMD, commonly expressed as a *T*-score (Table 1). A *T*-score represents a patient's bone density expressed as the number of standard deviations (SDs) above or below the mean BMD value for a normal young adult.

Although the WHO criteria were not intended as references for making treatment decisions, they may be used for this purpose. The WHO criteria are also useful for making public health and health policy decisions for populations of patients for whom no specific clinical information is available. In addition, the WHO BMD criteria are commonly accepted as standards for research purposes.

BACKGROUND

- Postmenopausal osteoporosis affects many people. Although white women are most often affected, women of all races and all ethnic origins are susceptible to osteoporosis and fracture. Men and younger women may also have osteoporosis; however, these guidelines are limited to postmenopausal osteoporosis.
- By the end of the first postmenopausal decade, half of white women have osteopenia or osteoporosis (Fig. 1).
- Low BMD at the femoral neck (*T*-score of −2.5 or below) is found in 21% of postmenopausal white American women, 16% of postmenopausal Mexican American women, and 10% of postmenopausal African American women.
- The prevalence of vertebral fractures among postmenopausal women is higher than 20%.

- Less than one-third of the cases of osteoporosis have been diagnosed, and only one-seventh of American women with osteoporosis receive treatment.
- By the year 2050, the number of people beyond age 65 years in the United States will increase from 32 million to 69 million, and more than 15 million people will exceed 85 years of age. The incidence of hip and spine fractures increases with advancing age.
- The national health-care cost of osteoporosis was estimated to be $13.8 billion in 1995 and may increase to as much as $240 billion during the next 50 years.

PATHOGENESIS

Bone mass increases during the first 3 decades of life; it approaches maximal (peak) levels in the late teen years, increases slightly during the third decade of life, and reaches its peak around age 30 years (Fig. 2). Peak bone mass is primarily determined by genetics but may also be modified by other factors such as physical activity, diet (for example, inadequate calcium intake), concomitant diseases (such as hyperthyroidism), and adverse lifestyle practices (such as smoking). The level of peak bone mass achieved at skeletal maturity is a major determinant of bone mass in later life and is therefore a factor in the ultimate development of osteoporosis.

At menopause, bone remodeling becomes unbalanced and results in bone loss at each remodeling site. In addition, an increase in number of remodeling (that is, bone turnover) sites results in an accelerated bone loss throughout the entire skeleton. Postmenopausal bone loss is most rapid during the first postmenopausal decade (Fig. 2). Certain nutritional and lifestyle factors (such as insufficient dietary calcium or cigarette smoking) or the presence of concurrent disease (such as hyperthyroidism) may accelerate bone loss independent of the effects of declining estrogen concentration; thus, the risk of postmenopausal osteoporosis can be further increased. The remodeling space, which represents skeletal tissue that is undergoing remodeling and is therefore structurally ineffective, can be extended (worsened) by further increases in bone turnover or recovered by therapeutic agents that reduce bone turnover.

Table 1
World Health Organization Diagnostic Criteria
for Women Without Fragility Fractures*

Diagnosis	BMD criteria
Normal	BMD value within 1 SD of the young adult mean
Osteopenia	BMD value between −1 SD and −2.5 SD below the young adult mean
Osteoporosis	BMD value at least −2.5 SD below the young adult mean

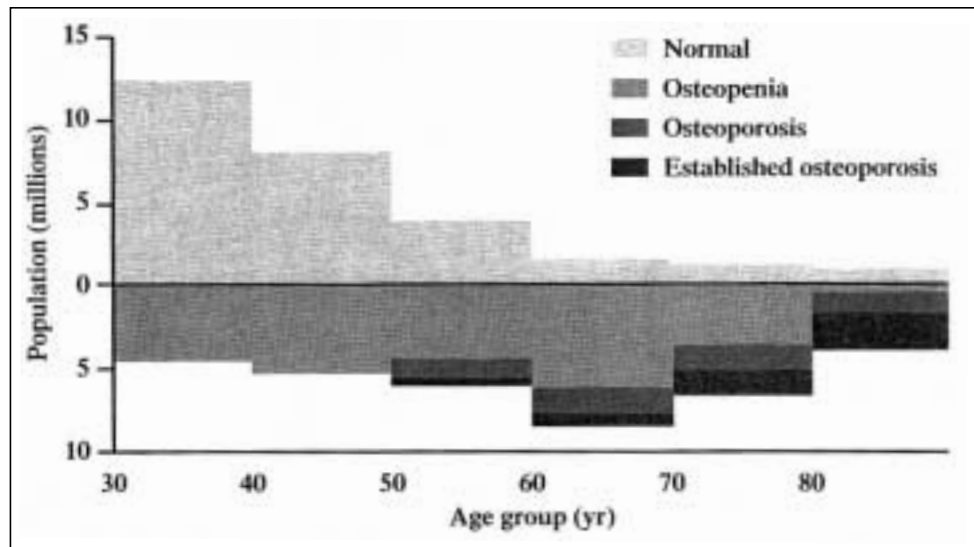*BMD = bone mineral density; SD = standard deviation.

Fig. 1. Estimated skeletal status (based on World Health Organization definitions—see Table 1) of white women in the United States, 1990, shown by age distribution. (Reproduced from Melton LJ III. How many women have osteoporosis now? *J Bone Miner Res.* 1995;10:175-177. By permission of Blackwell Science, Inc.)

Bone loss due to estrogen deficiency and advancing age affects the entire skeleton. In the early post-menopausal years, bone loss averages 1 to 2% per year. Because the rate of remodeling is greater in cancellous bone than in cortical bone, however, bone loss attributable to estrogen deficiency and aging may be more rapid and manifest earlier at predominantly cancellous skeletal sites such as the lumbar spine.

CLINICAL FEATURES AND COMPLICATIONS

Low Bone Mass

Low bone mass is a major, consistent characteristic of postmenopausal osteoporosis. A strong inverse relationship exists between bone mass and susceptibility to fracture. Therefore, bone mass is the primary indicator of fracture risk in women without fractures, although it is important to realize that individual patients may sustain a fracture at different BMD levels and that factors other than bone density influence fracture risk (see *BMD Measurement*). In itself, low bone mass is not associated with symptoms.

Fracture

Fracture is the single morbid event and the most clinically significant physical manifestation of post-menopausal osteoporosis. Osteoporosis-associated fractures may occur in any bone but are most likely to occur at sites of low bone mass and are usually precipitated by a fall or injury. A fragility fracture results from trauma that would not cause a normal bone to fracture or from a force equal to or less than that resulting from a fall from standing height.

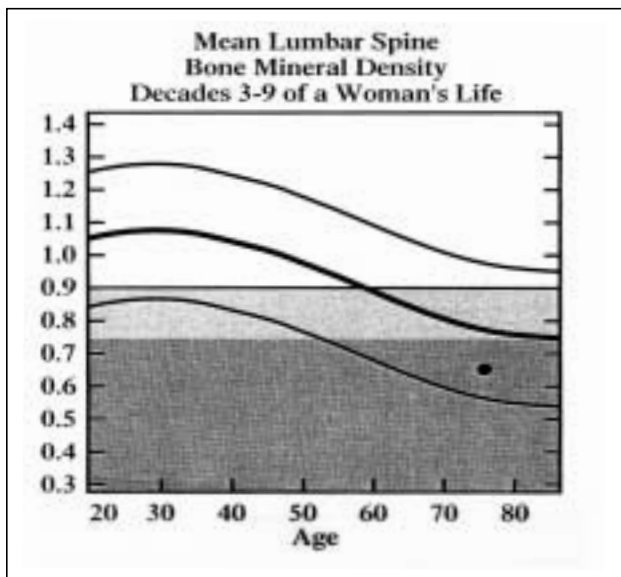Hip fractures are the most serious complication of osteoporosis:

Fig. 2. Mean bone mineral density (BMD) of the lumbar spine in women from the third through the ninth decades of life. Note that BMD decreases with advancing age, beginning in the third or fourth decade of life. *Dark curved line* = mean; *upper curve* = +2 standard deviations (SD); *lower curve* = −2 SD; *light shaded area* = consider preventive intervention; *dark shaded area* = consider therapeutic intervention. Diagram is intended to resemble a densitometry report. Sample *T*-score for 76-year-old woman = −3.68 SD, or approximately 63% of young adult mean BMD (each 10% increment above or below the mean represents 1 SD).

- They result in permanent disability in more than 30% of patients.

- Of patients with hip fracture, 12 to 20% die within 1 year after fracture.
- More than 50% of the survivors are unable to return to independent living; many require long-term nursing home care.

The following factors are important secondary complications of fractures:

- Pain
- Deformity
- Disability
- Physical deconditioning due to inactivity
- Changes in self-image

Adverse effects specific to spinal (vertebral) compression fractures include the following:

- Loss of height
- Kyphosis (dowager's hump)
- Crowding of internal organs
- Back pain (acute and chronic)
- Prolonged disability
- Increased mortality

RISK FACTOR ASSESSMENT

Risk Factors for Low Bone Mass

"Risk factors" for low bone mass are not sufficiently sensitive for diagnosis or exclusion of osteoporosis. Only BMD measurements can identify patients who have low bone mass.

Risk Factors for Fractures

Assessment of risk factors for fractures may be useful for the following:

- Identifying women at high risk of fractures
- Heightening clinical awareness of osteoporosis
- Developing societal strategies for prevention of fracture and treatment of osteoporosis

The most important risk factors for osteoporosis-related fractures are as follows:

- Prior low-trauma fracture as an adult
- Low BMD in patients with or without fractures

A low-trauma fracture as an adult (40 to 45 years of age or older) is of major importance because it establishes an unusual susceptibility to fractures and strongly predicts the potential for future fractures. Therefore, it is a clear indication for further evaluation and possible therapeutic intervention.

Other factors are associated with an increased risk of *hip* fractures, but no available data confirm that they also influence the risk of other fractures. Although their clinical significance is not fully understood, they may be valuable for determining a strategy for prevention and treatment. These risk factors include the following:

- History of hip fracture in a first-degree relative
- Weight loss and low body weight
- Cigarette smoking
- Increased likelihood of falling
- Tallness
- High bone turnover
- Advancing age

Because more than one-third of women with osteoporosis have a coexisting cause of bone loss (Table 2), the fracture risk profile must consider secondary causes of osteoporosis (see *Medical Evaluation*).

Risk of Falling

Falls pose substantial problems for patients at high risk for fracture. The following factors are some common causes of falling:

- Frailty and associated deconditioning
- Poor visual acuity
- Impaired hearing
- Use of medications with neurologic effects that compromise protective neuromuscular reflexes (for example, long-acting benzodiazepines)

EVALUATION

The following patients should undergo assessment for postmenopausal osteoporosis:

- All women 65 years old or older
- All adult women with a history of a fracture (or fractures) not caused by severe trauma (such as a motor vehicle accident)
- Younger postmenopausal women who have clinical risk factors for fractures (who have low body weight—that is, less than 57.6 kg [127 lb]—or a family history of spine or hip fracturing)

The evaluation should include the following items:

- A comprehensive medical examination
- Assessment of risk factors for fractures (see *Risk Factors for Fractures*)
- BMD measurements in younger postmenopausal women who have risk factors and in all women 65 years old or older
- Assessment of the patient's reliability, understanding, and willingness to accept available interventions

Medical Evaluation

A comprehensive medical evaluation, including a complete history and physical examination, is indicated in all women with postmenopausal osteoporosis in order to

Table 2
Causes of Generalized Secondary Osteoporosis in Adults*

Endocrine disease or metabolic causes	Nutritional conditions	Drugs	Disorders of collagen metabolism	Other
Hypogonadism	Malabsorption	Vitamin D toxicity	Osteogenesis	Rheumatoid arthritis
Hyperadrenocorticism	syndromes and	Phenytoin	imperfecta	Myeloma and some
Thyrotoxicosis	malnutrition	Glucocorticoids	Homocystinuria due	cancers
Anorexia nervosa	Chronic liver disease	Phenobarbital	to cystathionine	Immobilization
Hyperprolactinemia	Gastric operations	Excessive thyroid	deficiency	Renal tubular
Porphyria	Vitamin D	medication	Ehlers-Danlos	acidosis
Hypophosphatasia	deficiency	Heparin	syndrome	Hypercalciuria
in adults	Calcium deficiency	Gonadotropin-	Marfan syndrome	COPD
Diabetes mellitus,	Alcoholism	releasing hormone		Organ transplantation
type 1		antagonists		Cholestatic liver
Pregnancy				disease
Hyperparathyroidism				Mastocytosis
Acromegaly				Thalassemia

*COPD = chronic obstructive pulmonary disease.

identify coexisting medical conditions that cause or contribute to bone loss.

The following laboratory tests should be considered for any woman who has osteoporosis. These tests will establish baseline conditions or definitively exclude secondary causes of osteoporosis, even in the absence of other clinical indications:

- Complete blood cell count
- Serum chemistry studies (especially calcium, phosphorus, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, and electrolytes)
- Urinary calcium excretion

If the medical history or physical findings suggest secondary causes of bone loss, additional laboratory evaluations are warranted and may include (but are not limited to) the following tests:

- Serum thyrotropin
- Erythrocyte sedimentation rate
- Serum parathyroid hormone concentration (for possible primary or secondary hyperparathyroidism)
- Serum 25-hydroxyvitamin D concentration
- Urinary free cortisol and other tests for suspected adrenal hypersecretion
- Acid-base studies
- Biochemical markers of bone turnover (for example, bone-specific alkaline phosphatase and urine or serum collagen cross-links)
- Serum tryptase, urine *N*-methylhistamine, or other tests for mastocytosis

- Serum or urine protein electrophoresis (or both)
- Bone marrow aspiration and biopsy to look for marrow-based diseases
- Undecalcified iliac bone biopsy with double tetracycline labeling (consider only when osteoporosis is diagnosed and the patient has no apparent cause for the condition, no response to therapy, or suspected osteomalacia or mastocytosis)

The causes of secondary osteoporosis in adults are listed in Table 2.

Standard Radiography

In patients with known or suspected vertebral fractures or with unexplained loss of height, radiography of the thoracic and lumbar spine is indicated to identify and confirm the presence of those fractures. Radiographic studies are usually indicated to confirm the presence of fractures at other sites as well. The sensitivity and reliability of standard radiography to assess BMD are poor, and in the absence of vertebral fractures, this technique cannot be used to diagnose osteoporosis.

Biochemical Markers of Bone Turnover

Currently, the precise role of biochemical markers in the clinical management of osteoporosis has not been established. Several confounding issues must be resolved before a clear role for these measurements can be determined. Age, gender, menopausal status, meals, diurnal variation, and certain medications all influence resorption marker levels and can cause extreme variability. Moreover, a relationship has not been demonstrated between

changes in bone marker levels after treatment and reduced fracture risk. In addition, the relationship between changes in bone marker levels and bone balance is unclear.

Nevertheless, biochemical markers of bone turnover may be useful for the following specific situations:

- Assessing fracture risk in elderly patients
- Assessing therapeutic responses to antiresorptive agents, such as estrogen and bisphosphonates
- Identifying patients with high bone turnover (to predict rapid bone loss)

BMD Measurement

In women who are at risk for postmenopausal osteoporosis, BMD measurement can accomplish the following:

- Establish the diagnosis of postmenopausal osteoporosis
- Determine fracture risk (for every 1-SD decrease in age-adjusted BMD, the relative risk [RR] of fracture increases 1.5- to 2.5-fold)
- Identify candidates for intervention
- Assess changes in bone mass over time in treated and untreated patients
- Enhance acceptance of and adherence to treatment

Measurement Techniques

Dual x-ray absorptiometry of the lumbar spine and proximal femur provides reproducible values at important sites of osteoporosis-associated fracture. These central sites are also more likely than peripheral sites to show a response to treatment and are preferred for baseline and serial measurements. The most reliable comparative results for serial measurements are obtained when the same instrument and, ideally, the same technologist are used.

For bone mass measurement, several other techniques (listed here alphabetically) are available:

- Quantitative computed tomography for measurement of both central and peripheral sites
- Quantitative ultrasonometry
- Radiographic absorptiometry
- Single-energy x-ray absorptiometry

The various BMD measurement techniques are outlined in Table 3.

Measurement Sites

Peripheral measurements can identify patients with low bone mass. *T*-scores from peripheral devices, however, are not as sensitive or specific as those from central devices, and the risk of future fracture depends on the skeletal site even when *T*-scores from different skeletal sites are identical. Work is currently under way to redefine the thresholds for peripheral devices and resolve these discrepancies. In the meantime, peripheral measurements should be limited to the assessment of fracture risk.

Bone Density Reports

Bone density data are reported as *T*-scores and *Z*-scores. *T*-scores represent the number of SDs from the normal young adult mean bone density values, whereas *Z*-scores represent the number of SDs from the normal mean value for age- and sex-matched control subjects. Results showing *Z*-scores of −2.0 or lower may suggest a secondary cause of osteoporosis.

Bone density reports also include values for specific subregions within the proximal femur and for specific vertebrae. Diagnostic and therapeutic studies, cost analyses, and cost-effectiveness data, however, are based on total hip, femoral neck, or total lumbar spine measurements (or some combination of these measurements).

Table 3
Bone Mineral Density Measurement Techniques*

Technique	Sites measured	Unit of measure	Utility
DXA	PA spine, lateral spine, proximal femur, total body, forearm, heel, phalanges	Areal density (g/cm^2)	Diagnosis and monitoring
QCT	Spine	Volumetric density (g/cm^3)	Diagnosis and monitoring
pQCT	Forearm, hip	Volumetric density (g/cm^3)	Risk assessment
QUS	Heel, forearm, tibia, phalanges, metatarsals	SOS, BUA	Risk assessment
RA	Phalanges	Volumetric density (arbitrary units)	Risk assessment

*BUA = broadband ultrasound attenuation; DXA = dual x-ray absorptiometry; PA = posteroanterior; pQCT = peripheral quantitative computed tomography; QCT = quantitative computed tomography; QUS = quantitative ultrasonometry; RA = radiographic absorptiometry; SOS = speed of sound.

Role in Clinical Decision Making

A clinical diagnosis of osteoporosis can be made without BMD testing in women who have fragility fractures. Nevertheless, BMD measurement is advisable in these patients to establish a baseline for assessing the response to treatment and for quantifying fracture risk.

For women with no history of fragility fracture, the WHO definitions of osteopenia and osteoporosis (Table 1) represent BMD levels associated with a high risk of fracture, as determined from prospective trials. Cutoff values, however, cannot define a true "fracture threshold" or the naturally occurring limits of a disease process because osteoporosis exerts its pathologic effects over a continuum of bone density values.

It must also be recognized that factors other than bone density have an important role in the pathogenesis of fractures. The increases in bone density that result from therapeutic interventions are modest and explain less than 50% of the observed reductions in fracture rates. When BMD is used as a surrogate endpoint in therapeutic trials, the relationship between bone mass and fracture rate is highly variable and depends on the specific agent used. For example, the relationship is reasonably strong in bisphosphonate trials, weak in raloxifene trials, and absent in trials that have used high-dose sodium fluoride or calcitonin. Clearly, factors other than bone mass also contribute to fracturing.

Therefore, treatment decisions for individual patients with low BMD should be made after consideration of non-bone mass factors as well, including the following:

- Patient acceptance and understanding of the risks and benefits of the proposed treatment
- Age (fracture risk increases with advancing age independent of bone density)
- The patient's usual activity level and its historical effect on skeletal injury
- Patient expectations and functional needs
- Health status (for example, menopausal status and comorbidities)
- Lifestyle (such as use of tobacco and alcohol or risk-taking behavior)
- Medications (for example, postmenopausal women taking more than 7.5 mg of prednisone or its equivalent for more than 3 weeks should be considered for a preventive strategy with use of a bisphosphonate; women taking levothyroxine require periodic thyrotropin determinations and modification of thyroid hormone dose to normalize serum thyrotropin, if necessary)

Indications

The cost-effectiveness of BMD testing and the benefits to society are controversial. Clinicians, politicians, patients, industrial interests, and third-party payers all have different perspectives on the indications for and timing of BMD measurements. The following are recommendations intended to reflect the most effective and efficient use of this technology within the context of the endocrine specialty practice.

BMD measurements should be performed in the following settings:

- For risk assessment in perimenopausal or postmenopausal women who have risk factors for fractures and are willing to consider available interventions
- In women who have x-ray findings that suggest osteoporosis
- In women beginning or receiving long-term glucocorticoid therapy or other drugs associated with bone loss
- In all adult women with symptomatic hyperparathyroidism or other diseases or nutritional conditions associated with bone loss in whom evidence of bone loss would result in adjustment of management
- For establishing skeletal stability and monitoring therapeutic response in women receiving treatment for osteoporosis (baseline measurements should be made before intervention)
- In all women 40 years old or older who have sustained a fracture
- In all women beyond 65 years of age

PREVENTION OF OSTEOPOROSIS

Effective preventive strategies that can be implemented during skeletal development (infancy and childhood) and in later life are needed to minimize the physical, social, and economic consequences of osteoporosis. The following are goals of prevention programs:

- Optimize skeletal development and maximize peak bone mass at skeletal maturity
- Prevent age-related and secondary causes of bone loss
- Preserve the structural integrity of the skeleton
- Prevent fractures

General Principles

The following general principles are applicable to all individuals, particularly children and adolescents:

- *Promote a diet with adequate calcium content.* Adequate calcium intake is a fundamental element of any osteoporosis prevention or treatment program. The recommended daily calcium intake for various populations is outlined in Table 4, and a guide to calcium-rich foods is provided in Table 5. Calcium supplementation should be prescribed whenever it is needed to achieve the recommended daily intake levels (see *Pharmacologic Agents*). Although many of the effects of supplemental calcium on the developing skeleton are incompletely understood, it is well recognized that supplemental calcium substantially increases bone mass in physically active children.
- *Encourage good general nutrition.*
- *Promote adequate vitamin D intake (at least 400 IU/day; as much as 800 IU/day in the elderly).* Vitamin D is not widely available in natural food sources. It is primarily found in fish oils (including cod liver oil), some vegetables, and fortified milk, cereals, and

breads. Supplements of 400 IU daily should be prescribed for younger adults. Supplements of 800 IU daily should be prescribed for elderly patients (in whom vitamin D absorption may be reduced), malnourished patients, patients with intestinal malabsorption, and patients receiving long-term anticonvulsant or glucocorticoid therapy.

- *Advocate regular weight-bearing exercise.* Weight-bearing exercise enhances bone development in children and adolescents and may slow bone loss attributable to disuse in elderly persons. In addition, regular exercise promotes mobility, agility, and muscle strength, all of which may help prevent falls.
- *Strongly discourage use of tobacco.* Cigarette smokers tend to be thinner, undergo earlier menopause, have increased catabolism of endogenous estrogen, and experience more fractures.

Additional Measures

Consider the following additional measures in specific circumstances:

- *Pharmacologic agents* (in addition to calcium and vitamin D) to prevent bone loss in perimenopausal and postmenopausal women at high risk of developing osteoporosis
- *A bisphosphonate* (alendronate or risedronate) for all adult women who will require more than 7.5 mg of prednisone or its equivalent for more than 3 weeks (see *Pharmacologic Agents*)
- *Periodic monitoring of thyroid function*, and adjustment of the dose of thyroid hormone to normalize serum thyrotropin concentrations in all women receiving thyroid hormone replacement therapy for nonmalignant conditions

- *Identification and treatment of children and adolescents with constitutional delay of growth and puberty* and other states or conditions that predispose to low peak bone mass and osteoporosis in later life

Additional measures, listed in Table 6, should be personalized to the needs of each patient.

TREATMENT OF OSTEOPOROSIS

Goals

The following are goals of treatment of osteoporosis:

- Prevent fractures
- Stabilize or achieve an increase in bone mass
- Relieve symptoms of fractures and skeletal deformity
- Maximize physical function (for example, halt progressive deformity)

The ability to achieve these goals depends on the patient's and the physician's commitment to therapy and the potential for the chosen therapy to yield results.

Candidates for Treatment

The following women may benefit from pharmacologic treatment of osteoporosis:

1. Women with postmenopausal osteoporosis
   - Women with low-trauma fractures and low BMD
   - Women with BMD *T*-scores of −2.5 and below
2. Women with borderline-low BMD (e.g., *T*-scores of −1.5 and below) if risk factors are present
3. Women in whom nonpharmacologic preventive measures are ineffective (bone loss continues or low-trauma fractures occur)

Table 4
Recommended Daily Calcium Intake
for Various Populations

Age or life stage	Adequate calcium intake (mg/day)
1-3 yr	500
4-8 yr	800
9-18 yr	1,300
19-50 yr	1,000
>50 yr	1,200
Pregnancy or lactation	
<19 yr	1,300
19-50 yr	1,000

From Institute of Medicine. *Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* Washington, DC: National Academy Press, 1997.

Table 5
Calcium Content of Various Calcium-Rich Foods

Food	Serving size	Calcium per serving (mg)*
Dairy products		
Milk†	1 cup	290-300
Swiss cheese	1 oz (slice)	250-270
Yogurt	1 cup	240-400
American cheese	1 oz (slice)	165-200
Ice cream or frozen dessert	$^1/_2$ cup	90-100
Cottage cheese	$^1/_2$ cup	80-100
Parmesan cheese	1 Tbs	70
Powdered nonfat milk	1 tsp	50
Other		
Sardines in oil (with bones)	3 oz	370
Canned salmon (with bones)	3 oz	170-210
Broccoli	1 cup	160-180
Soybean curd (tofu)	4 oz	145-155
Turnip greens	$^1/_2$ cup, cooked	100-125
Kale	$^1/_2$ cup, cooked	90-100
Corn bread	$2^1/_2$-inch square	80-90
Egg	1 medium	55
Calcium-fortified food (bread, cereals, fruit juices)‡	1 serving	Varies

*The bioavailability of calcium varies depending on the food source and overall diet. For example, increasing fiber intake has long been associated with negative calcium balance. In cereals, phytic acid is the main constituent of fiber that binds calcium and makes it unavailable for absorption. In contrast, calcium absorption from low-oxalate vegetables (for example, kale, broccoli, collard greens) is as good as it is from milk.
†All milks (skim, 1%, 2%, and whole) have the same calcium content.
‡Breads and cereals, unless fortified with calcium, are relatively low sources of calcium but still contribute substantially to calcium intake because these foods constitute such a large part of the diet.

Nonpharmacologic Measures

Nonpharmacologic measures were reviewed in the section on preventive strategies (see *General Principles*).

Pharmacologic Agents

AACE and the American College of Endocrinology recommend the following pharmacologic agents when pharmacotherapy is indicated:

- *First priority:* agents approved by the US Food and Drug Administration (FDA) for the prevention or treatment (or both) of osteoporosis
- *Second priority:* agents that are not approved by the FDA but for which level 1 or level 2 evidence of efficacy and safety is available (these agents are appropriate for patients who are unable to take approved agents or who have complex and extenuating medical problems that preclude the effective use of approved agents)

Agents approved by the FDA for prevention or treatment of osteoporosis include (listed alphabetically) bisphosphonates (alendronate, risedronate), calcitonin, estrogen, and raloxifene. These agents suppress bone resorption, improve bone density, and reduce the risk of fractures. Level 1 evidence of efficacy in reducing the risk of vertebral fractures is available for bisphosphonates, calcitonin, and raloxifene. Level 2 evidence of antifracture efficacy is available for estrogen. Only bisphosphonates have been shown to reduce the risk of hip and other nonvertebral fractures in prospective controlled trials (level 1 evidence).

Table 6
Preventive Measures
for Decreasing the Risk
of Osteoporosis in High-Risk Women

All women
　Identify and remedy secondary causes (Table 2)

Perimenopausal and postmenopausal women
　Identify and treat women with osteoporosis-related
　　fractures and women with low bone mass
　Identify and treat sensory defects, neurologic disease,
　　and arthritis, which can contribute to frequency of
　　falls
　Adjust dosage of drugs with sedative effects, which
　　could slow reflexes or decrease coordination and
　　impair patient's ability to break impact of a fall
　Recommend appropriate lifestyle changes, including
　　smoking cessation, increased weight-bearing
　　activities, and dietary improvements
　Minimize risk of falls and injuries with gait and
　　balance training

Elderly women
　Same as perimenopausal and postmenopausal group
　　plus:
　　　Anchor rugs
　　　Minimize clutter
　　　Remove loose wires
　　　Use nonskid mats
　　　Install handrails in bathrooms, halls, and
　　　　along stairways
　　　Light hallways, stairwells, and entrances
　　　Encourage patient to wear sturdy, low-heeled
　　　　shoes

Calcium and Vitamin D Supplementation

Role in Clinical Practice.—Adequate calcium and vitamin D intake is fundamental to all prevention and treatment programs for postmenopausal osteoporosis.

Available Forms and Recommended Dosing.—The available forms and recommended dosages of calcium supplements are outlined in Table 7. To minimize gastrointestinal side effects and enhance absorption, patients should take calcium in conjunction with food (with meals or a bedtime snack).

Efficacy.—Calcium (500 to 1,000 mg/day) and vitamin D (400 to 800 IU/day) supplementation can reduce the rate of bone loss in women who are more than 5 years postmenopausal. The fracture reduction efficacy of calcium and vitamin D supplementation has been demonstrated in women beyond 75 years of age.

Side Effects.—The most common side effects of calcium are intestinal gas and constipation. These problems occur most frequently with calcium carbonate and are less likely with calcium citrate. Hypercalciuria is unusual at dosages of less than 2 g/day.

Contraindications.—Contraindications to use of calcium supplements include hypercalciuria (urinary calcium excretion of more than 300 mg/24 h) that cannot be controlled with a thiazide.

Duration of Treatment.—Calcium and vitamin D supplementation can be administered safely to most women indefinitely.

Bisphosphonates: Alendronate

Role in Clinical Practice.—Alendronate, a nitrogen-containing bisphosphonate, is approved by the FDA for prevention of bone loss in recently menopausal women, treatment of established postmenopausal osteoporosis, and treatment of glucocorticoid-induced osteoporosis.

Available Forms and Recommended Dosing.—The approved dosage of alendronate for prevention of bone loss in recently menopausal women and for treatment of corticosteroid-induced osteoporosis in men and estrogen-replete women is 5 mg daily (or 35 mg once weekly). For treatment of established postmenopausal osteoporosis and for treatment of corticosteroid-induced osteoporosis in estrogen-deficient women, 10 mg of alendronate daily (or 70 mg once weekly) is the approved dosage. Once-weekly dosing (that is, 70 mg once weekly) has been shown to be equivalent to daily dosing (10 mg/day), as reflected by changes in BMD and biochemical markers (level 2 evidence), but no fracture data are available.

Alendronate is supplied in 5- and 10-mg tablets for daily administration. It is also available in 35- and 70-mg tablets for once-weekly administration for prevention and treatment of postmenopausal osteoporosis, respectively. Alendronate should be taken with plain water on an empty stomach, at least $1/2$ hour before the first food, beverage, or orally administered medication of the day. Taking alendronate in conjunction with food, any beverage other than plain water, or certain medications, or ingesting it within 2 hours after a meal, may substantially reduce or abolish the absorption of alendronate. In order to avoid irritation of the esophagus, alendronate should be taken with approximately 8 ounces of water, and the patient should remain upright (seated or standing) until food has been eaten.

Efficacy.—Alendronate therapy has been shown in prospective, randomized, double-blind, placebo-controlled trials (level 2 evidence) to prevent bone loss and increase BMD at the spine and hip by 5 to 10%. Alendronate therapy has also been shown to prevent bone loss at the forearm and reduce the risk of fractures of the spine and nonvertebral sites such as the hip and wrist by 40 to 50% (level 1 evidence). The effects of alendronate on BMD at the spine and hip are maintained for at least 2 years after use of the drug is discontinued in older, but not in younger, patients (level 2 evidence). Alendronate has also been shown to be effective for the treatment of glucocorticoid-associated osteoporosis.

Side Effects.—Side effects of alendronate are generally mild and primarily affect the upper gastrointestinal system. In large-scale clinical trials, no apparent difference in tolerability has been noted between alendronate

Table 7
Some Commercially Available Calcium Preparations

Product (% elemental Ca)	Elemental Ca	Tablets/day to supply 1,000 mg of elemental Ca	Comment
AdvaCal	450	3	Multimineral/amino acid supplement
Alka-Mints	340	3	Antacid
Calci-Chew	500	2	…
Calci-Mix	500	2	Pull-apart capsules
Calcium carbonate (40%)	200	5	Most commonly used calcium preparation for
	240	4	osteoporosis
	260	4	Gastrointestinal acid converts calcium
	500	2	carbonate into soluble calcium salts; food
	600	2	improves absorption in achlorhydric patients in fasting state
Calcium lactate (13%)			
Generic	42.2	24	Impractical; large number of tablets required
Plain	84.5	12	
Calesium	100	10	Also contains magnesium
Caltrate			
600	600	2	Caltrate Plus also contains vitamin D,
600 + D	600	2	magnesium, zinc, copper, manganese, and
600 + soy	600	2	boron
600 Plus Chewables	600	2	
Citracal			
Ultradense	200	5	
Caplets + D	315	4	Calcium citrate has better absorption in
Liquitab Effervescent	500	2	fasting state than calcium carbonate
Plus	250	4	Citracal Plus also contains multiminerals
Equilet Chewable	200	5	…
Essential calcium			
Caplets	1,000	1	Caplets also contain magnesium,
Ionic supplement	500	2 servings	hyaluronidase, certain chelated minerals, vitamin B_6, betaine HCl, and joint mobility cofactors (silica, *Equisetum arvense*, glucosamine sulfate)
			Calcium citrate (caplets only) has better absorption in fasting state than calcium carbonate
			Ionic supplement, to be mixed with water, also contains vitamin D, magnesium, and boron
Healthy Woman Bone Health Supplement	600	2	Also contains vitamin D

Table 7 (*continued*)
Some Commercially Available Calcium Preparations

Product (% elemental Ca)	Elemental Ca	Tablets/day to supply 1,000 mg of elemental Ca	Comment
Mylanta			
Ultra CalciTabs	1,000	1	…
Extra-Strength			
CalciTabs	750	2	Antacid
Nutravescent	1,000	2	Calcium citrate has better absorption in fasting state than calcium carbonate
One-A-Day			
Bone Strength	500	2	Bone Strength also contains vitamin D and soy
Calcium Plus	500	2	Calcium Plus also contains magnesium and vitamin D
Os-Cal			
Chewable	500	2	…
250 + D	250	4	
500	500	2	
500 + D	500	2	
Posture	600	2	Calcium phosphate
Titralac			
Chewable	168	6	…
Extra-strength	300	4	
Tums			
Chewable	200	5	Antacid
E-X	300	4	
500	500	2	
Ultra	400	3	
Viactiv	500	2	Soft, flavored chew; also contains vitamins D and K

and placebo. In clinical practice, however, upper gastrointestinal symptoms such as heartburn, indigestion, substernal discomfort, and pain with swallowing can occur, and rare instances of esophageal erosion, ulceration, or bleeding have been described. Serious problems have been reported in approximately 1 of 10,000 alendronate users and can often be explained by patient selection or dosing errors. The cause for upper gastrointestinal side effects is unclear. If side effects occur, use of alendronate should be discontinued until symptoms are resolved, after which a rechallenge should be considered. Safety data for longer than 7 years of treatment are not available.

Contraindications.—Contraindications to alendronate therapy include hypersensitivity to alendronate, hypocalcemia, inability to follow the dosing regimen (that is, inability to remain upright for at least $1/2$ hour), and presence of esophageal abnormalities that might delay transit of the tablet (for example, achalasia or stricture). Use of alendronate is relatively contraindicated in patients with active upper gastrointestinal disease. Hypocalcemia and other disturbances of mineral metabolism must be corrected before any bisphosphonate therapy is initiated. No dose adjustment of alendronate is necessary for patients who have mild to moderate renal insufficiency (creatinine clearance of 35 to 60 mL/min). Alendronate should be used with caution in patients who have more severe renal insufficiency.

Duration of Treatment.—The therapeutic efficacy of alendronate has been demonstrated for 7 years. Efficacy and safety beyond 7 years have not yet been established. When alendronate therapy is discontinued, no acceleration of bone loss relative to placebo has been noted, although slow bone loss may occur.

Bisphosphonates: Risedronate

Role in Clinical Practice.—Risedronate, a nitrogen-containing bisphosphonate, is approved by the FDA for prevention of bone loss in recently menopausal women, treatment of established osteoporosis, and prevention and treatment of glucocorticoid-induced osteoporosis in men and women.

Available Forms and Recommended Dosing.—Risedronate is supplied as 5- and 30-mg tablets. The approved dosage for prevention or treatment of osteoporosis is 5 mg daily. The use of once-weekly dosing for the treatment of osteoporosis is being investigated.

Risedronate should be taken with plain water on an empty stomach, at least $1/2$ hour before the first food, beverage, or orally administered medication of the day. After taking risedronate, the patient should remain upright (seated or standing) until food has been eaten.

Efficacy.—Controlled clinical trial data show that risedronate increases BMD at the spine and hip, prevents bone loss at the forearm, and reduces the risk of fractures of the spine, hip, and other nonvertebral sites by 30 to 50% (level 1 evidence). Risedronate also preserves bone mass and reduces the incidence of vertebral fractures in glucocorticoid-treated patients.

Side Effects.—Adverse events associated with risedronate therapy in clinical trials did not differ from those associated with placebo. Whether the gastrointestinal tolerability of risedronate is different from that of alendronate is not known. Postmarketing experience suggests satisfactory tolerability. Safety data for longer than 3 years of treatment with risedronate are not available.

Contraindications.—Contraindications to risedronate therapy include hypocalcemia and hypersensitivity to risedronate. Hypocalcemia and other disturbances of mineral metabolism must be corrected before initiation of bisphosphonate therapy.

Duration of Treatment.—The therapeutic efficacy of risedronate has been demonstrated for a 3-year period. The efficacy and safety beyond 3 years have not yet been established, and the effect of termination of treatment on the rate of bone loss has not been assessed.

Other Bisphosphonates

Etidronate and *pamidronate* are available but have not been approved for prevention or treatment of osteoporosis. These agents are used "off label" for patients with osteoporosis.

- *Etidronate* has antifracture efficacy (level 1 evidence) and has been approved for treatment of osteoporosis in several countries. It is an alternative for patients who have gastrointestinal intolerance of approved orally administered bisphosphonates. Etidronate for treatment of osteoporosis is given in an intermittent cyclic regimen, 400 mg daily for 14 days, with cycles repeated every 3 months.
- *Pamidronate*, given by intravenous infusion, may be used for patients who cannot tolerate orally administered bisphosphonates or who may not absorb orally taken bisphosphonates because of gastrointestinal disease (level 2 evidence). A typical treatment schedule for pamidronate is a loading dose of 90 mg followed by 30 mg every third month given by intravenous infusion in dextrose or saline during a 2-hour period.

Calcitonin

Role in Clinical Practice.—Injectable salmon calcitonin was approved by the FDA for treating osteoporosis in 1984. Its use was limited by the need for subcutaneous injection and side effects such as nausea and flushing that occurred in approximately 20% of subjects. Nasal spray salmon calcitonin has been available since 1995.

Available Forms and Recommended Dosing.—Injectable calcitonin is available in sterile solution. For maximal effect, 100 IU/day is administered subcutaneously or intramuscularly. Nasally administered calcitonin is available in a spray bottle that delivers 200 IU per puff. The recommended dosage is one spray (200 IU) daily.

Efficacy.—Several prospective, randomized, double-blind, placebo-controlled trials have shown modest increases in spinal BMD (level 2 evidence) with injectable calcitonin, but adequate trials to evaluate the effects of injectable calcitonin on fracture have not been conducted.

Nasal spray salmon calcitonin was approved by the FDA in 1995 for the treatment of postmenopausal osteoporosis, on the basis of preliminary data showing effects on BMD and an ongoing fracture trial. This 5-year trial, now completed, showed a 36% reduction in the incidence of new vertebral fractures with use of 200 IU of nasally administered calcitonin daily. Studies to assess the effect of calcitonin nasal spray on hip fractures or other nonvertebral fractures (level 1 evidence) have not been conducted.

Side Effects.—Common side effects of parenterally administered calcitonin, which occur in up to 20% of patients, include nausea, local inflammatory reactions at the injection site, and vascular symptoms, including generalized flushing and tingling of the hands.

The gastrointestinal side effects noted with parenterally administered calcitonin are rarely seen with the nasal spray. The major side effect of nasally administered calcitonin is nasal discomfort, including rhinitis, irritation of the nasal mucosa, and occasional epistaxis.

Contraindications.—The main contraindication to use of both forms of calcitonin is hypersensitivity. For patients with suspected sensitivity to the drug, skin testing is recommended before treatment.

Duration of Treatment.—The optimal duration of treatment with calcitonin (either the parenterally or the nasally administered form) is unknown.

Estrogen Replacement Therapy

Role in Clinical Practice.—In the United States, orally and transdermally administered forms of estrogen are approved for prevention of bone loss in recently menopausal women. A progestin should be administered concomitantly in women who have not undergone hysterectomy.

Available Forms and Recommended Dosing.—Continuous daily estrogen replacement therapy (ERT) is recommended to prevent estrogen-deficiency symptoms and to promote compliance. The available dosages of estrogens indicated for preventing or treating osteoporosis are outlined in Table 8.

For maximal skeletal protection, therapy with estrogen should begin at the time of menopause or oophorectomy. At any time after menopause, however, therapy can be initiated because correction of estrogen deficiency at any age prevents or slows bone loss in postmenopausal women with osteoporosis.

Efficacy.—Epidemiologic evidence and meta-analyses of pooled data (level 2 evidence) indicate that women exposed to ERT for more than 7 years have a 50% lower incidence of osteoporosis-related fractures than do nonusers. Prospective studies (level 2) have demonstrated increases in bone mass and reduced fracture rates over shorter periods of observation. Nevertheless, long-term estrogen users may still experience age-related bone loss, and continued ERT may be less likely to arrest bone loss or prevent fractures in women after age 75 years. A pooled estimate of the RR of hip fracture comparing estrogen users with nonusers is 0.7 (level 2 evidence).

Nonskeletal Effects.—Conjugated estrogen therapy is associated with a significant increase in serum high-density lipoprotein cholesterol levels and a reduction in serum concentrations of total cholesterol and low-density lipoprotein cholesterol. Similar changes also occur with continuous combined and cyclic conjugated estrogens/medroxyprogesterone acetate therapies.

Observational and retrospective studies suggest that the incidence of cardiovascular events and mortality associated with cardiovascular disease are one-third to one-half lower in women who receive ERT in comparison with those who do not (level 2 evidence). In contrast, however, a recent, large prospective secondary prevention trial showed that ERT was associated with no significant reductions in cardiovascular events in women with established coronary artery disease. Furthermore, women in this study who received ERT had more coronary artery disease events during the first year of therapy but fewer in years 4 and 5. AACE does not recommend prescribing estrogen for its putative cardioprotective effect until this question has been clarified by further studies.

Side Effects.—Women who have not undergone hysterectomy and who receive unopposed estrogen therapy have an increased possibility of developing endometrial neoplasia and malignancy. When appropriate dosages of progestin are added to the regimen, this risk diminishes and is comparable to that of women who are not taking hormone replacement therapy (HRT).

Table 8
Available Estrogens Indicated for Prevention of Postmenopausal Osteoporosis*

Preparation	Recommended dosing (mg/day)	Available strengths (mg)	Comment
Conjugated estrogens			
Premarin tablets†	0.625	0.625, 0.9, 1.25, 2.5	…
Cenestin	0.625	0.625, 0.9	…
Estropipate			
Ortho-Est	0.75	0.75, 1.5	Recommended for 25 days
Ogen	0.75	0.75, 1.5, 3.0	of a 31-day cycle
Estradiol, micronized			
Estrace	0.5	0.5, 1.0, 2.0	…
Estradiol, transdermal			
Climara	0.025	0.025, 0.05, 0.075, 0.1	Once weekly
Vivelle	0.025	0.025, 0.0375, 0.05, 0.075, 0.1	Twice weekly
Estraderm	0.05	0.05, 0.1	Once weekly

*Although some product labeling recommends cyclic therapy for osteoporosis, continuous administration is preferable for treatment of perimenopausal or postmenopausal women, to prevent cyclic recurrence of vasomotor symptoms.
†Combination conjugated estrogens/medroxyprogesterone acetate preparations (Prempro, Premphase) are also indicated for osteoporosis prevention.

Irregular vaginal bleeding can occur in women who have not undergone hysterectomy and who are taking a combined estrogen-progestin regimen. This risk diminishes with time, and up to 80% of women receiving a continuous combined regimen consisting of 0.625 mg of conjugated estrogens daily plus an appropriate dose of medroxyprogesterone acetate become amenorrheic within 1 year after initiation of treatment.

ERT increases the risk of cholelithiasis twofold. Moreover, fluid retention, mastalgia, abdominal pain, and headache may occur but may be ameliorated by use of a lower dose of estrogens.

In women who receive estrogen therapy in comparison with those who do not, the risk of venous thromboembolism is increased approximately threefold. The absolute risk is small (~3 in 1,000 to 3 in 10,000).

A small but significant increase in the RR of breast cancer is associated with use of ERT and HRT. Pooled estimates of RR range from 1.1 for only ERT to 1.4 when progestin is added. The risk increases with the duration of estrogen use (RR = 1 + 0.01 per year of use for ERT to 1 + 0.08 per year for HRT). Inconclusive evidence suggests that this risk is higher when cyclic HRT is taken for more than 4 years.

Contraindications.—The following factors are contraindications to estrogen or combination estrogen-progestin therapy:

- Known or suspected pregnancy
- Known or suspected cancer of the breast
- Known or suspected estrogen-dependent neoplasm
- Undiagnosed, abnormal genital bleeding
- Active thrombophlebitis or thromboembolic disorders or a history of thromboembolic disease
- Hypersensitivity to the hormones

Side effects not tolerated by the patient, as well as a substantial and uncontrollable increase in serum triglyceride levels, are valid reasons for discontinuing estrogen or estrogen-progestin therapy.

Duration of Treatment.—Estrogen therapy may be continued indefinitely. Direct evidence suggests that bone loss recurs after estrogen treatment is discontinued.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators activate estrogen receptors in target organs selectively to produce quantitatively variable estrogenic effects on estrogen-responsive tissues. Raloxifene has been approved by the FDA for prevention and treatment of postmenopausal osteoporosis. Raloxifene has agonistic effects on bone and lipoprotein production but has antagonistic effects on breast tissue and neutral effects on uterine mucosa.

Role in Clinical Practice.—Raloxifene is FDA approved for the treatment of postmenopausal osteoporosis and the prevention of bone loss in recently menopausal women.

Available Forms and Recommended Dosing.—Raloxifene is available as a 60-mg tablet. The dosage of raloxifene for prevention of bone loss in recently menopausal women and for treatment of established osteoporosis is 60 mg daily.

Efficacy.—Among postmenopausal women with osteoporosis studied for 36 months, raloxifene (60 and 120 mg daily) reduced the risk of vertebral fractures by 30 to 50% (level 1 evidence). Raloxifene did not reduce nonvertebral fractures, but this study had insufficient statistical power for full assessment of the effects of this agent on nonvertebral fractures. Raloxifene increased BMD in the spine by 2.7% and in the femoral neck by 2.4% over placebo, and it reduced bone turnover to premenopausal levels.

Nonskeletal Effects.—Raloxifene reduces total cholesterol and low-density lipoprotein cholesterol fractions by about 7 and 11%, respectively, but it has no observable effect on concentrations of high-density lipoprotein cholesterol. The potential cardiovascular risks or benefits of raloxifene have not been studied.

In the Multiple Outcomes of Raloxifene Evaluation (MORE) Study of 5,129 postmenopausal women with osteoporosis treated with raloxifene, a 76% overall reduction of breast cancer and a 90% reduction in estrogen receptor-positive breast cancer were noted in comparison with placebo. A large study in patients at high risk for breast cancer is currently being conducted.

Side Effects.—As with estrogen, raloxifene is associated with an approximate threefold increase in venous thromboembolic diseases in comparison with placebo (RR 3.1), although the absolute risk is low. Other side effects include hot flashes, leg cramps, peripheral edema, and accumulation of endometrial fluid in the absence of endometrial disease.

Contraindications.—Raloxifene is contraindicated in women who are or are capable of becoming pregnant, who have had venous thromboembolic disease, or who are known to be hypersensitive to any component of raloxifene tablets.

Duration of Treatment.—Efficacy and safety have been determined for up to 40 months.

Concomitant Use of Therapeutic Agents

No data firmly establish that the combined use of two antiresorptive agents (for example, bisphosphonates plus ERT or raloxifene; estrogen plus calcitonin) has an additive effect on fracture reduction. Additive effects on bone mass and bone turnover have been observed. Until the effect of combined therapy on fracture risk is understood, however, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis.

Unapproved and Adjuvant Pharmaceutical Therapies

The unapproved and adjuvant therapies for postmenopausal osteoporosis are summarized in Table 9.

Table 9
Unapproved and Adjuvant Pharmacotherapies
for Postmenopausal Osteoporosis*

Agent	Efficacy		Evidence†	FDA status	Therapeutic potential
	Fracture	BMD			
Human parathyroid hormone	Yes	Yes	Level 1	Pending	High
Sodium fluoride	No	Yes	Level 2	Inactive	Uncertain
Phytoestrogens	Unknown	Unknown	Level 2	None	Uncertain

*BMD = bone mineral density; FDA = US Food and Drug Administration.
†Level 1 = studies that used fracturing as the clinical endpoint in randomized, double-blind, prospective investigations; level 2 = cross-sectional studies, studies that tested smaller or nonrandomized patient populations, or studies that used secondary or surrogate clinical endpoints for fracture (for example, bone mineral density measurement or bone turnover markers).

Follow-Up

The efficacy and safety of preventive and therapeutic strategies should periodically be reassessed, reinforced, and revised as needed. AACE recommends annual reassessment, which should include the following:

- Interim history
- Complete medical examination, including breast and pelvic examinations, mammography, and Papanicolaou smear if indicated
- Assessment of adherence to recommended program, including calcium, vitamin D, exercise, and any pharmacologic therapy
- Assessment of stature and skeletal integrity, including radiographic assessment of new deformities or newly symptomatic osseous deformities
- Reinforcement of the therapeutic program and evaluation of the patient's level of understanding and concern
- Periodic assessment of BMD

BMD for Monitoring Treatment

Serial BMD measurements are useful for monitoring changes in bone mass. Each technique for evaluation of bone density has an inherent variability (that is, precision error) that must be considered when the clinical significance of BMD changes is assessed. With dual x-ray absorptiometry, for example, a BMD difference between measurements must be in the range of 3 to 5% to be clinically significant. Patients treated with bisphosphonates often demonstrate changes of this magnitude at the spine within a year and at the hip after 2 or more years. No change or even a slight reduction of BMD, however, is not evidence of treatment failure and does not warrant alteration of therapy.

Until specific data about the most efficient use of BMD for monitoring become available, the following general guidelines for performing follow-up BMD measurements may be used:

- *For patients with "normal" baseline BMD (T-score more than −1.0)*, consider a follow-up measurement every 3 to 5 years. Patients whose bone density is well above the minimal acceptable level may not need further BMD testing.
- *For patients in an osteoporosis prevention program*, perform a follow-up measurement every 1 to 2 years until bone mass stability is documented. After BMD has stabilized, perform follow-up measurements every 2 to 3 years.
- *For patients on a therapeutic program*, perform a follow-up measurement yearly for 2 years. If bone mass has stabilized after 2 years, perform a follow-up measurement every 2 years. Otherwise, continue with annual follow-up measurements until stability of bone mass is achieved.

ACKNOWLEDGMENT

SELECTED BIBLIOGRAPHY

Other Evidence-Based Guidelines

1. **Johnston CC Jr.** Development of clinical practice guidelines for prevention and treatment of osteoporosis. *Calcif Tissue Int.* 1996;59(Suppl 1):S30-S33.
2. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis [executive summary]. *Osteoporos Int.* 1998;8(Suppl 4):S3-S6.

General Information

1. **Jensen ME, Evans AJ, Mathis JM, Kallmes DF, Cloft HJ, Dion JE.** Percutaneous polymethylmethacrylate verte-broplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. *Am J Neuro-radiol.* 1997;18:1897-1904.
2. **Kano K.** Relationship between exercise and bone mineral density among over 5,000 women aged 40 years and above. *J Epidemiol.* 1998;8:28-32.
3. **McClung MR.** Therapy for fracture prevention. *JAMA.* 1999;282:687-689.
4. **Meunier PJ.** Evidence-based medicine and osteoporosis: a comparison of fracture risk reduction data from osteoporosis randomised clinical trials. *Int J Clin Pract.* 1999;53:122-129.
5. **Wolff I, van Croonenborg JJ, Kemper HC, Kostense PJ, Twisk JW.** The effect of exercise training programs on bone mass: a meta-analysis of published controlled trials in pre- and postmenopausal women. *Osteoporos Int.* 1999;9:1-12.

Bone Density Measurement

1. **Cummings SR, Palermo L, Browner W, et al (Fracture Intervention Trial Research Group).** Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. *JAMA.* 2000;283:1318-1321.
2. **Garton MJ, Cooper C, Reid D.** Perimenopausal bone density screening—will it help prevent osteoporosis? *Maturitas.* 1997;26:35-43.
3. **Orwoll ES, Bauer DC, Vogt TM, Fox KM (Osteoporotic Fractures Research Group).** Axial bone mass in older women. *Ann Intern Med.* 1996;124:187-196.
4. **Wasnich RD, Miller PD.** Antifracture efficacy of antiresorptive agents are related to changes in bone density. *J Clin Endocrinol Metab.* 2000;85:231-236.
5. **Watts NB.** Understanding the bone mass measurement act. *J Clin Densitom.* 1999;2:211-217.

Biochemical Markers of Bone Turnover in Osteoporosis

1. **Garnero P, Delmas PD.** Biochemical markers of bone turnover: applications for osteoporosis. *Endocrinol Metab Clin North Am.* 1998;27:303-323.
2. **Hannon R, Blumsohn A, Naylor K, Eastell R.** Response of biochemical markers of bone turnover to hormone replacement therapy: impact of biological variability. *J Bone Miner Res.* 1998;13:1124-1133.
3. **Looker AC, Bauer DC, Chesnut CH III, et al.** Clinical use of biochemical markers of bone remodeling: current status and future directions. *Osteoporos Int.* 2000;11:467-480.

Alendronate

1. **Black DM, Cummings SR, Karpf DB, et al (Fracture Intervention Trial Research Group).** Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet.* 1996;348:1535-1541.
2. **Black DM, Thompson DE, Bauer DC, et al (FIT Research Group).** Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab.* 2000;85:4118-4124.

3. **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.
4. **de Groen PC, Lubbe DF, Hirsch LJ, et al.** Esophagitis associated with the use of alendronate. *N Engl J Med.* 1996;335:1016-1021.
5. **Devogelaer JP, Broll H, Correa-Rotter R, et al.** Oral alendronate induces progressive increases in bone mass of the spine, hip, and total body over 3 years in postmenopausal women with osteoporosis [erratum in *Bone.* 1996;19:78]. *Bone.* 1996;18:141-150.
6. **Downs RW Jr, Bell NH, Ettinger MP, et al.** Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women. *J Clin Endocrinol Metab.* 2000;85:1783-1788.
7. **Ensrud KE, Black DM, Palermo L, et al.** Treatment with alendronate prevents fractures in women at highest risk: results from the Fracture Intervention Trial. *Arch Intern Med.* 1997;157:2617-2624.
8. **Felsenberg D, Alenfeld F, Bock O, Hammermeister C, Gowan W (Fosamax International Trial [FOSIT] Study Group).** Placebo-controlled multicenter study of oral alendronate in postmenopausal osteoporotic women. *Maturitas.* 1998;31:35-44.
9. **Hosking D, Chilvers CE, Christiansen C, et al (Early Postmenopausal Intervention Cohort Study Group).** Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. *N Engl J Med.* 1998;338:485-492.
10. **Karpf DB, Shapiro DR, Seeman E, et al (Alendronate Osteoporosis Treatment Study Groups).** Prevention of nonvertebral fractures by alendronate: a meta-analysis. *JAMA.* 1997;277:1159-1164.
11. **Liberman UA, Weiss SR, Broll J, et al (Alendronate Phase III Osteoporosis Treatment Study Group).** Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med.* 1995;333:1437-1443.
12. **Lowe CE, Depew WT, Vanner SJ, Paterson WG, Meddings JB.** Upper gastrointestinal toxicity of alendronate. *Am J Gastroenterol.* 2000;95:634-640.
13. **Pols HA, Felsenberg D, Hanley DA, et al (Fosamax International Trial Study Group).** 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. *Osteoporos Int.* 1999;9:461-468.
14. **Ravn P, Weiss SR, Rodriguez-Portales JA, et al (Alendronate Osteoporosis Prevention Study Group).** Alendronate in early postmenopausal women: effects on bone mass during long-term treatment and after withdrawal. *J Clin Endocrinol Metab.* 2000;85:1492-1497.
15. **Ribeiro A, DeVault KR, Wolfe JT III, Stark ME.** Alendronate-associated esophagitis: endoscopic and pathologic features. *Gastrointest Endosc.* 1998;47:525-528.
16. **Saag KG, Emkey R, Schnitzer TJ, et al (Glucocorticoid-Induced Osteoporosis Intervention Study Group).** Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. *N Engl J Med.* 1998;339:292-299.
17. **Schnitzer T, Bone HG, Crepaldi G, et al (Alendronate Once-Weekly Study Group).** Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. *Aging (Milano).* 2000;12:1-12.

18. **Stock JL, Bell NH, Chesnut CH III, et al.** Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. *Am J Med.* 1997;103:291-297.

19. **Tonino RP, Meunier PJ, Emkey R, et al (Phase III Osteoporosis Treatment Study Group).** Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. *J Clin Endocrinol Metab.* 2000;85:3109-3115.

20. **Watts N, Freedholm D, Daifotis A.** The clinical tolerability profile of alendronate. *Int J Clin Pract Suppl.* 1999; 101:51-61.

Risedronate

1. **Cohen S, Levy RM, Keller M, et al.** Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 1999;42:2309-2318.

2. **Eastell R, Devogelaer JP, Peel NF, et al.** Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. *Osteoporos Int.* 2000;11:331-337.

3. **Harris ST, Watts NB, Genant HK, et al (Vertebral Efficacy With Risedronate Therapy [VERT] Study Group).** Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA.* 1999; 282:1344-1352.

4. **McClung MR, Geusens P, Miller PD, et al (Hip Intervention Program Study Group).** Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med.* 2001;344:333-340.

5. **Reginster J, Minne HW, Sorensen OH, et al (Vertebral Efficacy with Risedronate Therapy [VERT] Study Group).** Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. *Osteoporos Int.* 2000;11:83-91.

6. **Reid DM, Hughes RA, Laan RF, et al.** Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial; European Corticosteroid-Induced Osteoporosis Treatment Study. *J Bone Miner Res.* 2000;15:1006-1013.

7. **Watts N, Roux C, Genant H, et al.** Risedronate reduces vertebral fracture risk after the first year of treatment in postmenopausal women with established osteoporosis. *J Bone Miner Res.* 1999;14:S136.

Other Bisphosphonates

1. **Heikkinen JE, Selander KS, Laitinen K, Arnala I, Vaananen HK.** Short-term intravenous bisphosphonates in prevention of postmenopausal bone loss. *J Bone Miner Res.* 1997;12:103-110.

2. **Lees B, Garland SW, Walton C, Ross D, Whitehead MI, Stevenson JC.** Role of oral pamidronate in preventing bone loss in postmenopausal women. *Osteoporos Int.* 1996;6:480-485.

3. **Miller PD, Watts NB, Licata AA, et al.** Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment [erratum in *Am J Med.* 1998;104:608]. *Am J Med.* 1997;103: 468-476.

4. **Orr-Walker B, Wattie DJ, Evans MC, Reid IR.** Effects of prolonged bisphosphonate therapy and its discontinuation on bone mineral density in post-menopausal osteoporosis. *Clin Endocrinol (Oxf).* 1997;46:87-92.

5. **Peretz A, Body JJ, Dumon JC, et al.** Cyclical pamidronate infusions in postmenopausal osteoporosis. *Maturitas.* 1996;25:69-75.

6. **Recker RR, Stakkestad JA, Felsenberg D, et al.** A new treatment paradigm: quarterly injections of ibandronate reduce the risk of fractures in women with postmenopausal osteoporosis (PMO): results of a 3-year trial. *Osteoporos Int.* 2000;11:S209.

7. **Roux C, Oriente P, Laan R, et al (Ciblos Study Group).** Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. *J Clin Endocrinol Metab.* 1998;83:1128-1133.

8. **Watts NB.** Treatment of osteoporosis with bisphosphonates. *Endocrinol Metab Clin North Am.* 1998;27:419-439.

Calcitonin

1. **Chesnut CH III, Silverman S, Andriano K, et al (PROOF Study Group).** 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.

Estrogen and Hormone Replacement Therapy

1. **Eiken P, Kolthoff N, Nielsen SP.** Effect of 10 years' hormone replacement therapy on bone mineral content in postmenopausal women. *Bone.* 1996;19(5 Suppl):191S-193S.

2. **Ettinger B, Friedman GD, Bush T, Quesenberry CP Jr.** Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstet Gynecol.* 1996;87:6-12.

3. **Evans SF, Davie MW.** Low and conventional dose transdermal oestradiol are equally effective at preventing bone loss in spine and femur at all post-menopausal ages. *Clin Endocrinol (Oxf).* 1996;44:79-84.

4. **Gapstur SM, Morrow M, Sellers TA.** Hormone replacement therapy and risk of breast cancer with a favorable histology: results of the Iowa Women's Health Study. *JAMA.* 1999;281:2091-2097.

5. **Hulley S, Grady D, Bush T, et al (Heart and Estrogen/ Progestin Replacement Study [HERS] Research Group).** Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA.* 1998;280:605-613.

6. **Komulainen M, Kroger H, Tuppurainen MT, et al.** Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D3 in early postmenopausal women: a population-based 5-year randomized trial. *J Clin Endocrinol Metab.* 1999;84:546-552.

7. **Komulainen MH, Kroger H, Tuppurainen MT, et al.** HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women: a 5 year randomized trial. *Maturitas.* 1998;31:45-54.

8. **McNagny SE.** Prescribing hormone replacement therapy for menopausal symptoms. *Ann Intern Med.* 1999;131:605-616.

9. **Recker RR, Davies KM, Dowd RM, Heaney RP.** The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women: a randomized, controlled trial. *Ann Intern Med.* 1999;130:897-904.

10. **Ross RK, Paganini-Hill A, Wan PC, Pike MC.** Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst.* 2000;92:328-332.

11. **Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R.** Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA.* 2000; 283:485-491.

Raloxifene

1. **Cummings SR, Eckert S, Krueger KA, et al.** The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial; Multiple Outcomes of Raloxifene Evaluation [erratum in *JAMA.* 1999;282:2124]. *JAMA.* 1999;281:2189-2197.
2. **Delmas PD, Bjarnason NH, Mitlak BH, et al.** Effects of raloxifene on bone mineral density, serum cholesterol concentrations, and uterine endometrium in postmenopausal women. *N Engl J Med.* 1997;337:1641-1647.
3. **Ettinger B, Black DM, Mitlak BH, et al (Multiple Outcomes of Raloxifene Evaluation [MORE] Investigators).** Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial [erratum in *JAMA.* 1999;282:2124]. *JAMA.* 1999;282:637-645.

Combination Pharmacologic Therapy

1. **Lindsay R, Cosman F, Lobo RA, et al.** Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab.* 1999;84:3076-3081.
2. **Ravn P, Bidstrup M, Wasnich RD, et al.** Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study; a randomized, controlled trial. *Ann Intern Med.* 1999;131:935-942.

Unapproved Pharmacologic Agents

1. **Feskanich D, Willett WC, Stampfer MJ, Colditz GA.** A prospective study of thiazide use and fractures in women. *Osteoporos Int.* 1997;7:79-84.
2. **Finkelstein JS, Klibanski A, Arnold AL, Toth TL, Hornstein MD, Neer RM.** Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): a randomized controlled trial. *JAMA.* 1998;280: 1067-1073.
3. **Gambacciani M, Cappagli B, Piaggesi L, Ciaponi M, Genazzani AR.** Ipriflavone prevents the loss of bone mass in pharmacological menopause induced by GnRH-agonists. *Calcif Tissue Int.* 1997;61(Suppl 1):S15-S18.
4. **Gambacciani M, Ciaponi M, Cappagli B, Piaggesi L, Genazzani AR.** Effects of combined low dose of the isoflavone derivative ipriflavone and estrogen replacement on bone mineral density and metabolism in postmenopausal women. *Maturitas.* 1997;28:75-81.
5. **Gennari C, Agnusdei D, Crepaldi G, et al.** Effect of ipriflavone—a synthetic derivative of natural isoflavones—on bone mass loss in the early years after menopause. *Menopause.* 1998;5:9-15.
6. **Hodsman AB, Fraher LJ, Watson PH, et al.** A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab.* 1997;82:620-628.

7. **Ishimi Y, Miyaura C, Ohmura M, et al.** Selective effects of genistein, a soybean isoflavone, on B-lymphopoiesis and bone loss caused by estrogen deficiency. *Endocrinology.* 1999;140:1893-1900.
8. **Lindsay R, Nieves J, Formica C, et al.** Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet.* 1997;350: 550-555.
9. **Lippuner K, Haenggi W, Birkhaeuser MH, Casez JP, Jaeger P.** Prevention of postmenopausal bone loss using tibolone or conventional peroral or transdermal hormone replacement therapy with 17beta-estradiol and dydrogesterone. *J Bone Miner Res.* 1997;12:806-812.
10. **Meunier PJ, Sebert JL, Reginster JY, et al.** Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVO Study. *Osteoporos Int.* 1998;8:4-12.
11. **Pak CY, Zerwekh JE, Antich PP, Bell NH, Singer FR.** Slow-release sodium fluoride in osteoporosis. *J Bone Miner Res.* 1996;11:561-564.
12. **Pavlov PW, Ginsburg J, Kicovic PM, van der Schaaf DB, Prelevic G, Bennink HJ.** Double-blind, placebo-controlled study of the effects of tibolone on bone mineral density in postmenopausal osteoporotic women with and without previous fractures. *Gynecol Endocrinol.* 1999;13:230-237.
13. **Reginster JY, Meurmans L, Zegels B, et al.** The effect of sodium monofluorophosphate plus calcium on vertebral fracture rate in postmenopausal women with moderate osteoporosis: a randomized, controlled trial. *Ann Intern Med.* 1998;129:1-8.
14. **Studd J, Arnala I, Kicovic PM, Zamblera D, Kroger H, Holland N.** A randomized study of tibolone on bone mineral density in osteoporotic postmenopausal women with previous fractures. *Obstet Gynecol.* 1998;92(4 Pt 1):574-579.

Epidemiology

1. **Ensrud KE, Thompson DE, Cauley JA, et al (Fracture Intervention Trial Research Group).** Prevalent vertebral deformities predict mortality and hospitalization in older women with low bone mass. *J Am Geriatr Soc.* 2000; 48:241-249.
2. **Grainge MJ, Coupland CA, Cliffe SJ, Chilvers CE, Hosking DJ (Nottingham EPIC Study Group).** Cigarette smoking, alcohol and caffeine consumption, and bone mineral density in postmenopausal women. *Osteoporos Int.* 1998;8:355-363.
3. **Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR (Study of Osteoporotic Fractures Research Group).** Vertebral fractures and mortality in older women: a prospective study. *Arch Intern Med.* 1999;159:1215-1220.
4. **Melton LJ III, Egan KS, O'Fallon WM, Riggs BL.** Influence of fracture criteria on the outcome of a randomized trial of therapy. *Osteoporos Int.* 1998;8:184-191.
5. **Ray NF, Chan JK, Thamer M, Melton LJ III.** Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. *J Bone Miner Res.* 1997;12:24-35.