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SYSTEMS IMPROVEMENT

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# Health Care Guideline

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- researchers;
- federal, state and local government health care policy makers and specialists; and
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**Work Group Leader**

Christine Simonelli, MD  
*Internal Medicine, HealthEast Clinics*

**Work Group Members**

**Endocrinology**

Bart Clarke, MD  
*Mayo Clinic*

**Family Practice**

Daniel Cohan, DO  
*North Clinic*

**Gynecology**

Richard Kopher, MD  
*HealthPartners Medical Group*

**Internal Medicine**

Dana Battles, MD  
*Aspen Medical Group*

Robert Florence, MD  
*Aspen Medical Group*

Philip Hoversten, MD  
*Allina Medical Clinic*

Philip Hoversten, MD  
*Allina Medical Clinic*

Philip Hoversten, MD  
*Allina Medical Clinic*

**Rheumatology**

John Schousboe, MD  
*Park Nicollet Health Services*

**Pharmacy**

VyVy Vo, PharmD  
*HealthPartners Medical Group*

**Nursing**

Renee Compo, RN, CNP  
*HealthPartners Medical Group*

Sharon Verville, Tech  
*Sioux Valley Health System*

**Measurement/  
Implementation Advisor**

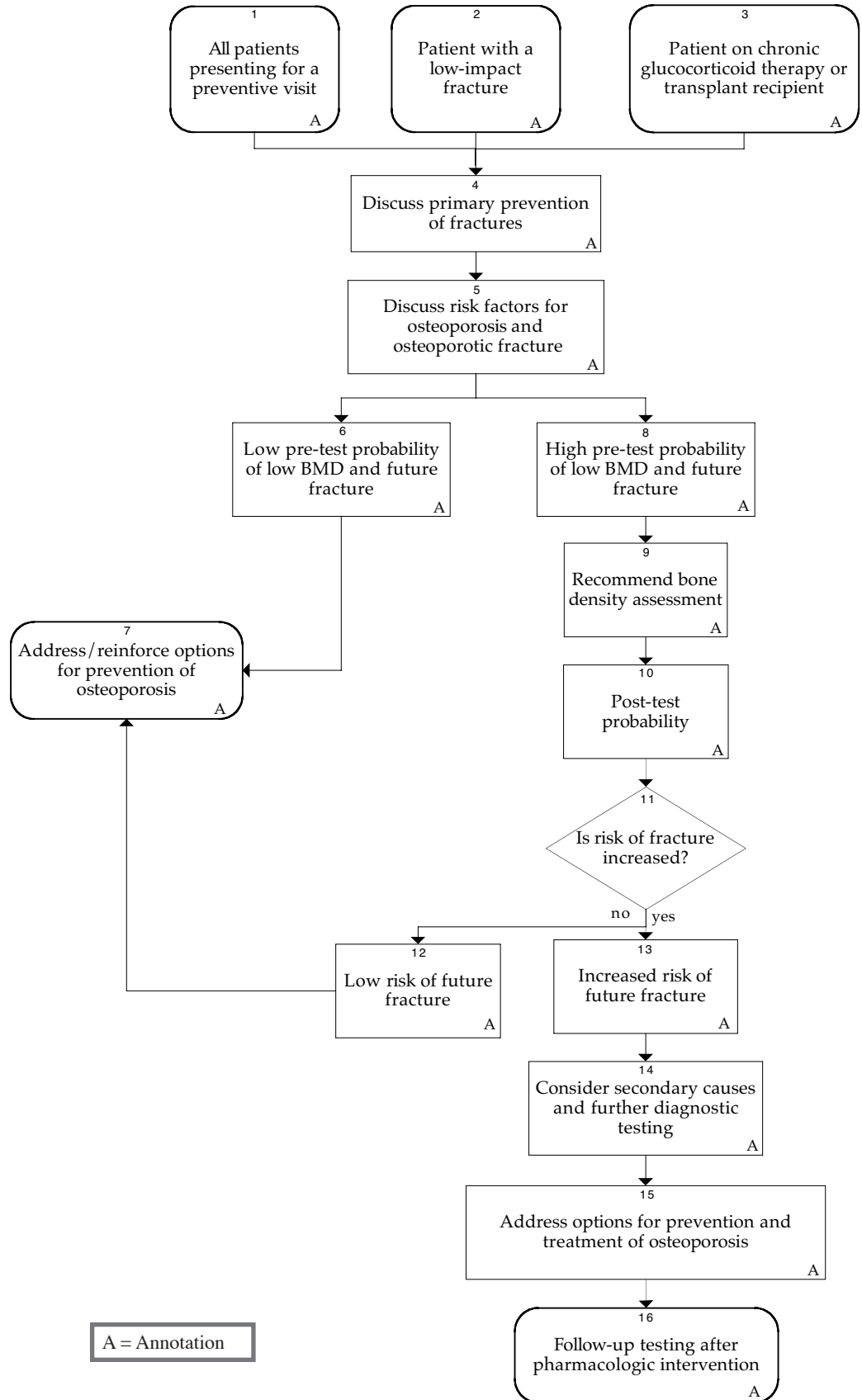
Sylvia Robinson, BSN, MBA  
*ICSI*

Sylvia Robinson, BSN, MBA  
*ICSI*

**Facilitator**

Linda Setterlund, MA  
*ICSI*

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# Foreword

## Scope and Target Population

This guideline is targeted toward identification of patients at risk for osteoporosis, as well as identification and treatment of those patients with osteoporosis.

## Clinical Highlights and Recommendations

- Discuss risk factors for osteoporosis, and primary prevention with all patients presenting for preventive health visits. (*Annotations #4, 5*)
- Patients with a high pre-test probability of low BMD and future fracture should have bone density testing to further define their fracture risk. (*Annotations #8, 9*)
- Address pharmacologic options for prevention and treatment of osteoporosis with appropriate patients at risk for or who currently have signs and symptoms of osteoporosis. (*Annotation #15*)

## Priority Aims

1. Improve diagnostic and therapeutic follow-up of adults presenting with a history of low-impact fracture. (Refer to Algorithm Box 2)
2. Increase the evaluation for osteoporosis risk factors in all adults presenting for a preventive visit, and stratify into appropriate risk group.

## Related ICSI Scientific Documents

### Related Guidelines

- Menopause and Hormone Therapy (HT): Collaborative Decision Making and Management
- Preventive Services for Adults

### Technology Assessment Reports

- Biochemical Markers for Bone Turnover in Osteoporosis (#53, 2001)
- Densitometry as a Diagnostic Tool for the Identification and Treatment of Osteoporosis in Women (#31, 2000)
- Vertebroplasty and Balloon-Assisted Vertebroplasty for the Treatment of Osteoporotic Compression Fractures (#79, 2004)

### Patient and Family Guidelines

- Diagnosis and Treatment of Osteoporosis for Patients and Families

## **Evidence Grading**

Individual research reports are assigned a letter indicating the class of report based on design type: A, B, C, D, M, R, X.

Key conclusions are assigned a conclusion grade: I, II, III, or Grade Not Assignable.

A full explanation of these designators is found in the Supporting Evidence section of the guideline.

## **Disclosure of Potential Conflict of Interest**

In the interest of full disclosure, ICSI has adopted the policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic. The reader should not assume that these financial interests will have an adverse impact on the content of the guideline, but they are noted here to fully inform readers. Readers of the guideline may assume that only work group members listed below have potential conflicts of interest to disclose.

Christine Simonelli, MD receives research grant support from Novartis, Eli Lilly, and Roche-GSK serves as a consultant for Procter & Gamble, Roche GSK, NPS Pharm and Merck, and is a DSMB member for Amgen.

Bart Clarke, MD, is a DSMB member for Amgen.

Robert Florence, MD, receives speaker's fees from Eli Lilly, Procter & Gamble, Roche GSK, Aventis.

John Schousboe, MD, receives research grant support from Hologic, Inc.

No other work group members have potential conflicts of interest to disclose.

ICSI's conflict of interest policy and procedures are available for review on ICSI's website at <http://www.icsi.org>.

## Algorithm Annotations

### 1. All Patients Presenting for a Preventive Visit

Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved peak bone mass, or both. We recommend maintaining peak bone mass for all patients. To achieve and maintain maximum bone density, patients should have risks for osteoporosis reviewed when they present to their provider offices. In addition to reviewing historical risk factors (discussed in Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture"), it is important to record accurate serial height measurements with a stadiometer and observe posture for kyphosis. Patients with significant acquired kyphosis and/or a height loss of one inch should have lateral vertebral assessment with DXA or thoracic and lumbar spine radiographs and bone density testing (*NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001*).

*Supporting evidence is of class: R*

### 2. Patient With a Low-Impact Fracture

#### Key Points:

- Low-impact fracture defines osteoporosis and requires therapy.

Discuss osteoporosis risk with any adult who has a history of a low-trauma fracture that may be related to osteoporosis. For the purpose of this guideline, a low-impact fracture will be defined as a fracture occurring spontaneously or from a fall at a height no greater than the patient's standing height. This includes fractures from activities such as a cough, sneeze or abrupt movement (e.g., opening a window), and patients who have vertebral compression fracture documentation on radiographs regardless of their degree of symptoms. Many adults do not realize that having one fracture in their adult lifetime indicates an increased risk of future fractures, especially in the first few years following the fracture, and may be an indication for bone density testing. This historical risk factor provides information that may be additive to bone mineral density information. The occurrence of a fracture, particularly in the limbs, is followed by accelerated bone loss, not completely reversible, which could lead to an increased risk of subsequent fracture. And, there may be mechanical influences caused by having had one fracture, that increase subsequent risk by altering balance and increasing fall risk (*Johnell, 2004*).

#### Post-Fracture Recommendations

- Consider all adults with a history of vertebral fracture, hip fracture, or distal forearm fracture at higher than average risk for a future fracture.
- Review lifestyle risk factors for osteoporosis. Discuss adequacy of total calcium and vitamin D intake. Address home safety, fall prevention and specific exercises for muscle strength.
- Consider bone density testing in fracture patients willing to accept treatment.
- Consider all men\* and postmenopausal women with low-impact fracture as potential candidates for pharmacologic and physical medicine treatment.
- Women over age 70 with prior fracture are candidates for osteoporosis therapy even without bone density testing.

\* Although we have the best data on postmenopausal women, there may be a similar risk in men and we are including men in this guideline recommendation (*Melton, 1998*).

**Algorithm Annotations**

It is estimated that 50% of women over age 50 will develop a fracture in their remaining lifetime and the annualized risk increases with age. Twenty-five percent of women over age 50 will experience an osteoporotic vertebral fracture, so that by age 75 more than one in three women have at least one vertebral fracture.

The presence of a vertebral compression fracture (VCF) increases the risk for subsequent fracture beyond the risk indicated by bone density alone (*Kanis, 1997; Lindsay, 2001; National Osteoporosis Foundation, 1999*).

Black, et al., examined data from the Study of Osteoporotic Fractures, a prospective study of 9,704 postmenopausal women over age 65. After a mean of 3.7 years, patients with a prevalent vertebral fracture had an increase in subsequent radiographically documented vertebral fracture, hip fractures, and all non-vertebral fractures combined. After adjusting for age, there was not a statistically significant increase in wrist fractures (*Black, 1999*). Other studies support this observation (*Davis, 1999; Huopio, 2000*).

**Relative Risk of Fracture at Various Sites in the Presence of a Radiographic Vertebral Compression Deformity**

Site of Subsequent Fracture	Relative Risk (95% CI)
Vertebral	5.4 (4.4, 6.6)
Hip	2.8 (2.3, 3.4)
Any non-vertebral site	1.9 (1.7, 2.1)

In 1991, Ross, et al., demonstrated that a combination of bone mineral density (BMD) and history of vertebral fracture provided an even stronger predictive value of risk of subsequent fractures. For example, a patient with "low" BMD and one vertebral fracture has a 25-fold higher risk for subsequent vertebral fracture compared with a patient with "high" BMD and no fracture. Often overlooked is the statistical finding that a patient with a "medium" BMD and an existing vertebral fracture actually has twice the risk for a subsequent fracture compared with a patient with low BMD and no fracture (*Ross, 1991*).

Non-vertebral fractures can also be indicators of increased risk for subsequent fracture. Schroeder, et al., reviewed 256 second hip fractures in 3,898 adults. Ninety-two percent were contralateral and half the repeat fractures occurred in less than three years after the index fracture. Although the risk of the first hip fracture was 1.6 per 1,000 men and 3.6 per 1,000 women, the risk for a second hip fracture was 15 per 1,000 men and 22 per 1,000 women (*Schroder, 1993*).

Fractures of the wrist (Colles' fractures) can also be indicators of significant risk for osteoporosis or future fractures (*Schousboe, 2005*). The prospective study by Earnshaw, et al., reported bone densities in men and women with a history of Colles' fracture. In patients less than 65 years, BMD was lower in the hip and non-fractured distal radius than age-matched controls (*Earnshaw, 1998*). A retrospective case-control study of patients in Sweden who sustained non-osteoporotic fractures early in life was reported (*Karlsson, 1993*). They reported an odds ratio of subsequently developing an osteoporotic fracture after ankle fracture of 1.8 (range 1.3-2.7) over 14 years. The overall increase in risk from any non-osteoporotic fracture for men was 2.3 (range 1.4-3.6) and for women 1.6 (range 1.04-2.3). Gunnes reported similar results from a population-based, retrospective study of 29,802 postmenopausal women. Again an odds ratio for hip fracture after ankle fracture was 1.6 (95% CI 1.1-2.3) and 3.0 (95% CI 2.4-5.0) for a previous humerus fracture (*Gunnes, 1998*).

Women with prior fracture and low bone density are the most responsive to anti-resorptive therapy and pharmaceutical trials suggests that women with prior fracture can reduce their risk for subsequent fractures by 30%-50%. This has been shown for FDA approved osteoporosis therapies. The largest therapy-induced BMD increase is observed in patients with the lowest BMD and vertebral fractures, the population at highest risk (*Ettinger, 1999; Hochberg, 1999*).

### **Risk of Subsequent Hip Fracture**

Overall, prior fracture at any site is a clear risk factor for the development of a future hip fracture (RR=1.8; 95% CI: 1.5, 2.2). Klotzbuecher performed a statistical synthesis of studies with reported relative risk and confidence intervals to derive a summary estimate of the relative risk of future hip fracture (*Klotzbuecher, 2000*).

*Supporting evidence is of classes: A, B, C, D, M, R*

## **3. Patient On Chronic Glucocorticoid Therapy or Transplant Recipient**

### **Key Points:**

- Glucocorticoid therapy compounds fracture risk beyond that as determined by BMD.

### **Glucocorticoid Therapy**

Osteoporosis prevention and treatment measures and bone mineral density testing should be considered for anyone who is started on or has been on exogenous glucocorticoid therapy (at a dose of more than 5 mg prednisone or equivalent per day for 3 or more months). Osteoporosis prevention measures should also be considered for those who have been or can be expected to be on a daily high-dose inhaled glucocorticoid for several years. While it is never too late in the course of glucocorticoid therapy to prevent or treat osteoporosis, it is preferable to start preventive measures against bone loss when glucocorticoid therapy is started for two reasons. First, the greatest amount of bone is lost during the first several months of glucocorticoid use. Second, the risk of fracture at any given level of bone mineral density is greater in those on chronic glucocorticoid therapy than in those who are not on a glucocorticoid. That is, fracture risk is disproportionately increased in those with glucocorticoid-induced low bone density relative to those with low bone density associated with the aging process and/or the postmenopausal state (*Kanis, 2004*).

### **Bone Mineral Density Loss and Fractures Associated with Oral Glucocorticoid Use**

Oral glucocorticoids cause a biphasic loss of bone, with up to 15% bone loss during the initial phase lasting a few months. This is characterized by an increase in bone resorption and a decrease in bone formation.

After that initial phase, bone loss is slower, characterized by lower rates of bone resorption and formation. The degree of bone loss is correlated with both the average daily and total cumulative dose of glucocorticoids used, regardless if glucocorticoids are used daily or on alternate days. Retrospective cohort studies have shown a significant increased rate of fracture in these patients. In three studies, 11% percent of asthma patients suffered a fracture after one year of corticosteroids, 30% of patients with giant cell arteritis after two years of treatment, and 34% of women with rheumatoid arthritis after 5 years of treatment.

Oral glucocorticoids have also been shown to be associated with reduced bone mass and vertebral fracture in children with asthma or juvenile rheumatoid arthritis (*Boot, 1998; Lane, 1998; Reid, 1990; Ruegsegger, 1983; Sinigaglia, 2000; Varanos, 1987*).

### **Bone Mineral Density Loss Associated with Inhaled Glucocorticoids**

Although not as profound as with oral glucocorticoids, inhaled high-potency glucocorticoids used to treat asthma and chronic obstructive airways disease have been shown to cause bone loss when used over an extended time period. A recent cross-sectional study showed that cumulative exposure to 5,000 mg of beclomethasone (2,000 mcg/day for 7 years) was associated with enough loss of bone mineral density to double fracture risk. One three-year longitudinal study of inhaled triamcinolone therapy in chronic obstructive

pulmonary disease showed significant bone loss compared to those treated with a placebo inhaler. No studies documenting or suggesting increased rates of fracture attributable to inhaled or nasal glucocorticoids have been done (*Lipworth, 1999; Lung Health Study Research Group, The, 2000; Wong, 2000*).

### **Mechanisms of Bone Loss**

Glucocorticoids reduce the activity of osteoblasts (cells responsible for new bone formation) resulting in reduction of bone collagen synthesis. Up to 30% less bone is formed during the bone remodeling cycle and osteoblasts undergo earlier programmed cell death (apoptosis). Osteoclasts (cells that resorb bone) are more active during the early phase of glucocorticoid therapy, but the mechanisms of this are controversial. Osteocyte apoptosis is also increased by glucocorticoids, which may impair repair of microfractures and damage. Most investigators have found that glucocorticoids decrease intestinal absorption of calcium, and increase urinary calcium loss. Glucocorticoids may reduce testosterone levels in men, and estrogen levels in women by decreasing pituitary secretion of the gonadotropins FSH and LH, and adrenal androgens in postmenopausal women.

The microanatomy and histomorphometry of glucocorticoid induced osteoporosis differs from that of postmenopausal osteoporosis in many respects. While a similar loss of trabecular bone occurs with both, glucocorticoid-induced osteoporosis is associated with a greater degree of trabecular thinning and less trabecular rupture than postmenopausal osteoporosis, and greater decreases of indices of bone formation (*Aaron, 1989; Dempster, 1983; Weinstein, 1998*).

### **Organ Transplantation**

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation (*Maalouf, 2005*).

### **Pre-transplantation Bone Loss**

Patients accepted for solid organ or allogeneic bone marrow transplantation may develop significantly decreased bone mineral density before transplantation. The decrease in bone mineral density before transplantation is multifactorial, with contributing factors including systemic effects of end-organ disease, hypogonadism, chronic steroid therapy, chronic anticoagulation, effects of other medications and relative immobilization. Atraumatic or minimally traumatic fractures may occur in patients waiting for transplantation.

### **Post-transplantation Bone Loss**

Solid organ and allogeneic bone marrow transplantation are associated with a rapid decrease in bone mineral density at all skeletal sites during the first year after transplantation. The rapid decrease is caused by multiple factors, but predominantly due to high-dose steroid therapy in the first 6 months to 1 year after transplantation. Other factors include the effects of other immunosuppressive drugs, particularly cyclosporine and tacrolimus, persistent hypogonadism, and immobilization early after transplantation. Bone mineral density typically stabilizes during the second year after transplantation, and then begins to recover to some degree toward baseline during the third year after transplantation. Atraumatic or mildly traumatic fractures occur fairly frequently in patients after transplantation, especially in the first few months to years after receiving a graft.

On the basis of these observations, it is recommended that all patients have a baseline bone mineral density test at acceptance into a transplantation program, and that follow-up bone mineral density testing be performed yearly prior to transplantation. If patients are taking high-dose steroid medication before transplantation, bone mineral density testing should be performed every 6 months until stable.

After solid organ or allogeneic bone marrow transplantation, all patients should have bone density testing once a year to detect ongoing bone loss, if it is present. Most patients lose in the range of 8-10% of their

pre-transplant bone density in the first year after transplant, often worse at the hip than the lumbar spine, if therapy to prevent this is not initiated at the time of transplant.

*Supporting evidence is of classes: B, D*

## **4. Discuss Primary Prevention of Fractures**

### **Key Points:**

- Healthy lifestyle discussion at primary prevention visits are important for osteoporosis prevention.

### **Body Habitus**

Low BMI (less than 20) is a strong independent risk factor for osteoporosis and fracture. Weight less than 127 pounds, associated with small bones, is a risk factor for osteoporosis. Primary prevention should include counseling patients on achievement and maintenance of a healthy body weight (BMI between 20 and 25). A balanced diet including dairy products and appropriate nutrition should be discussed with patients (*Hannan, 2000; Hoidrup, 1999*). Also see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture."

*Supporting evidence is of class: B*

### **Gonadal Hormonal Status**

Women who are prematurely hypogonadal and hypogonadal men who are at increased risk for fracture should be considered for replacement therapy. For further information, please see Annotation #14, "Consider Secondary Causes and Further Diagnostic Testing" as well as Annotation #15, "Address Options for Prevention and Treatment of Osteoporosis."

### **Exercise**

Exercise is well known for its many benefits both short-term and long-term. Weight bearing and muscle strengthening exercises have been shown to be an integral part of osteoporosis prevention as well as a part of the treatment process.

Regular physical exercise has numerous benefits for individuals of all ages. There is strong evidence that physical activity early in life contributes to higher peak bone mass. Physical activity during early age was more strongly associated with higher BMD at all sites than was physical activity in the past 2 years. Lifetime weight-bearing is more strongly associated with higher BMD of the total and peripheral skeleton than is non-weight-bearing exercise. Exercise during the later years in the presence of adequate calcium and vitamin D probably has a modest effect on slowing the decline in BMD.

It is clear that exercise late in life, even beyond 90, can increase muscle mass and strength two-fold or more in frail individuals. It will also improve function, delay in loss of independence, and contribute to improved quality of life (*Ulrich, 1999*).

Physical activity, particularly weight-bearing exercise, is thought to provide the mechanical stimuli or "loading" important for the maintenance and improvement of bone health. Resistance training may have more profound site-specific effect than aerobic exercise. High intensity resistance training may have added benefits for decreasing osteoporosis risks by improving strength and balance, and increasing muscle mass.

High impact exercise and weight training stimulates accrual of bone mineral content in the skeleton. Lower impact exercises, such as walking, have beneficial effects on other aspects of health and function, although their effects on BMD have been minimal.

**Algorithm Annotations**

Randomized clinical trials have shown exercise to decrease the risk of falls by approximately 25%. Stronger back extensor muscles have been shown to decrease the risk of vertebral fractures independent of pharmacotherapy. Those who exercise may fall differently and decrease their fracture risks as a result. However, spinal flexion exercises have demonstrated an increased risk of vertebral fractures (*Layne, 1999; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001; Sinaki, 2002; Sinaki, 1984*).

All three components of an exercise program are needed for strong bone health: impact exercise such as jogging, brisk walking, stair climbing; strengthening exercise with weights; and balance training such as Tai Chi or dancing.

Patients should be encouraged and offered assistance in developing a lifetime program of exercise that they will continue to do and enjoy. As a result, as they age they will be stronger, more flexible, have improved balance and improved quality of life.

*Supporting evidence is of classes: A, C, D, R*

**Smoking Cessation**

Smoking cessation counseling should be done at every visit. Discussion can include helpful strategies such as nicotine replacement therapy with patches, gum, etc. Bupropion and available smoking cessation classes may also be discussed. For more information on smoking cessation, please consult the ICSI Tobacco Use Prevention and Cessation guidelines. Also see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture."

**Alcohol Restriction**

Limit alcohol use to *no more than* two drinks per day. One drink equals 12 ounces of beer, 5 ounces of wine or 1.5 ounces of 80-proof distilled spirits. This limit will help to protect bone health and reduce the risk of falls. See Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture."

**Calcium**

Adequate calcium intake from food sources and supplements promotes bone health. When food sources do not provide enough calcium, supplements can be used to meet this goal. Bioavailability of calcium in food sources and supplements is a factor in achieving daily calcium recommendations. Calcium supplement labels should indicate lead testing.

Daily elemental calcium recommendations for healthy individuals from diet and supplement include:

National Academy of Sciences, Institute of Medicine (1997)

9-18 years	1300 mg.
19-50 years	1000 mg.
Over 50 years	1200 mg.
Maximum limit	2500 mg.

However, for people with established osteoporosis, glucocorticoid therapy, pregnant or nursing women, or persons over the age of 65 it may be more appropriate to recommend 1500 mg (*Institute of Medicine, 1997*).

Both low fractional calcium absorption and low dietary calcium intake have been associated with increased fracture risk. Since fractional calcium absorption is affected by multiple factors and decreases with age, adequate lifetime dietary calcium is an important recommendation for bone health (*NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001, Weaver, 2000*).

## Algorithm Annotations

Generally, calcium absorption is similar from most foods, but calcium is poorly absorbed from foods rich in oxalic acid. An exception is soybeans. A variety of foods with calcium is recommended.

Bioavailability from calcium supplements is affected by meals, dose size and tablet disintegration. For calcium carbonate, absorption decreases at doses greater than 600 mg, therefore supplements should be taken with meals and in divided doses. Taking calcium carbonate supplements on an empty stomach may increase the risk of kidney stones. Heavy metal levels in calcium supplements vary, with some supplements exceeding the acceptable level (*Heller, 1999; Institute of Medicine, 1997; Ross, 2000*).

Calcium slows age-related bone loss. [*Conclusion Grade II: See Conclusion Grading Worksheet A – Annotations #4 & 5 (Calcium)*]

Calcium may reduce osteoporosis fracture risk. [*Conclusion Grade III: See Conclusion Grading Worksheet A – Annotations #4 & 5 (Calcium)*]

*Supporting evidence is of classes: A, D, R*

### Vitamin D

Adequate vitamin D intake supports calcium absorption and bone metabolism. Since sunlight exposure cannot be assumed to produce needed vitamin D, dietary sources are essential. Since many adults in northern climates are deficient in vitamin D, supplements are often needed to meet daily requirements. The following guidelines assume no vitamin D is synthesized from sunlight exposure:

Institute of Medicine (1997)\*

19-50 years	200 IU/day
51-70 years	400 IU/day
over 70 years	600 IU/day
Maximum limit	2000 IU/day

\* These guidelines are currently under revision and the recommendation for adults will likely be significantly increased to 800-1,000 IU/day. Another study suggests at least 800 IU/day of vitamin D is needed for maximum suppression of PTH, maximum absorption of calcium, and has been shown to prevent fractures in older adults (*Bischoff-Ferrari, 2005*). Supplementation should be made to maintain 25-OH vitamin D levels greater than 30 ng/mL.

Although milk is the only dairy source of vitamin D, studies have demonstrated highly variable levels of vitamin D fortification in milk in both the U.S. and Canada. Other food sources of vitamin D are affected by the time of year they are harvested (*Institute of Medicine, 1997*).

*Supporting evidence is of classes: M, R*

### Prevention of Falls

Preventing falls reduces fracture risk. Modifying environmental, personal risk and medication-related factors can be effective in reducing falls. Home visits may help with this. Hip protector pads for frail elderly adults have been shown to reduce hip fractures in some studies, but not in others. Measures to decrease kyphotic posture and improve unsteady gait can decrease falls.

Please see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture."

## **5. Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture**

The following are risk factors for osteoporosis and osteoporotic fracture:

- Female gender
- Advanced age (greater than age 65)
- Body habitus (weight less than 127 pounds; or BMI less than or equal to 20)
- Caucasian or Asian race
- Personal or family history of fracture (first-degree relative)
- Hypogonadism (estrogen or testosterone deficiency)
- Sedentary lifestyle
- Smoking
- Excessive alcohol intake (more than two drinks per day)
- Diet deficient in calcium or vitamin D without adequate supplementation
- Increased likelihood of falling

For a list of secondary causes of osteoporosis, please see Appendix A, "Secondary Causes of Osteoporosis."

Risk factors for osteoporosis and fractures are fixed or modifiable. Some risk factors for osteoporosis are also risk factors for fracture independent of bone mineral density. They are important to know so they can be assessed and modified if possible.

Advanced age, female gender, Caucasian and Asian race, and hypogonadal states are risk factors for osteoporosis. The only one of these that is modifiable is hypogonadism (with replacement therapy). African-American women have a decreased risk, partly because they begin menopause with a higher bone mineral density (BMD) and have a lower rates of bone loss after menopause. Of all these, age and prior fracture are also predictors of fracture independent of bone mineral density (*Bohannon, 1999; Hannan, 2000; Melton, 1999*).

### **Body Habitus**

Low body mass index (BMI, less than 20) or thinness (weight less than 127 pounds) have been identified as predictors for osteoporosis. BMD at the lumbar spine and hip have been correlated with weight, height, and BMI. During the Framingham Osteoporosis Study, women who gained weight also gained BMD or had little change, while women who had a lower baseline weight or weight loss lost BMD. Low BMI, therefore, is a modifiable risk factor for osteoporosis (*Hannan, 2000; Melton, 1999; Ravn, 1999*). Significant weight loss (intentional or not), is associated with accelerated bone loss (*Ensrud, 1997*).

### **Family History of Osteoporosis**

Family studies have shown a genetic component to BMD. Family history is an independent predictor of peak BMD and a family history of osteoporosis in a first degree relative is related to decreased peak BMD. Maternal fractures are associated with lower BMD and have been shown to be a site-specific predisposition to fracture. There is some evidence that maternal history of hip fracture, before age 70, is a risk factor for future fracture independent of bone mineral density (*Fox, 1998; Omland, 2000*).

### **Cigarette Smoking**

Cigarette smoking is a risk factor for osteoporosis. The rates of bone loss are approximately one and one-half to two times greater for current smokers than for nonsmokers. Smokers do not absorb dietary or supplemental calcium as efficiently as nonsmokers. While the mechanism is not clear, there is an increase in bone remodeling markers in heavy smokers suggesting decreased calcium absorption. There is also an increase in bone resorption. Both the increased risk among current smokers and the decline in risk ten years after smoking cessation are in part accounted for by the difference in BMI. Smoking is a modifiable risk factor (*Cornuz, 1999; Hannan, 2000; Huopio, 2000*).

### **Sedentary Lifestyle**

Sedentary life style is a risk factor for osteoporosis. The type of physical activity and optimal age for greatest benefit is still unclear. Studies do show that physical activity in youth was more strongly associated with higher BMD at all sites. Lack of continued physical activity may lead to bone loss.

Wolff's law states that stress or mechanical loading applied to the bone via the muscle and tendons had direct effect on bone formation and remodeling. Meta-analysis of several studies indicates that athletes have a 25% greater BMD than simply active people, and that active people have a 30% higher BMD compared to inactive people. An inactive person needs to be made aware of the increased risk to bone health. Some studies suggest that increased physical activity is modestly protective against fracture independent of bone mineral density (*Bemben, 1999; Branca, 1999*).

### **Alcohol Intake**

Alcohol use has been demonstrated to affect bone formation, even at moderate levels of 1-2 drinks/day. Alcohol has a direct, antiproliferative effect on osteoblasts. It also has a dose-dependent suppressive effect on osteocalcin levels. Some studies have reviewed the potential effect of alcohol on levels of parathyroid hormone, calcitonin and vitamin D metabolites, but no clear mechanism was identified (*Klein, 1997*).

A high level of alcohol intake is associated with decreased bone mineral density. There are conflicting data about the effects of moderate alcohol use on bone mineral density. Studies have reported an association between alcohol intakes greater than 28-30 g (~ one ounce/one drink) per day and decreased bone mineral density both at the trochanter site and in total BMD. In a four-year longitudinal evaluation by the Framingham Osteoporosis Study, this association was found in women, but not in men. An association between high levels of alcohol use by both men and women and hip fracture was found in a large prospective Danish study. In the Nurses' Health Study cohort (age 35-64 years), alcohol intake (more than 25 g or one drink per day) was associated with increased risk of hip fracture and forearm fracture when compared with non-drinkers. Other studies have not shown the fracture risk from alcohol to be independent of bone mineral density (*Hannan, 2000; Hoidrup, 1999*).

### **Low Calcium Intake**

Comprehensive reviews of the relationship of calcium intake and bone health reported that calcium sufficiency slows age-related bone loss (*Conclusion Grade II*) and may reduce osteoporotic fracture risk (*Conclusion Grade III*). Both dairy sources and calcium supplements are related to promoting bone health. Calcium enhances therapy with antiresorptive medication, such as estrogen. [See *Conclusion Grading Worksheet A – Annotations #4 & 5 (Calcium)*] (*Chapuy, 1992; Cumming, 1993; Dawson-Hughes, 1990; Heaney, 2000; Recker, 1996; Riggs, 1998*).

### **Inadequate Vitamin D**

Vitamin D is essential for calcium absorption and bone metabolism. Aging is associated with decreasing 25-OH vitamin D levels, progressive renal insufficiency, reduced sun exposure and reduced skin capacity

for vitamin D production. Vitamin D insufficiency and overt deficiency can cause secondary hyperparathyroidism, which in turn leads to increased bone turnover. Studies of combined calcium and vitamin D supplementation have demonstrated reductions in bone loss and reductions in hip and non-vertebral fractures. This supplement-induced benefit on bone mass can be lost when the calcium and vitamin D are discontinued (*Dawson-Hughes, 1997; LeBoff, 1999*). A meta-analysis of vitamin D<sub>3</sub> supplement greater than 700-800 IU/day was associated with a reduction of 26% in hip fractures and 23% reduction of all non-vertebral fractures. A supplemental dose of 400 IU/day did not afford fracture protection. The ideal recommendation 25-OH vitamin D levels is greater than 30 ng/ml (*Bischoff-Ferrari, 2005*). In contrast, another meta-analysis did not show fracture reduction with varying doses of vitamin D (*Avenell, 2005*).

### Increased Likelihood of Falling

Many factors increase the likelihood of falling, and most hip and wrist fractures occur after a fall. Included in these factors are impaired eyesight, certain medications, poor health, frailty, low physical function (such as slow gait and speed and decreased quadriceps strength), dementia and history of past falls. Age-related muscle loss (sarcopenia) may also predispose to fall risk (*Ensrud, 1997*). Preventing falls reduces fractures. Modifying environmental and personal risk factors can be effective in reducing falls. Home visits have been shown to help with this. Also, in some studies, soft hip protector pads have been shown to reduce hip fractures in frail, elderly adults in community-based health care centers (*Kannus, 2000; NSH Centre for Reviews and Dissemination, 1996; Sinaki, 2005*).

*Supporting evidence is of class: A, B, C, D, M, R*

## 6. Low Pre-Test Probability of Low BMD and Future Fracture

The following individuals are at low risk of low bone density and future fracture; bone density testing in general is not recommended:

1. Premenopausal women who have not had a fracture with minor trauma, are not on chronic glucocorticoid therapy, do not have secondary amenorrhea, and do not have a chronic disease associated with bone loss.
2. Eugonadal men who have not had a fracture with minor trauma, are not on glucocorticoid therapy, and do not have another chronic disease associated with bone loss.
3. Postmenopausal women under age 65 who have been on hormone replacement therapy since menopause and who do not have any significant additional risk factors.

## 7. Address/Reinforce Options for Prevention of Osteoporosis

Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved peak bone mass, or both. Because of this, providers are encouraged to periodically review historical risk factors (see Annotation #4, "Discuss Primary Prevention of Fractures") and primary prevention strategies (see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture") with their patients. Preventive health maintenance exams provide an excellent opportunity for this review.

## 8. High Pre-Test Probability of Low BMD and Future Fracture

### Key Points:

- Patients can be risk-stratified to determine the appropriateness of bone density testing.

The following individuals are at sufficiently high risk for low bone mass and future fracture that a bone mineral density test is justified to further define that risk. This assumes that the individual being tested is willing to consider pharmacologic treatment for low bone mass documented on a bone density test. The first three of these indicate individuals at particularly high risk of bone loss and future fracture.

1. Prior fracture with minor trauma (fall from standing height or less).
2. Those who have been, or are anticipated to be, on glucocorticoid therapy for 3 or more months at a dose equivalent to or greater than 5 mg prednisone per day.
3. Radiographic osteopenia, or vertebral deformity consistent with fracture.
4. All women 65 years of age or older.
5. Postmenopausal women less than age 65 with one of the following additional risk factors:
  - a. Body weight less than 127 lbs or a BMI of 20 or less.
  - b. History of nontraumatic fracture after age 45 in a first-degree relative.
  - c. Current smoker.
  - d. Not using hormone therapy.
  - e. Surgical menopause, or natural menopause before age 40.
6. Chronic diseases known to be associated with bone loss (see Appendix A, "Secondary Causes of Osteoporosis").
7. Premenopausal women with amenorrhea greater than 1 year.
8. Men with hypogonadism more than 5 years.
9. Prolonged severe loss of mobility (unable to ambulate outside of one's dwelling without a wheelchair for greater than one year).
10. Solid organ or allogenic bone marrow transplant recipient.
11. Medications for malignancy are likely to cause bone loss in patients.

In the ICSI algorithm, individuals are judged to be at high or low risk for bone loss based on their personal and family history, and medical evaluation. This implies that those in the high-risk group will be offered a bone density test.

Defining a group of individuals at "high risk" for osteoporosis is in fact daunting, because clinical risk factors in the absence of bone densitometry have poor sensitivity and specificity for osteoporosis. There is, nonetheless, broad consensus that assessment of clinical risk factors should be done to determine who should have a bone density test. Similarly, there is broad consensus that mass population screening of all individuals or even of all postmenopausal women is neither cost-effective nor appropriate. Many professional organizations, including the National Osteoporosis Foundation, the North American Menopause Society, National Institutes of Health and the American Association of Clinical Endocrinologists have published their

own guidelines describing whom to select for bone densitometry (*Hodgson, 1996; National Osteoporosis Foundation, 1999; North American Menopause Society, 2002; Surgeon General's Report, 2004*).

The National Osteoporosis Foundation (NOF) conducted a cost-effectiveness analysis (*Eddy, 1998*) regarding the prevention, detection and treatment of osteoporosis. They concluded that bone densitometry was reasonable for all women over age 65, and for postmenopausal women under age 65 with one of the following risk factors: thin body habitus, family history of fracture, and current cigarette smoking. In the guideline that NOF published based on this study, estrogen deficiency, lifelong low calcium intake, alcoholism, impaired eyesight, recurrent falls, inadequate physical activity, and poor health or frailty are also listed as reasons to get a bone density test for a postmenopausal woman under age 65.

Our guideline is based on the NOF guideline with a few modifications. Individuals who have had a prior low-trauma fracture, who are beginning or have been on chronic glucocorticoid therapy, or have had organ transplantation are at highest risk for future fracture. Height loss or kyphosis per se are not indications for a bone density test, but should prompt lateral vertebral fracture assessment with DXA or plain radiographs of the thoracic and lumbar spine. Any vertebral deformity consistent with fracture found radiographically indicates a higher risk of future fracture. We have not included risk of falls or poor eyesight, since these are not risk factors for low bone density per se, and because the majority of these individuals will be over age 65. Inadequate physical activity and lifelong low calcium intake are not included, since in other studies these have not added much predictive value for low bone mass to other groups of risk factors (*Lydick, 1998; Cadarette, 2000; Bauer, 1993*). Severe loss of mobility (prolonged immobilization), however, is a risk factor for osteoporosis and is included.

Chronic diseases such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, prolonged hyperthyroidism, and hyperparathyroidism are associated with bone loss, and for many individuals with these diseases a bone density test is indicated. Heavy alcohol intake is also an indication for a bone density test.

*Supporting evidence is of classes: C, D, M, R*

## 9. Recommend Bone Density Assessment

### Key Points:

- BMD measurement with DXA is the single best predictor of fracture risk as well as the best monitor of patient response to treatment.

Measurements of BMD with DXA can predict fracture risk, and allow for the identification of people who are at increased risk of fracture. Reviews of prospective cohort studies and case control studies have documented a direct relationship between decreasing BMD and increasing bone fracture risk. Additionally, there is strong evidence that stabilization or increases in BMD with therapy for osteoporosis are associated with substantial reductions in fracture incidence. Therefore, densitometry offers an objective measurement of a patient's response to treatment over time (*Hailey, 1998; Miller, 1999; Ringertz, 1997*).

Current practice is to describe an individual's bone mineral density as compared to a reference normal population. In this sense, a T-score is the number of standard deviations above or below the mean for a gender and ethnicity-matched young adult healthy population. A T-score is calculated from the following equation:

$$\text{[(measured BMD - young adult population mean BMD) / young adult population SD]}$$

A Z-score is the number of standard deviations above or below the mean for gender, ethnicity and age-matched healthy population. A Z-score is calculated from the following equation:

$$\text{[(measured BMD - age-matched population mean BMD) / age-matched population SD]}$$

## Algorithm Annotations

Normal, low bone density (osteopenia), and osteoporosis are defined by the lowest of lumbar spine (at least two evaluable vertebrae required), femoral neck, and total femur T-score according to the World Health Organization. The one-third radius site may be used if either the lumbar spine or femur is non-evaluable. Although the following classifications were originally drafted for Caucasian postmenopausal women, some controversy exists as to whether the same diagnostic criteria can be applied to other groups.

- Normal\*: A T-score greater than or equal to -1.
- Low bone density (osteopenia): A T-score between -1 and -2.5\*\*.
- Osteoporosis: A T-score less than or equal to -2.5.
- The term "severe osteoporosis" is reserved for patients with a fragility fracture(s) *and* a low bone density.

\* The absence of upper limits for BMD in the WHO criteria jeopardizes recognition of high BMD disease. This oversight requires correction using Z-scores. It has been proposed that Z-scores of localized BMD, at or above +2.5, warrant further study (*Whyte, 2005*).

\*\* Following a Position Development Conference on bone densitometry in 2005, the International Society of Clinical Densitometry recommends that the term "osteopenia" be retained, but "low bone mass" or "low bone density" are the preferred terms (*Binkley, 2006*).

For patients who decline bone density testing, reinforce osteoporosis prevention, consider gonadal hormone replacement therapy and follow-up discussion of osteoporosis at future preventive visits.

Z-scores are not used to define osteoporosis. However, a low Z-score is useful in identifying individuals with bone mineral densities lower than expected for age. The threshold for Z-score is theoretical. Expert opinion suggests the threshold should be somewhere between -1.0 to -2.0. Low Z-scores should prompt a search for secondary causes of osteoporosis (see Annotation #14, "Consider Secondary Causes and Further Diagnostic Testing") (*WHO Study Group, 1994*).

The Bone Mass Measurement Act of 1998 (*DHHS, 1998*) broadened the selective screening by mandating Medicare coverage for densitometry services for individuals at risk of osteoporosis as defined by the following criteria:

- An estrogen-deficient woman at clinical risk for osteoporosis
- An individual with vertebral abnormalities
- An individual receiving long-term glucocorticoid therapy greater than 7.5 mg prednisone/day for greater than 3 months (recent data suggests a threshold of 5.0 mg prednisone/day – this is the recommendation of the work group)
- An individual with primary hyperparathyroidism
- An individual being monitored to assess the response to or the efficacy of an FDA-approved drug for osteoporosis therapy

Universal bone densitometry screening of women age 65 and older is now recommended by nearly all specialty societies that have constructed guidelines for the diagnosis and management of osteoporosis, including the United States Preventive Services Task Force (*U.S. Preventive Task Force, 2002*). Moreover, universal screening with bone densitometry followed by treatment of those found to have osteoporosis has been found to be highly cost-effective for women age 65 and older, including those residing in nursing homes (*Schousboe, 2005*).

There are numerous techniques currently available to assess BMD. Densitometry was reviewed by ICSI, and a technology assessment publication is available on the subject.

Osteoporosis is considered to be a systemic disease. Measurements of BMD at any site correlate reasonably well with the BMD at other sites. However, measurement of the BMD at the site of interest is the best predictor of the future risk of fracture at that site. Vertebral and hip fractures carry the heaviest morbidity and mortality, and for this reason central measurements are preferred over peripheral BMD measurements. DXA scanning has become the preferred method to measure BMD. The recent NORA prospective non-vertebral fracture study showed that bone density measured by peripheral DXA or ultrasound, predicted future fracture risk. The threshold for defining increased fracture risk is different for central site DXA and peripheral site measurements, however. Peripheral densitometry has not been shown to be useful or reliable in assessing the response to therapy. At the present time, central sites will have to be measured both at baseline and thereafter if densitometry is going to be used to monitor the response to therapy. In settings where access to central DXA scanning is not possible, some assessment of bone mineral density, even if it is at a peripheral site, is better than no assessment at all (*Genant, 1996; Institute for Clinical Systems Improvement, 2000; Miller, 1999*).

The International Society of Clinical Densitometry (ISCD) was formed in 1993 to ensure uniformity in the interpretation of bone mineral density tests. ISCD certification has become the standard of care for physicians interpreting bone mineral density tests and technologists performing the exam. Bone densitometry should not be performed by individuals without ISCD certification. Uniformity in interpretation of densitometry results will improve patient care. The web address for ISCD is <http://www.iscd.org>.

### Limitations of Densitometry

BMD represents a continuous variable. There is overlap in BMD values between individuals with and without fragility fractures. DXA BMD measures areal bone density. This introduces potential size artifacts, whereby smaller individuals will have a lower areal bone density value than larger individuals. Thus, fracture risk is multifactorial and not solely defined by areal BMD. Computerized tomography (CT) is the only measure of volumetric bone density.

The three manufacturers of dual x-ray absorptiometry (DXA) densitometers have published equations to convert manufacturer-specific units to standardized, non-manufacturer specific units. Formulas are available for both spine BMD and femur BMD. Using these formulas, standardized BMD (sBMD) values obtained by scanning a patient on any one of these instruments should fall within 2%-5% (spine) or 3%-6% (total femur) of each other. sBMD use and incorporation of NHANES III BMD data into all machines will help decrease the limitations of T-score use (*Hanson, 1997; Looker, 1997; Steiger, 2000*).

*Supporting evidence is of classes: C, D, M, R*

## 10. Post-Test Probability

### Key Points:

- BMD test results provide good information in predicting future fracture risk.
- Other historical factors that relate to bone quality augment BMD data in modifying risk.

Fracture risk in an individual patient is defined as the likelihood of sustaining an osteoporotic fracture over an interval of time. Current fracture risk is defined as the likelihood of an osteoporotic fracture in the patient's remaining lifetime years.

Current fracture risk can be expressed in terms of absolute risk, relative risk, or incidence (annual) risk. Absolute fracture risk is the actual risk of fracture for a given patient. Relative risk of fracture is the ratio of the absolute risk of fracture for the patient compared to the absolute risk of fracture for a young adult-, gender-, and ethnicity-matched reference population. Relative risk of fracture is increased by 1.5-3.0 times for each 1.0 standard deviation decrease in bone density below the mean for young adults of the same gender and ethnicity. Fracture risk data in elderly postmenopausal women suggest that fracture prediction is nearly equal regardless of the skeletal site assessed or the type of technology used, with the exception that hip fracture risk is best predicted by proximal femoral bone mineral density measurement. Similar data are being accumulated for men, although the numbers of studies published so far are much smaller (*Melton, 1993; Melton, 1998*). Prospective data allows prediction of 10-year fracture risk based on age and bone mineral density alone in postmenopausal women. This risk must be adjusted according to other clinical findings (*Kanis, 2004*).

*Supporting evidence is of classes: B, C*

## 12. Low Risk of Future Fracture

Low fracture risk is clinically defined by a bone mineral density T-score above -1.0 (normal bone density by the WHO definition).

## 13. Increased Risk of Future Fracture

### Key Point:

- The T-score is best used in combination with other patient information to predict a given patient's fracture risk.

Even though osteoporosis is defined by a BMD T-score of less than -2.5, and low bone density (osteopenia) is defined as a T-score of -1 to -2.5, and the relative risk for fracture is directly correlated to T-score bone density, the absolute risk of fracture is not only related to bone density but also by bone quality and other non-bone density risk fractures for fracture.

Some patients with very low T-scores will never sustain an osteoporotic fracture, whereas some patients with normal T-scores will have fractures. Patients who fall infrequently are less likely to sustain osteoporotic fractures.

Previous osteoporotic fractures sustained by the patient, history of osteoporotic fractures sustained by the patient's family members, increased rate of bone turnover, the patient's risk of falling, and the use of medications that predispose to falling, also help predict future fracture risk (*Garnero, 1996; Riis, 1996*).

Bone mineral density is the single best predictor of future fracture. About 80% of the variance in bone strength and resistance to fracture in animal models is explained by bone mineral density, and numerous studies have demonstrated that fracture risk is predicted by bone mineral density (*Chandler, 2000; Cummings, 1995; Duppe, 1997*).

Patients found to have low risk of future fracture by bone mineral density testing should not automatically be assumed to remain at low risk of future fracture over their remaining lifetime years. Patients should be periodically reassessed by reviewing risk factors for osteoporosis, evaluating current primary prevention efforts, reviewing the clinical history for osteoporotic fractures subsequent to the initial bone density evaluation, and measuring bone mineral density. Clinical judgment must be used in determining the appropriate intervals between repeated measurements of bone mineral density over time. Whenever remeasure occurs, it is important to use the same densitometer. In some patients, such as those expected to have high bone turnover and rapid bone loss due to early postmenopausal status, initiation or continuation of steroid therapy,

organ transplantation, or other causes, it may be appropriate to remeasure bone density as soon as 6-12 months after the initial measurement. In those patients not expected to have high turnover or rapid loss, it is appropriate to remeasure bone density at an appropriate interval, such as two to five years after the initial measurement, in order to detect patients who lose significant bone density over time.

## **14. Consider Secondary Causes and Further Diagnostic Testing**

### **Key Points:**

- A minimum screening laboratory profile should be considered in all patients with osteoporosis.

At this time there is no consensus about the routine use of serum and/or urine markers of bone turnover in the evaluation of patients with osteoporosis. See the ICSI Technology Assessment Report #53, "Biochemical Markers for Bone Turnover in Osteoporosis," for more information.

Certain diseases are commonly associated with bone loss. These diseases are listed in Appendix A, "Secondary Causes of Osteoporosis." In broad categories, these include chronic inflammatory autoimmune conditions, endocrinopathies, malignancies, and malabsorptive states.

Consider the following evaluation for the patient with osteoporosis without prior workup:

- A biochemical profile that provides information on:
  - renal function
  - hepatic function
  - calcium (important if starting an antiresorptive or anabolic agent)
    - elevated in hyperparathyroidism
    - decreased in malabsorption, vitamin D deficiency
  - Alkaline phosphatase
    - elevated in Paget's Disease, prolonged immobilization, acute fractures and other bone diseases
  - Phosphorus
    - decreased in osteomalacia
- A complete blood count may suggest bone marrow malignancy or infiltrative process (anemia, low WBC, or low platelets) or malabsorption (anemia, microcytosis or macrocytosis).
- An elevated sedimentation rate or C-reactive protein may indicate an inflammatory process or monoclonal gammopathy
- TSH and thyroxine
- 25-OH vitamin D (optimal level greater than or equal to 30 ng/ml to maximally suppress PTH secretion.)
- Intact parathyroid hormone
- The 24-hour urinary calcium excretion on a high-calcium intake screens for malabsorption and hypercalciuria, a correctable cause of bone loss. Low 24-hour urine calcium suggests vitamin D deficiency, osteomalacia or malabsorption due to small bowel diseases such as celiac sprue.

## Algorithm Annotations

Consider adding the following tests if clinically indicated: *Osteoporosis and an age-matched bone density that is greater than one standard deviation below age-matched controls (Z-score <-1.0)*: In this population it is important to screen for treatable secondary causes of bone loss that may not be clinically evident in patients with a lower than expected bone density or premature osteoporotic fracture. (See Appendix A, "Secondary Causes of Osteoporosis" for a comprehensive list of secondary causes of osteoporosis) (Harper, 1998; Johnson, 1989; Tannenbaum, 2002).

- Testosterone (total and free) in men and estradiol (total and bioavailable) in women; LH and FSH and prolactin if evidence of hypogonadotropic hypogonadism
- Tissue transglutaminase if clinical suspicion for gluten enteropathy or low 25-OH vitamin D
- 24-hour urinary free cortisol or overnight dexamethasone suppression test if clinical suspicion of glucocorticoid excess
- Serum and urine protein electrophoresis, with a conditional immunoelectrophoresis

Refer to Appendix A, "Secondary Causes of Osteoporosis" for a table with the common causes of secondary osteoporosis.

*Supporting evidence is of classes: D, R*

## 15. Address Options for Prevention and Treatment of Osteoporosis

### Key Points:

- Lifestyle adjustments are traditionally first-line therapy for osteoporosis prevention and treatment.
- Bisphosphonates have the strongest data showing risk reductions in both vertebral and non-vertebral fractures.
- Estrogen is considered first-line therapy for the prevention of osteoporosis in prematurely menopausal women under the age of 50.
- Anabolic therapy with parathyroid hormone is indicated for patients with particularly high risk for future fracture, and data shows reduction in vertebral and non-vertebral fracture.
- Nasal calcitonin is not considered a first-line treatment for osteoporosis, but may be useful in some populations.
- SERM treatment with raloxifene has shown vertebral fracture risk reduction in postmenopausal osteoporosis.

Please see the medication tables in Appendix B, "Recommended Pharmacologic Agents" for specific information on pharmacologic agents for treatment and prevention of osteoporosis.

### Osteoporosis Prevention

Estrogen has traditionally been considered first-line therapy for prevention of osteoporosis in prematurely menopausal women under the age of 50. If the only reason hormone therapy has been prescribed is for osteoporosis prevention, other options should be considered. If the decision is made to discontinue estrogen,

a BMD should be obtained to determine if other bone loss prevention therapies are needed. Other medications for prevention include bisphosphonates and raloxifene.

### **Osteoporosis Treatment**

Bisphosphonates have the strongest data showing risk reductions in both vertebral, hip, and other nonvertebral fractures. Other treatments include raloxifene (see SERM in this annotation) and calcitonin.

Parathyroid hormone 1-34 (teriparatide) (PTH) is used for patients at highest risk for fracture. It could be first-line therapy for those patients.

### **Post-transplantation Bone Loss**

Antiresorptive therapy and calcitriol may be effective at preventing bone density loss after transplantation (*El-Agroudy, 2005*). Considering the rates of bone loss after transplantation described in Annotation #3, bone mineral density testing should be performed every 6 months to one year until bone mineral density is shown to be stable or improving on therapies for osteoporosis. Studies demonstrate that standard calcium and vitamin D supplementation, with or without calcitonin, is not able to prevent bone loss after transplantation. Other studies indicate that pharmacologic vitamin D preparations or intravenous bisphosphonates, such as pamidronate, or zoledronic acid, or oral bisphosphonates, such as alendronate or risedronate are more likely to prevent bone loss after transplantation.

### **Alternative and Complementary Agents for Prevention and Treatment of Osteoporosis**

There is conflicting data on a number of non-FDA approved substances for possible use in prevention and treatment of osteoporosis. These include phytoestrogens, synthetic isoflavones such as ipriflavone, natural progesterone cream, magnesium, vitamin K and eicosapentanoic acid. There is very limited data from randomized controlled trials of these agents for prevention or treatment of osteoporosis. A recently reported, multicenter randomized trial of ipriflavone showed no significant effect on bone density or risk of vertebral fractures.

*Supporting evidence is of classes: A, B, C, D, M, R*

In addition to calcium, vitamin D, physical therapy, surgical repair, and radiologic intervention as appropriate, the therapies listed below may be used. Clinicians should be aware that patient compliance with adherence to osteoporosis therapy has been historically poor.

### **Gonadal Hormone Therapy**

#### **Female gonadal hormone therapy**

The use of supplemental estrogen in the immediate postmenopause has been well accepted in preventing the rapid loss of bone that occurs in this interval (*Komulainen, 1997; Prince, 1991*).

Supplemental estrogen not only retards accelerated bone loss, but has also been shown to create a gain in bone density. In the PEPI trial after 3 years, the women receiving hormone replacement therapy had a mean 5% gain in bone density in the spine and 2% in the hip compared to a 2% loss in the placebo group. Preliminary evidence suggests that the gain in bone mass may persist beyond the first few years. In one study, women on estrogen-progestin therapy showed a persistent increase in density over 10 years, reaching 13% over baseline (*Eiken, 1996; Writing Group for the PEPI Trial, The, 1996*).

It is generally believed that estrogen therapy is most effective when started immediately after menopause. But estrogen therapy has also been shown to have a positive effect on bone mass long after menopause, creating gains of bone mass of 5%-10% over baseline over 1-3 years (*Lindsay, 1990; Quigley, 1987*).

The protective effects of estrogen on bone density are lost quickly after estrogen is discontinued (*Lindsay, 1978*).

Dose response effectiveness of hormone therapy on bone mass has recently undergone considerable scrutiny (*Cummings, 1998; Ettinger, 1998; Lindsay, 2002; Recker, 1999*).

Ultra-low estrogen supplementation has been shown to be effective in severely hypoestrogenic women in improving bone mass. Fracture data is pending.

Even though the combination of hormone therapy and bisphosphonates has shown improved bone density, the lack of fracture data and risks of hormone therapy negate this as a primary treatment option. Progestins in the C-21 family, such as medroxyprogesterone appear to have no supplemental effect on bone density compared to estrogen alone in the PEPI trial. C-19 progestins, such as norethisterone acetate, in combination with estrogen, have shown a more potent effect on bone mass than estrogen alone (*Christiansen, 1990; Cranney, 2002; Marcus, 1995; Riis, 1987*).

The WHI study showed that Prempro® and Premarin® alone significantly reduced the risk of both vertebral, hip fractures and all fractures (*Women's Health Initiative, The, 2004*). The other available data come mainly from observational and epidemiological trials. Meta- and decision analysis estimates have suggested a relative risk of hip fracture in estrogen treated women of 0.46-0.75. A long-term controlled trial of 10 years demonstrated a 75% reduction in radiologic vertebral fracture in oophorectomized women compared to controls. A shorter trial of one-year duration revealed a 60% reduction in the risk of vertebral fracture in women with osteoporosis using a 0.1 mg estradiol patch and medroxyprogesterone compared to controls (*Torgerson, 2001; Writing Group for the Women's Health Initiative Investigators, 2002*).

#### Male gonadal hormone therapy

The bone loss associated with male hypogonadism is reversed by testosterone therapy at least partly via aromatization to estrogen. Testosterone therapy, although not FDA-approved for osteoporosis, seems a reasonable first therapeutic intervention in men symptomatic with hypogonadism who do not have contraindications to the use of testosterone therapy (*Behre, 1997; Katznelson, 1996*).

*Supporting evidence is of classes: A, B, C, D, M*

#### Bisphosphonates

##### Treatment and prevention of osteoporosis in postmenopausal women

Alendronate has been shown to increase bone mineral density and reduce the incidence of vertebral, hip, and non-vertebral fractures in postmenopausal women having existing vertebral fractures, and those with low bone mineral density (approximately 2.1 SD below peak) compared to placebo (calcium and vitamin D). In the vertebral fracture arm of the Fracture Intervention Trial (FIT), 2,027 postmenopausal women with low BMD and at least one vertebral fracture at baseline were randomized to alendronate or placebo. In this arm of the study alendronate showed significant increases in BMD at the femoral neck, trochanter, total hip, posterior-anterior spine, lateral spine, whole body, and forearm (all  $p < 0.001$ ). Treatment with alendronate produced a 47% lower risk of new radiographic vertebral fractures ( $p < 0.001$ ). Hip fracture relative hazard for alendronate versus placebo was 0.49 (0.23-0.99) and for the wrist it was 0.52 (0.31-0.87) (*Black, 1996*).

Risedronate 5 mg has shown a 41% risk reduction in the number of new vertebral fractures after 3 years compared to placebo in the VERT trial. In the first year, a 65% risk reduction was seen. The trial also showed 39% fewer non-vertebral fractures in the risedronate group over 3 years (*Fogelman, 2000; Harris, 1999*).

McClung et al. showed that risedronate reduced the risk of hip fractures in women ages 70-79 with documented osteoporosis but not women greater than age 80 who entered the trial on the basis of risk fractures alone (*McClung, 2001*).

## Algorithm Annotations

Daily and intermittent ibandronate has been shown to improve bone density and reduce vertebral fractures in 2,946 postmenopausal women with osteoporosis and vertebral fractures compared with calcium and vitamin D alone. New vertebral fractures were reduced 60% with daily and 54% with intermittent dosing. Non-vertebral fractures were reduced only in a subpopulation with bone density T-scores < -3.0. A non-inferiority trial indicated equivalency of effect using surrogate markers of BMD and biomarkers for a monthly 150 mg dose (*Chestnut, 2004; Chestnut, 2005; Miller, 2005*).

The DIVA trial comparing intravenous ibandronate 3 mg every 3 months with daily ibandronate showed superiority in surrogate markers of bone mineral density and biomarkers of bone turnover. This offers an injectable bisphosphonate alternative in patients who are unable to use oral bisphosphonates (*Delmas, 2006*).

Excellent clinical trial data based on BMD and bio-markers supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal low bone density (osteopenia) or osteoporosis. The best clinical trials have been done with alendronate (Fosamax®), risedronate (Actonel®) and ibandronate (Boniva®). [*Conclusion Grade I: See Conclusion Grading Worksheet B – Annotation #15 (Bisphosphonates for Primary Osteoporosis)*]. (See Appendix B, "Recommended Pharmacologic Agents.")

Note: there are case reports of bisphosphonate-associated osteonecrosis of the jaw most often following dental extraction with exposed jaw bone in cancer patients undergoing intravenous bisphosphonate therapy. The prevalence is estimated to be approximately one in one million for patients without cancer taking oral bisphosphonates (*Migliorati, 2005*).

### **Treatment of osteoporosis in men**

Alendronate has been shown to increase bone mineral density at the spine, hip, and total body and prevents vertebral fractures and in height loss in men with osteoporosis (*Orwoll, 2000*).

Good clinical trial data support the use of alendronate for preventing bone loss in men diagnosed with osteoporosis. [*Conclusion Grade I: See Conclusion Grading Worksheet B – Annotation #15 (Bisphosphonates for Primary Osteoporosis)*]

### **Treatment and prevention of glucocorticoid-induced osteoporosis**

Alendronate increases lumbar spine, femoral neck, trochanter and total body bone mineral density in patients who require long-term (at least one year) glucocorticoid therapy at dosages of at least 7.5 mg daily (*Saag, 1998*).

Risedronate has also been shown to increase bone mineral density in patients receiving glucocorticoid therapy. Treatment with risedronate 5 mg a day did have a trend of reduced fracture incidence (*Cohen, 1999*).

Clinical trial data supports the use of oral bisphosphonates for reducing bone loss in men and women diagnosed with glucocorticoid-induced bone loss. The best clinical trials have been done with alendronate (Fosamax®) and risedronate (Actonel®). [*Conclusion Grade II: See Conclusion Grading Worksheet C – Annotation #15 (Bisphosphonates for Glucocorticoid-Induced Bone Loss)*].

Clinical trial data suggests that oral bisphosphonates may reduce fracture risk in men and women diagnosed with glucocorticoid-induced bone loss. [*Conclusion Grade III: See Conclusion Grading Worksheet C – Annotation #15 (Bisphosphonates for Glucocorticoid-Induced Bone Loss)*].

### **Post-transplantation**

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation.

Several studies have shown that intravenous pamidronate (Aredia®) and zoledronate (Zometa®) may prevent bone loss after organ transplantation. A few small studies have evaluated oral bisphosphonate therapy in post-transplant patients (*Aris, 2000; Crawford, 2006; Maalouf, 2005; Shane, 2004; Shane, 1998*).

*Supporting evidence is of classes: A, C, D, R*

### **Selective Estrogen Receptor Modulator (SERM)**

The only SERM approved for the prevention and treatment of postmenopausal osteoporosis is raloxifene.

#### **Prevention and treatment of osteoporosis in postmenopausal women:**

The MORE trial was a large 3-year randomized placebo-controlled study in postmenopausal women with osteoporosis. Raloxifene showed an increase in BMD and reduced the risk of vertebral fractures. The risk of non-vertebral fractures did not differ between placebo and raloxifene. There was an increased risk of venous thromboembolism compared with placebo (RR 3.1, 95% CI 1.5-6.2) (*Ettinger, 1999*).

The CORE 4-year trial extension of 4,011 women continuing from MORE (7,705) showed no difference in overall mortality, cardiovascular events, cancer or nonvertebral fracture rates (*Ensrud, 2006; Siris, 2005*).

### **Calcitonin**

#### **Treatment of osteoporosis in postmenopausal women**

Nasal salmon-calcitonin 200 IU daily has shown a 33% risk reduction in new vertebral fractures compared with placebo (RR 0.67, 95% CI 0.47-0.97,  $p = 0.03$ ). This occurred without significant effects on BMD. BMD measurements were not blinded to investigators and 59% (744) participants withdrew from the study early. Also, a dose response was not observed with respect to risk reduction of vertebral fractures. (*Chestnut, 2000*).

#### **Post-transplantation**

Several studies have shown that nasal spray calcitonin has little effect on prevention of bone loss after organ or bone marrow transplantation (*Valimaki, 1999a; Valimaki, 1999b*).

### **Anabolic Agents**

#### **Parathyroid hormone 1-34 (teriparatide)**

Daily subcutaneous injections of recombinant human PTH 1-34 (Forteo®) has been studied in both men and women, in combination with other agents and alone, and in glucocorticoid-induced osteoporosis and postmenopausal osteoporosis. It is universally effective at building bone and decreasing fractures, and its metabolic effects seem to continue even after discontinuation of the drug. PTH has been approved by the FDA for treatment of osteoporosis, but carries a black box warning about possible risk for osteosarcoma based on a rodent model (*Neer, 2001*).

In a study of 83 men with osteoporosis, bone density was increased significantly more with Forteo® alone than with either Forteo® and alendronate or alendronate alone ( $p < 0.001$ ). Femoral neck bone density was also significantly greater using teriparatide than alendronate ( $p < 0.001$ ) or combination therapy ( $p < 0.01$ ) (*Finkelstein, 2003*).

Using PTH 1-84 with alendronate in postmenopausal women, bone density was increased similarly by PTH alone, alendronate alone, and combination therapy with PTH and alendronate. Areal BMD was not as increased in the combination group at certain femur sites. The volumetric bone density of trabecular bone in spine was, however, significantly increased in the parathyroid treated patients (*Black, 2003*). Two years of alendronate following the PTH 1-84 was associated with significant increases in BMD (*Black, 2005*).

Current clinical practice does not recommend the use of bisphosphonates and teriparatides together.

*Supporting evidence is of class: A*

### **Strontium Ranelate**

Strontium ranelate, a divalent cation like calcium, is a novel anabolic agent for treatment of osteoporosis. The mechanism of action is felt to be a stimulation of bone formation related to an increase in osteoprogenitor cell replication and inhibition of bone resorption. The exact mechanism is unknown. Results of animal and human studies indicate this may be a useful, safe agent for osteoporosis. A double-blind, placebo-controlled trial in postmenopausal women with at least one vertebral fracture showed that 2 g of strontium ranelate daily for 3 years reduced new vertebral fractures 49% in the first year and 41% in three years (RR .59 [.48-.73]). Bone density increased 14.4% at the lumbar spine and 8.3% at the femur at three years (Meunier, 2004; Meunier, 2002; Rubin, 2003). All non-vertebral fractures were reduced 16% and hip fractures were reduced in women with a T-score of less than or equal to -2.4 (Reginster, 2005).

*Supporting evidence is of classes: A, R*

### **Combination Therapy**

#### **Estrogen and bisphosphonates**

To date there have been no combination therapy studies that have shown a fracture benefit. Therefore, it is unknown at this time whether combination therapy reduces the incidence of fractures (Bone, 2000; Harris, 2001; Lindsay, 1999). Combination therapy should be considered in cases of significant bone loss on a single anti-resorptive agent once other causes of such bone loss have been eliminated or if the pre-treatment fracture risk is quite high (Johnell, 2002).

### **Comparative Trials**

#### **Alendronate vs. intranasal calcitonin**

Alendronate 10 mg daily has been shown to significantly increase bone mineral density at the lumbar spine (p<0.001), femoral neck (p<0.001), and trochanter (p<0.001) compared with intranasal calcitonin 200 IU daily (Downs, 2000).

#### **Alendronate vs. risedronate**

The FACT trial (Rosen, 2005) is a 2-year trial that randomized 1,053 postmenopausal women with low bone mass to either alendronate 70 mg/week or risedronate 35 mg/week with BMD change and changes in biochemical markers of bone turnover as the primary endpoints. The published data showed a significantly greater gain in BMD with alendronate than risedronate. Although both agents decreased bone turnover into the premenopausal range, alendronate decreased bone turnover significantly greater than risedronate. The GI tolerability was comparable, including a subgroup of patients with pre-existing GI disorders. The clinical significance of this trial for fracture reduction differences between alendronate and risedronate is not known since it was not powered to measure fracture reduction differences between the two drugs (Bonnick, 2006).

*Supporting evidence is of class: A*

### **Calcitriol (1, 25-OH vitamin D)**

#### **Post-transplantation**

Stempfle et al. randomized 132 patients (111 men, 21 women) with a mean age of 51 years ± 25 months after cardiac transplantation to receive elemental calcium 1000 mg daily, hormone therapy (if hypogonadal), and calcitriol 0.25 mg daily, or calcium, hormone therapy, and placebo for 36 months.

They found that lumbar spine bone mineral density increased by  $5.7\% \pm 4.4\%$  in the calcitriol group and by  $6.1\% \pm 7.8\%$  in the placebo group over 36 months, without a statistical difference between the groups. Two percent of patients had incident fractures in the first year, 3.4% during the second year, and none the third year of the trial (*Stempfle, 1999*).

### Alternative and Complementary Agents

Routine supplementation with the following agents has either not been studied or not shown benefit for treatment or prevention of osteoporosis:

#### Phytoestrogens

Phytoestrogens are naturally occurring compounds contained in foods derived from plants and having some estrogen-like activity. Phytoestrogens derived from soy include the isoflavones daidzein and genistein. Other plants containing phytoestrogens include black cohosh, dong quai, red clover, alfalfa, and licorice root. A small number of short-term trials in postmenopausal women treated with soy protein extracts have conflicting results (*Alekel, 2000; Horiuchi, 2000; Potter, 1998*).

#### Ipriflavone

Ipriflavone is a synthetic isoflavone derivative, currently available as a dietary supplement. It is not recommended for osteoporosis prevention or treatment (*Alexandersen, 2001*).

#### Natural progesterone

In 1999, a one-year, randomized placebo-controlled trial by Leonetti showed no protective effect of transdermal progesterone on bone density. The study included 102 postmenopausal women (*Leonetti, 1999*).

#### Magnesium

Some epidemiologic studies have correlated increasing levels of dietary magnesium with higher bone density. There are very few data available on the effects of magnesium supplementation in osteoporosis (*Stendig-Lindberg, 1993*).

#### Vitamin K

A prospective analysis of the Nurses' Health Study found that women in the lowest group, based on vitamin K consumption, had the highest risk of hip fractures during the 10-year follow-up (*Feskanich, 1999; Shiraki, 2000*).

#### Eicosapentaenoic and gamma-linolenic acid supplementation

EPA (eicosapentaenoic acid) and GLA (gamma-linolenic acid) have beneficial effects on calcium absorption and bone mineralization in animal models (*Kruger, 1998*).

#### Kampo formulae

In China and Japan, kampo formulae (derived from plants) are used for the treatment of osteoporosis. Studies are underway to isolate their active components and characterize their biologic activity (*Li, 1998*).

*Supporting evidence is of classes: A, B, C, D*

## 16. Follow-Up Testing After Pharmacologic Intervention

### Key Points:

- Periodic follow-up central DXA on the same machine is recommended for following patients on pharmacologic therapy.
- The testing interval varies from 6-24 months depending on the clinical situation.

Sequential bone density testing using central DXA may be useful, and is generally recommended in monitoring drug therapy for the treatment of osteopenia or osteoporosis (*Miller, 1999*). Ideally, such testing should be performed at 12-24 months on the same machine as the pre-treatment bone density. A frequency as often as every 6-12 months may be indicated in the case of glucocorticoid treated patients or those on suppressive doses of thyroid hormone. Other patients at risk for accelerated bone loss include women at early menopause or those who have discontinued estrogen and are not on another bone protective agent\*. The lumbar spine and the total proximal femur have the highest reproducibility and are the preferred sites for monitoring therapy (*Bonnick, 1998*). Changes in BMD should only be reported as significant if they exceed the "least significant change" for the DXA center (*Bonnick, 1998; Faulkner, 1999; Miller, 1999*). Stability or increase in BMD indicates successful therapy. A significant decline in BMD may require further investigation.

A significant decrease in BMD on therapy may be due to:

- Poor drug adherence
- Improper medication administration technique in the case of bisphosphonates
- A missed secondary cause of osteoporosis (e.g., hyperparathyroidism, malabsorption)
- Inadequate calcium intake
- Untreated Vitamin D deficiency
- A true treatment failure due to the drug itself
- Malabsorption of orally administered drugs

Further follow-up BMD testing after stability or improvement over 3-4 years has been demonstrated is recommended by most experts. No study has been done as to whether follow-up BMD testing on therapy enhance fracture risk reduction but they may affect patient adherence to therapy (*Eastell, 2003*). Therapy should not be withheld if follow-up bone density testing is not available.

\*Medicare provides coverage for bone densitometry with central DXA every two years to monitor osteoporosis therapy.

*Supporting evidence is of classes: A, C, R*

## Appendix A – Secondary Causes of Osteoporosis

The chronic conditions most commonly seen in clinical practice have been printed in **bold** type.

### Secondary Causes of Osteoporosis

#### I. Endocrine disorders

- **Cushing's syndrome**
- **Male or female hypogonadism**
  - Hyperprolactinemia
  - Klinefelter's syndrome
  - Surgical removal of ovaries or testes
  - Turner's syndrome
  - Other causes of hypogonadism
- **Hyperthyroidism**
- **Primary hyperparathyroidism**
- Acromegaly
- Addison's disease
- Growth hormone deficiency
- Type 1 diabetes mellitus

#### II. Rheumatologic disorders

- **Ankylosing spondylitis**
- **Juvenile polyarticular arthritis**
- **Rheumatoid arthritis**
- **Systemic lupus erythematosus**

#### III. Malignancy

- Leukemia
- Multiple myeloma
- Systemic mastocytosis

#### IV. Pharmacotherapy

- **Anticonvulsants (phenytoin or phenobarbital)**
- **Glucocorticoid excess**
- Intravenous heparin
- **L-thyroxine over-replacement**
- Long-term warfarin use

- Chronic lithium therapy
  - Chronic phosphate binding (aluminum-containing) antacids
  - Drugs causing hypogonadism
    - Aromatase inhibitors
    - Chemotherapy (methotrexate or other antimetabolites)
    - Depo-medroxy progesterone acetate (Depo-provera®)
    - Gonadotropin-releasing hormone (GnRH) agonists (buserelin, leuprolide, nafarelin)
  - Extended tetracycline use, diuretics causing hypercalciuria, phenothiazine derivatives, cyclosporin A, or tacrolimus (FK506) may be associated with decreased bone density in humans, and are known to be toxic to bone in animals or to induce calciuria and/or calcium malabsorption in humans
- V. Chronic obstructive liver disease
- **Primary biliary cirrhosis**
- VI. Gastrointestinal disease
- **Celiac disease**
  - **Inflammatory bowel disease (Crohn's disease in particular)**
  - Gastrectomy, intestinal bypass surgery, or small/large bowel resection
  - Pernicious anemia
- VII. Renal insufficiency or failure**
- VIII. Miscellaneous causes
- **Vitamin D deficiency**
  - **Alcohol abuse**
  - **Anorexia nervosa or bulimia**
  - **Movement disorders (Parkinson's disease)**
  - Amyloidosis
  - Chronic obstructive pulmonary disease
  - Treatment for endometriosis
  - Epidermolysis bullosa
  - Hemophilia
  - Hemochromatosis
  - Idiopathic scoliosis
  - Lacto-vegetarian dieting
  - Lactose intolerance
  - Pregnancy and lactation (reversible)

- Prolonged parenteral nutrition
- Sarcoidosis

IX. Immobilization

- Prolonged bedrest or wheelchair-bound from any cause
- Space flight
- Spinal cord syndromes

X. Genetic diseases

- Congenital porphyria
- Ehlers-Danlos syndrome
- Gaucher's disease and other glycogen storage diseases
- Homocystinuria
- Hypophosphatasia
- Marfan's syndrome
- Menkes' syndrome
- Mitochondrial myopathies
- Multiple dystrophy
- Multiple sclerosis
- Osteogenesis imperfecta
- Riley-Day syndrome (familial dysautonomia)
- Sickle-cell anemia
- Thalassemia

XI. Idiopathic causes

- Idiopathic osteoporosis of young adults
- Juvenile osteoporosis
- Regional osteoporosis: reflex sympathetic dystrophy, transient osteoporosis of the hip, or regional migratory osteoporosis

# Appendix B – Recommended Pharmacologic Agents

## Recommended Pharmacologic Agents for Osteoporosis

Medication	Indications	Dose/Administration	Reduction in Fracture Risk <sup>2</sup>	Adverse Drug Reactions <sup>1</sup>	Contraindications
<b>Bisphosphonates</b>  Alendronate (Fosamax®)	<b>TREATMENT</b> • Postmenopausal osteoporosis • Increase bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women <b>PREVENTION</b> • Postmenopausal osteoporosis	<b>TREATMENT</b> • 10 mg orally daily • 70 mg tablet weekly • 70 mg /2800 IU vitamin D weekly <b>PREVENTION</b> • 70 mg buffered solution weekly • 5 mg orally once daily or one 35 mg tablet weekly <i>To be taken in the morning on an empty stomach (30 min before food/drink) with an 8 oz glass of water. Remain upright for at least 30 min and until after the first food of the day. Not to be taken at the same time as calcium supplementation or other medication.</i>	Vertebral: +++ Nonvertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia, flu-like symptoms (rare-post market experience)	• Abnormalities of the esophagus which delay esophageal emptying • Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with $\text{CaCl} \leq 35 \text{ ml/min}$ .
Ibandronate (Boniva®)	<b>TREATMENT</b> • Postmenopausal osteoporosis <b>PREVENTION</b> • Postmenopausal osteoporosis	<b>TREATMENT and PREVENTION</b> • 150 mg orally once monthly <i>To be taken in the morning on an empty stomach with an 8 oz glass of water. Remain upright and do not eat or drink anything but water for at least 60 minutes. Not to be taken at the same time as calcium supplementation or other medication</i> <b>TREATMENT</b> 3 mg intravenous injection every 3 months	Vertebral: +++ Nonvertebral: + Hip: -	• Esophagitis, abdominal pain, diarrhea • Influenza like illness, jaw osteonecrosis (rare) musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia	• Uncorrected hypocalcemia • Inability to stand or sit upright at least 60 minutes • Hypersensitivity • Not recommended for patients with $\text{CaCl} \leq 30 \text{ ml/min}$ .
Risedronate (Actonel®)	<b>TREATMENT</b> • Postmenopausal osteoporosis • Glucocorticoid-induced osteoporosis <b>PREVENTION</b> • Postmenopausal osteoporosis • Glucocorticoid-induced osteoporosis	<b>TREATMENT and PREVENTION</b> • 5 mg orally daily • 35 mg orally weekly <i>To be taken in the morning on an empty stomach (30 min before food/drink) with an 8 oz glass of water. Remain upright for at least 30 min. Not to be taken at the same time as calcium supplementation or other medication.</i>	Vertebral: +++ Nonvertebral: ++ Hip: +++	• Esophagitis, abdominal pain, diarrhea • Jaw osteonecrosis (rare), musculoskeletal pain, dyspepsia, acid regurgitation, esophageal ulcer, dysphagia	• Inability to stand or sit upright for at least 30 minutes • Hypersensitivity • Uncorrected hypocalcemia • Not recommended for patients with $\text{CaCl} \leq 30 \text{ ml/min}$ .
<b>Selective Estrogen Receptor Modulator (SERM)</b>  Raloxifene (Evista®)	<b>TREATMENT</b> • Postmenopausal osteoporosis <b>PREVENTION</b> • Postmenopausal osteoporosis	<b>TREATMENT and PREVENTION</b> • 60 mg orally daily	Vertebral: +++ women without fx ++ women with fx Nonvertebral: - Hip: -	• Hot flashes • Leg cramps • Increased risk of venous thromboembolic events	• Pregnancy • History of venous thromboembolism • Hypersensitivity

1. Based on patient specific data  
2. ++++ >50% reduction; ++ 40-50% reduction; + <40% reduction; - Unable to show reduced risk; N/A No data available from RCT  
Note: This data comes from pharmaceutical-sponsored trials and are not head-to-head comparisons.

# Recommended Pharmacologic Agents for Osteoporosis (cont)

Medication	Indications	Dose/Administration	Reduction in Fracture Risk <sup>2</sup>	Adverse Drug Reactions <sup>1</sup>	Contraindications
<b>Parathyroid Hormone (PTH)</b> Teriparatide (Forteo®)	<b>TREATMENT</b> <ul style="list-style-type: none"> <li>Postmenopausal osteoporosis with high risk for fracture (history of osteoporotic fracture, multiple risk factors, failed/intolerant of previous therapy)</li> <li>Increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk of fracture (history of osteoporotic fracture, multiple risk factors, failed/intolerant of previous therapy)</li> </ul>	<b>TREATMENT</b> <ul style="list-style-type: none"> <li>20 mcg subcutaneous daily for not more than 2 years</li> </ul>	Vertebral: +++ Nonvertebral: +++ Hip: N/A	<b>BLACK BOX WARNING:</b> shown to cause an increase in the incidence of osteosarcoma in male and female rats, dependant on dose and duration of treatment. <ul style="list-style-type: none"> <li>Orthostatic hypotension</li> <li>Increase in serum calcium</li> <li>Increase in urinary calcium</li> <li>Increase in serum uric acid</li> </ul>	<ul style="list-style-type: none"> <li>Paget's disease</li> <li>Any prior therapeutic radiation involving the skeleton</li> <li>Bone metastases or history of skeletal malignancies</li> <li>Metabolic bone disease (other than osteoporosis)</li> <li>Hypercalcaemia</li> <li>Pregnant and nursing women</li> <li>Unexplained elevated alkaline phosphatase</li> <li>Hypersensitivity, pediatric populations or young adults with open epiphyses</li> </ul>
<b>Calcitonin</b> Calcitonin-salmon (Miacalcin® and Fortical® nasal spray)	<b>TREATMENT</b> <ul style="list-style-type: none"> <li>Postmenopausal osteoporosis in women with at least 5 years postmenopause with low bone mass relative to healthy premenopausal females</li> </ul> <p><b>Please refer to the ICSI HT and Management of Menopause guideline for more brand specific information on estrogens</b></p>	<ul style="list-style-type: none"> <li>Nasal spray: 200 IU intranasally daily, alternate nostrils daily</li> </ul>	Vertebral: + Nonvertebral: - Hip: -	<ul style="list-style-type: none"> <li>Nausea</li> <li>Flushing</li> <li>Rhinitis with nasal spray</li> </ul>	<ul style="list-style-type: none"> <li>Hypersensitivity</li> </ul>
<b>Estrogens</b> Estrogens	<b>PREVENTION</b> <ul style="list-style-type: none"> <li>Postmenopausal osteoporosis</li> </ul>	<ul style="list-style-type: none"> <li>Varies by manufacturer</li> </ul>	Vertebral: +++ Nonvertebral: ++ Hip: +++	<ul style="list-style-type: none"> <li>Bloating</li> <li>Breast tenderness</li> <li>Uterine bleeding</li> <li>Those with an intact uterus must also take a progestin to prevent endometrial cancer</li> <li>Breast cancer</li> <li>Increased risk of myocardial infarction, stroke, venous thrombosis or pulmonary embolism.</li> <li>Comments: Dementia, gall bladder disease, hypercalcaemia, visual abnormalities hypertension are also mentioned</li> </ul>	<ul style="list-style-type: none"> <li>Pregnancy</li> <li>History of thromboembolic disorders</li> <li>Breast cancer (except appropriately selected patients treated for metastatic disease)</li> <li>Estrogen dependent neoplasia</li> <li>Undiagnosed abnormal vaginal bleeding</li> <li>Hypersensitivity</li> <li>Liver dysfunction or disease, active or recent (within 1 year)</li> <li>Stroke or MI</li> </ul>

1. Based on patient specific data  
2. +++ >50% reduction; ++ 40-50% reduction; + <40% reduction; - Unable to show reduced risk; N/A No data available from RCT

## Pharmacologic Bone Active Agents Non-FDA Approved for Osteoporosis

Medication	Comments
<b>Bisphosphonates</b>	
Etidronate (Didronel®)	Low oral absorption. Inconvenient dosing cycle but is the least expensive bisphosphonate.
Pamidronate (Aredia®)	Available only as an intravenous dosage form*.
Zoledronic Acid (Zometa®)	A potent bisphosphonate indicated for hypercalcemia of malignancy*.
<b>Others</b>	
Calcitriol (Rocaltrol®)	Insufficient data. Most often used in renal failure and renal osteodystrophy.
Cholecalciferol (Vitamin D <sub>3</sub> ): Ergocalciferol (Calciferol®, Vitamin D <sub>2</sub> )	Conflicting data as monotherapy. See Annotation #5 Insufficient data. Less potent than D <sub>3</sub> .
Nandrolone deconoate	Insufficient data. Adverse effects would limit use.
Sodium fluoride	Mixed results from clinical trials. Monotherapy may cause osteomalacia or other bone abnormalities.
Tamoxifen (Nolvadex®)	Insufficient data. Increases bone mineral density. Adverse effects would limit use in general population.
Testosterone (various products available)	To treat underlying condition of hypogonadism in men.
Tibolone	A synthetic agent with progestogenic, estrogenic, and androgenic activity. Not yet an FDA approved product.
Strontium Ranelate	Increases BMD and reduces fractures. Not yet available in U.S.

\* Intravenous bisphosphonates have been associated with osteonecrosis of the jaw following dental extraction. Most reported cases have been in cancer patients (Woo, 2006).

### Availability of references

References cited are available to ICSI participating member groups on request from the ICSI office. Please fill out the reference request sheet included with your guideline and send it to ICSI.

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### Original Work Group Members

Dana Battles, MD  
*Internal Medicine*  
**Aspen Medical Group**

Bart Clarke, MD  
*Endocrinology*  
**Mayo Clinic**

Renee Compo, RN, CNP  
*Nursing*  
**HealthPartners Medical Group**

Dianne Eggen, MPH  
*Health Education*  
**HealthPartners Health Plan**

Jane Flad, MD  
*Family Practice*  
**Family HealthServices Minnesota**

J. Michael Gonzalez-Campoy, MD, PhD  
*Endocrinology*  
**Aspen Medical Group**

Beth Green, MBA, RRT  
*Measurement/Implementation Advisor*  
**ICSI**

Richard Kopher, MD  
*Gynecology*  
**HealthPartners Medical Group**

Michelle Kotten, PharmD  
*Pharmacy*  
**HealthPartners Medical Group**

Jenelle Meyer, RN  
*Facilitator*  
**ICSI**

John Schousboe, MD  
*Rheumatology*  
**Park Nicollet Health Services**

Christine Simonelli, MD  
*Internal Medicine, Work Group Leader*  
**HealthEast Clinics**

### Contact ICSI at:

8009 34th Avenue South, Suite 1200; Bloomington, MN 55425; (952) 814-7060; (952) 858-9675 (fax)  
Online at <http://www.ICSI.org>

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# Evidence Grading System

## I. CLASSES OF RESEARCH REPORTS

### A. Primary Reports of New Data Collection:

- Class A: Randomized, controlled trial
- Class B: Cohort study
- Class C: Non-randomized trial with concurrent or historical controls  
Case-control study  
Study of sensitivity and specificity of a diagnostic test  
Population-based descriptive study
- Class D: Cross-sectional study  
Case series  
Case report

### B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

- Class M: Meta-analysis  
Systematic review  
Decision analysis  
Cost-effectiveness analysis
- Class R: Consensus statement  
Consensus report  
Narrative review
- Class X: Medical opinion

## II. CONCLUSION GRADES

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system defined in Section I, above, and are assigned a designator of +, -, or  $\emptyset$  to reflect the study quality. Conclusion grades are determined by the work group based on the following definitions:

**Grade I:** The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

**Grade II:** The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

**Grade III:** The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results from different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

**Evidence Grading System**

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**Grade Not Assignable:** There is no evidence available that directly supports or refutes the conclusion.

The symbols **+**, **-**, **∅**, and **N/A** found on the conclusion grading worksheets are used to designate the quality of the primary research reports and systematic reviews:

**+** indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis;

**-** indicates that these issues have not been adequately addressed;

**∅** indicates that the report or review is neither exceptionally strong or exceptionally weak;

**N/A** indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

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# Conclusion Grading Worksheet A – Annotations #4 & 5 (Calcium)

**Work Group's Conclusion:** Calcium slows age-related bone loss.

**Conclusion Grade:** II

**Work Group's Conclusion:** Calcium may reduce osteoporosis fracture risk.

**Conclusion Grade:** III

Author/Year	Design Type	Class	Quality +,-,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Dawson-Hughes, et al. (1990)	RCT	A	0	-Women ages 40 to 7 yrs old; good general health, normal ambulation, at least 6 mos since last menses, normal physical exam and screening lab tests -Half had usual calcium intake <400 mg/d; half had intake of 400-650 mg/d (also included 7 with intake of 668-925 mg/day) -Excluded: history of nontraumatic fracture; renal, hepatic, gastrointestinal disorders associated with abnormal calcium or bone metabolism; used estrogen, glucocorticoids, or other medications that affect calcium or bone metabolism in past yr; evidence of compression fracture, spine BMD of $\geq 2$ SD below age-matched mean -Analyzed separately those who had undergone menopause $\leq 5$ yrs earlier and those >5 yrs -Randomized to placebo, 500 mg calcium carbonate, or 500 mg calcium citrate malate (stratified by usual intake) -Follow-up every 6 mos	-362 randomized; 46 (13%) dropped out during 2 yr study; 14 were excluded from analyses <b>Early Postmenopausal Women (n=67)</b> -All 3 treatment groups lost bone at spine ( $p<0.01$ vs. baseline) by 2 years; femoral neck and radius did not change significantly for any treatment group <b>Late Postmenopausal Women (n=169)</b> -Calcium citrate malate group had no significant loss of BMD at any site; spine BMD decreased significantly in other groups; femoral neck BMD decreased significantly in placebo group -By calcium intake: in women with lower dietary calcium intake greater decreases in BMD at 2 yrs in placebo group (at spine, femoral neck, and radius vs. calcium citrate malate group and at radius vs. calcium carbonate group; all $p<0.05$ ); in women with higher dietary intake there were no differences at any site -Significant bone loss from the spine ( $\geq 1.6\%$ at 2 yrs) was observed in all groups except low calcium intake receiving calcium citrate malate; significant bone loss from femoral neck ( $\geq 2.4\%$ at 2 yrs) and radius ( $\geq 2.6\%$ at 2 yrs) occurred only in placebo group with lower calcium intake	-In early postmenopausal women, bone loss from the spine was not affected by supplementation with 500 mg calcium. Among late postmenopausal women who received placebo, a higher dietary calcium intake was associated with reduced bone loss from the radius. In late postmenopausal women with low dietary intakes, calcium citrate malate prevented bone loss from the spine; both calcium supplements prevented bone loss from the femoral neck and radius. Late postmenopausal women with higher dietary intakes maintained BMD at the hip and radius but lost BMD at the spine despite supplementation.  NOTES: compliance was 98%; no vitamin D supplementation  <i>Work Group's Comments: Inclusion/exclusion criteria defined; volunteers; same observation schedule for all groups; no indication of sample size estimation; double-blind study; intention-to-treat analysis; no baseline comparison of subgroups; no fracture data reported; compliance monitored</i>

**Conclusion Grading Worksheet A – Annotations #4 & 5 (Calcium)**

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Chapuy, et al. (1992)	RCT	A	6	<p>-Women ages 69 to 106 yrs old; ambulatory; no serious medical conditions; life expectancy <math>\geq 18</math> mos</p> <p>-Excluded: drugs known to alter bone metabolism in past year; fluoride salts for <math>&gt;3</math> mos; vit D or calcium in past 6 mos or for <math>&gt;1</math> yr in past 5 yrs</p> <p>-Randomized to vit D<sub>3</sub>+calcium (1.2 g calcium, 800 IU vit D<sub>3</sub>) or placebo</p> <p>-Baseline assessment of calcium intake and frequency of falls</p> <p>-Assessed for fractures at 6, 12, &amp; 18 mos; subset of 142 had serum analysis at baseline &amp; every 6 mos; subset of 56 had BMD at baseline &amp; 18 months</p>	<p>-1634 in vit D<sub>3</sub>+calcium group; 1636 in placebo; no differences in age, wt, ht, dietary calcium or % with <math>\geq 1</math> fall in 3 months before study; dietary calcium was low (mean of 513 mg/day); vit D intake estimated at 123 IU/day</p> <p>-54% (1765) treated and followed for 18 mos; dropout rates similar in 2 groups</p> <p>-For those 1765: 32% fewer non-vertebral fractures (p=0.02); 43% fewer hip fractures (p=0.04) in the vit D<sub>3</sub>+calcium group (vs. placebo)</p> <p>-Active tx analysis (treatment for varying lengths of time): 28% fewer non-vertebral fractures (p=0.02); 31% fewer hip fractures (p=0.04)</p> <p>-Intention-to-treat analysis: 25% fewer non-vertebral fractures (p&lt;0.001); 27% fewer hip fractures (p=0.004)</p> <p>-Odds ratio=1.7 (95%CI: 1.0-2.8) for hip fractures in placebo group vs. vit D<sub>3</sub>+calcium group; for non-vertebral fractures OR=1.4 (95%CI: 1.4-2.1)</p> <p>-Treatment reduced age-related risk of fracture at 18 mos (p=0.007 for hip fractures; p=0.009 for all non-vertebral fractures)</p> <p>-In BMD subgroup, total proximal femoral BMD increased 2.7% in vit D<sub>3</sub>+calcium group and decreased 4.6% in placebo group (p&lt;0.001)</p> <p>-40 in vit D<sub>3</sub>+calcium group and 28 in placebo group had gastrointestinal symptoms that led to discontinuation of treatment</p>	<p>-Vit D<sub>3</sub>+calcium supplements reduced the risk of hip fracture and other non-vertebral fractures and increased the BMD of the proximal femur in elderly women. The supplements were safe.</p> <p>NOTES: women with past fractures or who had taken or were taking estrogen or thiazide diuretics were eligible; &lt;1% received estrogen after menopause; treatments taken in presence of nurse to ensure compliance; sample size based on reduction of 30% in annual hip-fracture rate could be detected; active treatment and intention-to-treat analyses; rate of vertebral fractures not studied because many are asymptomatic, interpretation of X-rays can be complicated by other conditions, and the sample size was large</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria defined; volunteers; same observation schedule for all groups (except subgroup of 56 women for BMD); did sample size estimation; unclear if investigators were blinded; active tx and intention-to-treat analyses; groups comparable at baseline; fracture data reported; compliance monitored; 46% withdrawn in each group</i></p>

**Conclusion Grading Worksheet A – Annotations #4 & 5 (Calcium)**

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Recker, et al. (1996)	RCT	A	+,-,0	<p>-Healthy white women volunteers; 60 yrs (mean 73.5±7.1 yrs); ambulatory; living independently; calcium intake estimated at &lt;1g/day</p> <p>-2 groups: those with prevalent spine fractures (PF) &amp; those without (NPF)</p> <p>-Excluded: other diagnoses or treatments that affect skeleton</p> <p>-Randomized to calcium (600 mg BID) or placebo</p> <p>-Bone mineral content (BMC) of radius every 6 mos (SPA)</p> <p>-Spine x-rays every yr</p> <p>-Mean follow-up of 4.3 years</p>	<p>-197 in analysis (94 PF, 103 NPF; each with calcium and placebo); 4 subgroups similar at baseline in age and calcium intake; higher BMC in NPF groups (p&lt;0.002)</p> <p>-36 in PF group had 86 incident vertebral deformities; 25 in NPF group had 59 incident vertebral deformities</p> <p>-Calcium reduced the rate of incident fractures in PF group (p=0.02) but not NPF group; more fractures in PF placebo group than NPF placebo group (p=0.002)</p> <p>-Univariate analysis: prevalent fracture (Hazard Ratio=1.9; 95%CI:1.14-3.18) and lower initial BMC (HR=1.43; 95%CI:1.10-1.87) were significant risk factors for incident vertebral fracture</p> <p>-Multivariate analysis: non-treatment of PF cases associated with risk of incident fracture (HR=2.45; 95%CI:1.42-4.20 adjusted for initial BMC)</p> <p>-Calcium prevented bone loss in PF group (p&lt;0.001) but not NPF group (p&lt;0.2); rate of bone loss greater in PF placebo group than NPF placebo group (p=0.03)</p>	<p>-Supplemental calcium in elderly women with low self-selected calcium intakes reduces the risk of incidence spine fractures in those with fractures and halts measurable bone loss for at least 4 years.</p> <p>NOTES: 750 screened, 499 didn't enroll because of calcium intake &gt;1g/day (50%) or personal choice (50%); 54 more excluded from analysis (&lt;1 yr of observation); randomization not stratified by fracture status; median compliance 64%; 5% of each group refused to accept assigned treatment after randomization (retained for intention-to-treat analysis); no vitamin D supplementation</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria defined; volunteers; same observation schedule for all groups; no indication of sample size estimation; double-blind study; intention-to-treat analysis (see NOTES); fracture data reported; compliance monitored</i></p>

**Conclusion Grading Worksheet A – Annotations #4 & 5 (Calcium)**

Author/Year	Design Type	Class	Quality +,-,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Riggs et al. (1998)	RCT	A	0	<p>Women ages 61 to 70 yrs old; ambulatory; postmenopausal for ≥10 yrs; no history of osteoporotic fractures or x-ray evidence of vertebral fracture; normal BMD for age and gender; not taking estrogen, large doses of vit D (&gt;800 IU/d) or calcium (&gt;500 mg/d), or other drugs that affect bone; no history of use of fluoride or bisphosphonates</p> <p>-Excluded: renal lithiasis, impaired renal function, hypercalcemia, hypercalciuria; disease known to affect bone or calcium metabolism</p> <p>-Randomized to 1600 mg/day calcium or placebo</p> <p>-Follow-up every 6 mos for 4 yrs; BMD every 6 mos, urine collected every 6 mos, serum every 12 mos, x-rays at baseline and end of study</p>	<p>-236 women randomized (119 calcium, 117 placebo); no differences between groups at baseline</p> <p>-177 (75%) completed 4 yrs of study (88 calcium, 89 placebo); 16 discontinued because of side effects (10 calcium, 6 placebo)</p> <p>-No difference in numbers of new vertebral fractures (8 in calcium group, 8 in placebo), or new non-vertebral fractures (11 in calcium group; 12 in placebo), or total new fractures</p> <p>-Mean dose of calcium in tx group was 1,234 mg/d; no change in dietary calcium over course of study for either group</p> <p>-Changes in BMD from baseline were significantly different between groups at 1 year for lumbar spine, proximal femur, and total body (all p≤0.003); at 4 yrs only proximal femur and total body differed between group (both p&lt;0.02)</p> <p>-Serum calcium (p&lt;0.001), parathyroid hormone (p=0.001), &amp; osteocalcin (p=0.04) and urinary calcium &amp; free pyridinoline (p=0.001) differed between groups at 4 yrs</p> <p>-Intention-to-treat analysis and analysis of those completing 4 yrs of study produced similar results for BMD and biochemical measures</p>	<p>-Daily administration of 1600 mg of calcium to elderly women for 4 years decreases age-related increases in parathyroid hormone and bone resorption and decreases the rate of bone loss. The calcium supplements were safe and well-tolerated.</p> <p>NOTES: to maintain urinary calcium at &lt;350 mg/day the dose was decreased in about 1/3 of calcium group; average dietary calcium intake was about 700 mg/day; no vitamin D supplementation</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria defined; volunteers; same observation schedule for all groups; no indication of sample size estimation; double-blind study; intention-to-treat analysis; fracture data reported; compliance monitored</i></p>

# Conclusion Grading Worksheet B – Annotation #15 (Bisphosphonates for Primary Osteoporosis)

**Work Group's Conclusion:** Excellent clinical trial data based on BMD and bio-markers supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal low bone density osteopenia or osteoporosis. The best clinical trials have been done with alendronate (Fosamax®), risedronate (Actonel®), and ibandronate (Boniva®).

**Conclusion Grade: I**

**Work Group's Conclusion:** Good clinical trial data support the use of alendronate for preventing bone loss in men diagnosed with osteoporosis.

**Conclusion Grade: I**

Author/Year	Design Type	Class	Quality +,-,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Lieberman, et al. (1995)	RCT	A	0	<p>-Women ages 45-80 years old; <math>\geq 5</math> yrs postmenopausal; lumbar spine BMD <math>\geq 2.5</math> SD below mean for premenopausal women</p> <p>-Excluded: other causes of osteoporosis; other disorders of bone &amp; mineral metabolism; abnormal hepatic function; abnormal lumbar spine precluding BMD measurement; history of hip fracture; prior treatment with bisphosphonates; prior treatment (last 12 months) with HRT, calcitonin, fluoride, or anabolic steroid</p> <p>-Randomized to receive placebo or 5, 10, or 20 mg alendronate per day for 2 years; in 3<sup>rd</sup> year women receiving 20 mg were switched to 5 mg; all received 500 mg calcium/day</p> <p>-BMD of lumbar spine, femoral neck, trochanter, forearm, and total body with DXA</p> <p>-Lateral spine films for vertebral fractures at baseline and after 1, 2, &amp; 3 yrs of treatment</p>	<p>-Paired spine films of 881 women (355 in placebo group, 526 in alendronate groups combined)</p> <p>-Groups similar at baseline in age, years since menopause, body-mass index, % with vertebral fractures, % with no vertebral deformities, Spine Deformity Index, BMD</p> <p>-All treatment groups had significantly increased BMD of spine, femoral neck, trochanter, and total body at 36 mos; placebo group significantly decreased at all sites; 10 mg dose was significantly more effective than 5 mg dose (all sites) and as effective as 20 mg followed by 5 mg</p> <p>-10 mg group had significantly greater BMD than placebo at all sites (<math>p &lt; 0.001</math>)</p> <p>-6.2% of placebo group and 3.2% of treatment groups had <math>\geq 1</math> new vertebral fracture during the study (with treatment, RR=0.52; 95%CI: 0.28-0.95); decreased risk observed when stratified by age or previous vertebral fracture; fewer multiple fractures in alendronate groups</p> <p>-Spine Deformity Index increased in 33% of alendronate group and 41% of placebo group (<math>p=0.03</math>)</p> <p>-Mean loss of height at 36 mos was 3.0mm in alendronate group and 4.6mm in placebo (<math>p=0.005</math>)</p> <p>-Non-vertebral fractures occurred in 83 women; trend toward fewer in treatment group (7.5% of women vs. 9.6%)</p> <p>-Adverse effects comparable in treatment and placebo groups</p>	<p>-Daily treatment with oral alendronate for 3 years resulted in increases in BMD of the spine, hip, and total body in women with postmenopausal osteoporosis. Treatment reduces the risk of vertebral fracture, the progression of vertebral deformities, and height loss in postmenopausal women with osteoporosis. Continuous treatment with 10mg per day provided maximal efficiency, was well tolerated, and is, therefore, the optimal dose.</p> <p>NOTES: Pooled data from 2 identical multicenter studies (pooling was planned); study was originally intended to be open-label in 3<sup>rd</sup> year but before 24 months decision was made to continue double-blind therapy with 20 mg group switched to 5 mg; 994 randomized, 909 completed <math>\geq 1</math> yr of study</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria clearly defined; patients appeared to be volunteers; same observation schedule for both treatment groups; no indication of sample size estimation; double-blind study; analysis by intention-to-treat; groups comparable at baseline, fracture data reported; compliance with treatment not reported</i></p>

**Conclusion Grading Worksheet B – Annotation #15  
(Bisphosphonates for Primary Osteoporosis)**

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Harris, et al. (1999)	RCT	A	+	<p>-Ambulatory women <math>\leq 85</math> yrs; <math>\geq 5</math> yrs postmenopausal; either <math>\geq 2</math> vertebral fractures on x-ray or 1 vertebral fracture and low lumbar spine BMD (2 SDs below young adult mean)</p> <p>-Excluded: condition that might interfere with eval. of spinal bone loss; received drugs known to affect bone metabolism in past month; anabolic steroids, estrogen, or progestins within past 3 months; bisphosphonates, fluoride, or subcutaneous estrogen in past 6 months</p> <p>-Randomized to risedronate (5 mg/d or 2.5 mg/d) or placebo; all received calcium (1000 mg/d) and vitamin D (up to 500 IU/d) if low baseline level</p> <p>-Lateral thoracic and lumbar spine x-rays at baseline and annually</p> <p>-BMD of lumbar spine and femoral neck at baseline and 6 month intervals</p>	<p>-2,458 women were enrolled (815 in placebo group, 813 to 2.5 mg group, 813 to 5 mg group with 19 not treated after randomization)</p> <p>-55% of placebo group and 60% of 5 mg group completed 3 years of treatment</p> <p>-86% of those who experienced vertebral fractures during the study had a least 1 new fracture (previously normal vertebra); over 3 yrs - 41% reduction in risk of new fracture in 5 mg risedronate group vs. placebo (p=0.003)</p> <p>-Cumulative incidence of non-vertebral fractures was lower by 39% in the 5 mg group vs. placebo (p=0.02)</p> <p>-5 mg risedronate group experienced significant increases from baseline BMD at lumbar spine, femoral neck, and femoral trochanter and BMD at each site was significantly greater than placebo (all p&lt;0.05)</p> <p>-Overall incidence of adverse events and withdrawals for adverse events was similar across treatment groups</p>	<p>-Daily oral risedronate therapy decreased the incidence of vertebral fractures within 1 year and non-vertebral fractures within 3 years. BMD was increased within 6-12 months at clinically important skeletal sites. The overall safety profile was similar to placebo.</p> <p>NOTES: study designed to have <math>\geq 90\%</math> power to detect 40% reduction in vertebral fracture risk with annual new fracture incidence of 10% in placebo group (assume 50% withdrawal rate); after study began, new information indicated 2.5 mg dose less effective (group discontinued); 96% of subjects were white; study was conducted at 110 study centers in North America</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria clearly defined; patients appeared to have volunteered for study; same observation schedule for both treatment groups; did sample size estimation; double-blind study; analysis by intention-to-treat; groups comparable at baseline; fracture data reported; compliance monitored; large proportion of withdrawals planned for in sample size estimation</i></p>

**Conclusion Grading Worksheet B – Annotation #15  
(Bisphosphonates for Primary Osteoporosis)**

Author/Year	Design Type	Class	Quality +,-,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Fogelman, et al. (2000)	RCT	A	0	<p>-Women up to 80 yrs old; postmenopausal for <math>\geq 1</math> yr; lumbar spine T-score of <math>\leq -2</math></p> <p>-Excluded: hyperparathyroidism; hyperthyroidism; osteomalacia within past yr; history of cancer; abnormalities that would interfere with measurement of lumbar spine BMD; treatment known to affect bone metabolism in past 6-12 mos</p> <p>-Randomized to risedronate (2.5 mg/d or 5 mg/d) or placebo; 2.5 mg/d group was discontinued at 9 of 13 sites based on other data; all received 1 g/d calcium</p> <p>-BMD of lumbar spine, femoral neck, and trochanter at baseline, 6, 12, 18, &amp; 24 mos</p> <p>-Spine x-rays at baseline and end of study</p>	<p>-543 enrolled (180 placebo, 184 2.5 mg risedronate, 179 5 mg risedronate); 355 completed 24 mos of treatment (143 placebo, 73 2.5 mg risedronate [protocol discontinued], 139 5 mg risedronate)</p> <p>-Groups were comparable at baseline</p> <p>-BMD of lumbar spine increased from baseline by 4% at 24 months in 5 mg group vs. no change in placebo group (<math>p &lt; 0.001</math> for difference between groups); comparable increase in BMD of lumbar spine in subgroups postmenopausal <math>\leq 5</math> yrs or <math>&gt; 5</math> yrs</p> <p>-BMD of femoral neck increased by 1.3% at 24 mos in 5 mg group and decreased by 1% in placebo group (<math>p &lt; 0.001</math> between groups)</p> <p>-BMD of trochanter increased by 2.7% in 5 mg group and decreased by -0.6% in placebo group (<math>p &lt; 0.001</math> between groups)</p> <p>-At 24 months, vertebral fractures were present in 14% of patients with known fracture status in placebo group vs 7% of 5 mg group</p> <p>-No difference in overall incidence of adverse events among groups; no difference in withdrawals due to adverse events</p>	<p>-Five mg of risedronate significantly increased BMD at the lumbar spine, femoral neck, and femoral trochanter in postmenopausal women with low bone mass. The changes were similar whether the women had experienced menopause more than 5 yrs before entry into the study or less than 5 yrs. Risedronate was well-tolerated.</p> <p>NOTES: 180 patients per group needed to detect a 6% difference between placebo and risedronate groups in change in BMD from baseline to 24 months with 90% power; study not powered to detect effects on fractures; study conducted at 13 centers in Europe</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria defined; patients appeared to have volunteered for study; same observation schedule for both treatment groups; did sample size estimation (BMD change); double-blind study; analysis by intention-to-treat; groups comparable at baseline; compliance not reported; fracture - trend data</i></p>

**Conclusion Grading Worksheet B – Annotation #15  
(Bisphosphonates for Primary Osteoporosis)**

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
McClung, et al. (2001)	RCT	A	+	<p>-2 parallel groups of ambulatory postmenopausal women  <b>Group A:</b> 70-79 yrs old; osteoporosis (femoral neck BMD T-score of -4 or lower or T-score of -3 with <math>\geq 1</math> nonvertebral fracture)  <b>Group B:</b> <math>\geq 80</math> yrs; at least 1 nonvertebral fracture, femoral neck T-score of lower than minus 4, or T-score lower than -3 with hip-axis length of <math>\geq 11.1</math> cm</p> <p>-Excluded: major illness, another metabolic bone disease in past yr, abnormal results of routine lab tests, recent use of drugs known to affect bone, allergy to bisphosphonates, history of bilateral hip fractures                      -Randomized to risedronate (2.5 mg/d or 5 mg/d) or placebo; all received 1000 mg calcium and, if needed, vitamin D                      -X-rays of spine at baseline; fractures during study were confirmed by x-ray                      -BMD at 6-month intervals (at 44 study sites)</p>	<p>-Total of 9,331 enrolled and received <math>\geq 1</math> dose of study drug; 2.5 and 5 mg groups were combined for analysis; within enrollment groups, risedronate and placebo groups were comparable at baseline; mean follow-up was 2.3 yrs                      -Of 9,331 women in study, 232 had hip fractures during study (2.8% of risedronate group and 3.9% of placebo group); incidence of non-vertebral fractures was 9.4% in risedronate group vs. 11.2% for placebo (RR=0.8; 95%CI:0.7-1.0; p=0.03)                      -Adverse events (any event, a serious event, or an event causing withdrawal) were similar in all treatment groups  <b>Group A (70-79 yrs old with osteoporosis)</b>                      -Of 5,445 enrolled, 3,768 had complete follow-up data (3,086 completed treatment)                      -1.9% of risedronate and 3.2% of placebo group had hip fractures (RR=0.6; 95%CI:0.4-0.9; p=0.009); for women with vertebral fracture at baseline RR=0.4 (95%CI:0.2-0.8; p=0.003); with no vertebral fracture at baseline RR=0.6 (95%CI: 0.3-1.2)                      -For non-vertebral fractures RR=0.7 (95%CI:0.5-0.9; p=0.01) favoring risedronate group  <b>Group B (<math>\geq 80</math> yrs old with <math>\geq 1</math> risk factor)</b>                      -Of 3,886 in <math>\geq 80</math> yrs group, 2,239 had complete follow-up data (1,591 completed treatment)                      -Risedronate had no effect on incidence of fracture (RR=0.8; 95%CI:0.6-1.2) regardless of BMD                      -No treatment effect for non-vertebral fractures</p>	<p>-Risedronate prevented hip fracture in women who had osteoporosis (as indicated by a low BMD - <b>Group A</b>) but not in those with clinical risk factors for hip fracture (but not necessarily osteoporosis - <b>Group B</b>).                      NOTES: intention-to-treat analysis included those who received at least one dose of treatment (those who discontinued treatment were requested to return to study center at 3 yrs after enrollment); 98% of the women were white; study was conducted at 183 sites worldwide  <i>Work Group's Comments: Inclusion/exclusion criteria clearly defined; patients appeared to have volunteered for study; only 31% of Group B had baseline BMD data; complete follow-up data for 69% of Group A and 58% of Group B; same observation schedule for all treatment groups; no indication of sample size estimation; not clear if double-blind study; analysis by intention-to-treat (see NOTES); groups comparable at baseline; fracture data reported; compliance monitored (50% completed treatment)</i></p>

**Conclusion Grading Worksheet B – Annotation #15  
(Bisphosphonates for Primary Osteoporosis)**

Author/Year	Design Type	Class	Quality +,-,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>																		
Orwoll, et al. (2000)	RCT	A	0	<p>-Men age 31 to 87 years; femoral neck BMD <math>\geq 2</math> SDs below mean for normal young men and lumbar spine BMD <math>\geq 1</math> SD below mean or femoral neck BMD <math>\geq 1</math> SD below mean and at least 1 vertebral deformity or a history of osteoporotic fracture</p> <p>-Excluded: secondary causes of osteoporosis except low serum free testosterone concentrations; other bone diseases, vitamin D deficiency, renal disease, severe cardiac disease, history of cancer, recent history of peptic ulcer or esophageal disease, esophageal abnormalities; history of treatment for osteoporosis</p> <p>-Randomized to 10 mg alendronate or placebo (3:2); all received calcium (500 mg/d) and vitamin D (400-450 IU/d)</p> <p>-Spine x-rays at baseline and 2 years</p> <p>-BMD at baseline and 6, 12, 18, &amp; 24 mos</p>	<p>-146 in alendronate group, 95 in placebo group; groups were comparable at baseline; in each group 36% had low serum-free testosterone concentrations; approx. 50% had vertebral fractures at baseline (29% with multiple fractures); 83% of placebo group and 86% of alendronate group completed the study</p> <p>-BMD changes from baseline at 2 years:</p> <table border="1"> <thead> <tr> <th></th> <th>Placebo</th> <th>Alendronate</th> </tr> </thead> <tbody> <tr> <td>Lumbar spine</td> <td>1.8%</td> <td>7.1%*</td> </tr> <tr> <td>Femoral neck</td> <td>-0.1%</td> <td>2.5%*</td> </tr> <tr> <td>Trochanter</td> <td>1.3%</td> <td>4.3%*</td> </tr> <tr> <td>Hip</td> <td>0.6%</td> <td>3.1%*</td> </tr> <tr> <td>Total body</td> <td>0.4%</td> <td>2.0%*</td> </tr> </tbody> </table> <p>*p&lt;0.001 vs. baseline and vs. placebo</p> <p>-Changes in lumbar spine BMD with alendronate treatment were similar regardless of serum-free testosterone concentrations and regardless of serum estradiol concentrations</p> <p>-Effect of alendronate was independent of age</p> <p>-Height decreased 2.4 mm in placebo group vs. 0.6 mm in alendronate group (p=0.02 for difference between groups); decrease in height was greater in those with new vertebral fractures during the study</p> <p>-Vertebral fractures occurred in 7.1% of placebo group and 0.8% of alendronate group (p=0.02); no difference in occurrence of non-vertebral fractures</p> <p>-11% of placebo group and 3% of alendronate group withdrew because of adverse effects (p=0.02)</p>		Placebo	Alendronate	Lumbar spine	1.8%	7.1%*	Femoral neck	-0.1%	2.5%*	Trochanter	1.3%	4.3%*	Hip	0.6%	3.1%*	Total body	0.4%	2.0%*	<p>-In men with osteoporosis, 10 mg/d of alendronate for 2 years increased BMD of the spine, hip, and total body. The effects were independent of baseline serum-free testosterone or estradiol concentrations. Alendronate reduced the incidence of vertebral fractures and prevented decreases in height. It was generally well tolerated.</p> <p>NOTES: analysis by intention-to-treat (all men with BMD at baseline and at least once after randomization); approx. 98% of men were white; in addition to 14 withdrawals for adverse effects, 14 withdrew for personal reasons and 5 were lost to follow-up; study was conducted at 20 centers worldwide</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria defined; patients appeared to have volunteered for study; same observation schedule for both treatment groups; no indication of sample size estimation; double-blind study; analysis by intention-to-treat (see NOTES); groups comparable at baseline; fracture data reported; compliance not reported</i></p>
	Placebo	Alendronate																						
Lumbar spine	1.8%	7.1%*																						
Femoral neck	-0.1%	2.5%*																						
Trochanter	1.3%	4.3%*																						
Hip	0.6%	3.1%*																						
Total body	0.4%	2.0%*																						



## Conclusion Grading Worksheet C – Annotation #15 (Bisphosphonates for Glucocorticoid-Induced Bone Loss)

**Work Group's Conclusion:** Clinical trial data supports the use of oral bisphosphonates for reducing bone loss in men and women diagnosed with glucocorticoid-induced bone loss. The best clinical trials have been done with alendronate (Fosamax®) and risedronate (Actonel®).

**Conclusion Grade: II**

**Work Group's Conclusion:** Clinical trial data suggests that oral bisphosphonates may reduce fracture risk in men and women diagnosed with glucocorticoid-induced bone loss.

**Conclusion Grade: III**

Author/Year	Design Type	Class	Quality +,-,0	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Saag, et al. (1998)	RCT	A	0	-Men and women, 17-83 yrs of age, underlying diseases requiring oral glucocorticoid therapy (≥1 yr) of at least 7.5 mg prednisone or equivalent -Excluded: evidence of metabolic bone disease (other than glucocorticoid-induced or postmenopausal osteoporosis); low serum vitamin D; treatment with drugs that affect bone turnover (HRT was permitted with same dose throughout study); pregnancy or lactation; renal insufficiency, severe cardiac disease, major upper GI disease (past year) -Randomized to alendronate (2.5 mg/d, 5 mg/d, 10 mg/d) or placebo; treatment for 48 weeks; all received 800-1000 mg/d calcium and 250-500 IU/d vit D -BMD of lumbar spine, hip, and total body at baseline, 12, 24, 36, and 48 wks -Spine x-rays baseline, 48 wks	-477 patients randomized to either 5 mg/d (n=161) or 10 mg/d (n=157) of alendronate or placebo (n=159); no differences between groups at baseline -At baseline, 32% had osteoporosis (lumbar spine BMD >2SD below peak for healthy young adults) -At 48 wks, BMD of both alendronate groups increased significantly at lumbar spine, trochanter, and femoral neck (total body BMD increased for 10 mg/d group only) (all p<0.01 vs. baseline and vs. placebo) -Changes in lumbar spine BMD were not significantly affected by duration of prior therapy, underlying disease, sex, or menopausal status -17% of placebo group and 15% in alendronate groups had vertebral fractures at baseline; new fractures during the 48 wk study were uncommon; postmenopausal women experienced 82% of fractures with a trend (p=0.05) toward a higher percentage in placebo group -Incidence of non-vertebral fractures did not differ between groups -Incidence of adverse effects that were serious or led to withdrawal from study was similar in the two groups	-Alendronate significantly increased lumbar spine, hip, and total-body BMD in patients receiving glucocorticoid therapy. The efficacy of alendronate did not differ according to previous duration or current dose of corticosteroid therapy.  NOTES: 2 parallel studies – a) 232 patients, 15 centers in U.S.; b) 328 patients, 22 centers in 15 other countries; 83 patients (non-U.S.) randomized to 2.5 mg/d alendronate – these patients excluded from analysis; analysis by intention-to-treat (excluded data from patients who violated protocol)  <i>Work Group's Comments: Inclusion/exclusion criteria defined; patients appeared to have volunteered for study; same observation schedule for both treatment groups; no indication of sample size estimation; double-blind study; analysis reported to be by intention-to-treat (see NOTES); groups comparable at baseline; fracture data reported; compliance not reported; unclear why BMD analysis included 433 patients</i>

**Conclusion Grading Worksheet C – Annotation #15**  
**(Bisphosphonates for Glucocorticoid-Induced Bone Loss)**

Author/Year	Design Type	Class	Quality	Population Studied/Sample Size	Primary Outcome Measure(s)/Results (e.g., p-value, confidence interval, relative risk, odds ratio, likelihood ratio, number needed to treat)	Authors' Conclusions/ <i>Work Group's Comments (italicized)</i>
Cohen, et al. (1999)	RCT	A	+,-,0	<p>-Ambulatory patients; 18-85 yrs of age; began taking corticosteroids (<math>\geq 7.5</math> mg/day prednisone or equivalent) for underlying disease within past 3 mos &amp; expected to continue for another 12 mos; women at least 1 yr postmenopausal, surgically sterile, or using birth control</p> <p>-Excluded: history of hyperparathyroidism, hyperthyroidism, or osteomalacia in past yr; drugs known to affect bone metabolism in past year; any treatment with corticosteroids prior to current therapy; condition that interferes with evaluation of lumbar spine BMD</p> <p>-Randomized to receive risedronate (2.5 mg/d or 5 mg/d) or placebo for 12 mos; all received 500 mg/d calcium</p> <p>-BMD of lumbar spine, femoral neck, and trochanter, at baseline, 3, 6, and 12 mos; radius at baseline and 12 mos</p> <p>-Spine x-rays baseline, 12 mos</p>	<p>-228 patients randomized (77 to placebo, 75 to 2.5 mg/d risedronate, 76 to 5 mg/d risedronate); groups were similar at baseline except 5 mg/d group older than other 2 groups (p=0.02)</p> <p>-150 completed 12 mos (57 placebo, 31 2.5 mg/d risedronate, 62 5 mg/d risedronate)</p> <p>-Lumbar spine, femoral neck, and trochanter BMD decreased at 12 mos in placebo group (p&lt;0.05 at each site vs. baseline)</p> <p>-Lumbar spine and femoral neck BMD maintained at 12 mos and trochanter BMD increased (p&lt;0.05 vs. baseline) at 12 mos in 5 mg/d risedronate group (all p&lt;0.001 vs. placebo)</p> <p>-In 2.5 mg/d risedronate group, BMD did not increase from baseline; 12-month values at lumbar spine and trochanter differed from placebo (p&lt;0.005)</p> <p>-BMD of radius did not change in any treatment group at 12 mos</p> <p>-Adjustment for mean dose and duration of therapy did not affect results</p> <p>-Non-vertebral fractures occurred in 5.2% of placebo group, 4% of 2.5 mg/d group, and 3.9% of 5 mg/d group</p> <p>-New vertebral fractures occurred in 17% of placebo group, 11% of 2.5 mg/d group, and 5.7% of 5 mg/d group (NS)</p> <p>-Percentages reporting adverse events, serious adverse events, and dropout due to adverse events were similar in the 3 groups</p>	<p>-Daily oral risedronate therapy prevented significant bone loss relative to placebo therapy in patients initiating long-term glucocorticoid therapy for a variety of disorders. Risedronate was well tolerated.</p> <p>NOTES: 2.5 mg/d dose discontinued based on other studies (majority completed 6 mos of treatment and &gt;40% completed 12 mos); 74 withdrew before completing 12 mos (19 in placebo group, 42 in 2.5 mg group, 13 in 5 mg group); did analyses by intention-to-treat (with patients receiving at least 1 dose of study drug up to time of withdrawal or study completion) and by carrying the last observation forward; study was conducted at 28 centers in the U.S. and Canada</p> <p><i>Work Group's Comments: Inclusion/exclusion criteria defined; patients appeared to have volunteered for study; same observation schedule for both treatment groups; no indication of sample size estimation (but not powered to show fracture reduction); double-blind study; analysis by intention-to-treat (see NOTES); groups comparable at baseline (except age); fracture data reported; compliance not reported; missing BMD and fracture data</i></p>

This section provides resources, strategies and measurement specifications for use in closing the gap between current clinical practice and the recommendations set forth in the guideline.

The subdivisions of this section are:

- Priority Aims and Suggested Measures
  - Measurement Specifications
- Key Implementation Recommendations
- Knowledge Products and Resources
- Other Resources Available

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## Priority Aims and Suggested Measures

1. Improve diagnostic and therapeutic follow-up of adults presenting with a history of low-impact fracture. (Refer to Algorithm Box 2)

Possible measures for accomplishing this aim:

- a. Percentage of adults presenting with a history of low-impact fracture who have had bone densitometry.
  - b. Percentage of postmenopausal women and men with a history of low-impact fracture evaluated and offered treatment for osteoporosis.
  - c. Percentage of adults with a history of low-impact fracture offered treatment undergoing evaluation for secondary causes of osteoporosis.
  - d. Percentage of adults with a history of low-impact fracture with documentation of discussion with a health care provider of osteoporosis risk offered treatment for osteoporosis.
  - e. Percentage of adults with a low-impact fracture on therapy for osteoporosis with documentation of calcium and vitamin D intake meeting the minimum thresholds for treatment.
2. Increase the evaluation for osteoporosis risk factors in all adults presenting for a preventive visit.

Possible measures for accomplishing this aim:

- a. Percentage of patients presenting for a preventive visit with documentation of assessment of risk factors for osteoporosis.
- b. Percentage of patients at risk for fracture presenting for a preventive visit who are offered bone densitometry.
- c. Percentage of patients presenting for a preventive visit with documentation that vitamin D and calcium issues have been addressed.

At this point in development for this guideline, there are no specifications written for possible measures listed above. ICSI will seek input from the medical groups on what measures are of most use as they implement the guideline. In a future revision of the guideline, measurement specifications may be included.

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# Knowledge Products and Resources

## Criteria for Selecting Resources

The following resources were selected by the *Diagnosis and Treatment of Osteoporosis* guideline work group as additional resources for providers and/or patients. The following criteria were considered in selecting these resources.

- The site contains information specific to the topic of the guideline.
- The content is supported by evidence-based research.
- The content includes the source/author, and contact information.
- The content clearly states revision dates or the date the information was published.
- The content is clear about potential biases, noting conflict of interest and/or disclaimers as appropriate.

## Resources Available to ICSI Members Only

The following materials are available to ICSI members only. Also available is a wide variety of other knowledge products including tool kits on CQI processes and Rapid Cycling that can be helpful. To obtain copies of these or other Knowledge Products, go to <http://www.icsi.org/knowledge>.

To access these materials on the Web site you must be logged in as an ICSI member.

### Recorded Presentations

#### Video

- Osteoporosis – Be Informed (HealthEast Care System)
- Hormone Therapy – Clinical Evidence Roundtable
- Osteoporosis – Clinical Evidence Roundtable

### Educational Resources

#### Guideline Pilot Reports

- Osteoporosis Guideline Pilot Report

#### Patient Education PDFs

- Osteoporosis (by Park Nicollet Health Services)

## Other Resources Available

Title/Description	Audience	Author/Organization	Websites/Order Information
Professional organization site	Professionals and public	American Academy of Orthopedic Surgeons	<a href="http://www.aaos.org">http://www.aaos.org</a>
Professional organization site	Arthritis and related disorders/ professionals	American College of Rheumatology	<a href="http://www.rheumatology.org">http://www.rheumatology.org</a>
Professional organization site	General medical/ professionals	American Medical Association	<a href="http://www.ama-assn.org">http://www.ama-assn.org</a>
Current information about osteoporosis and research	Osteoporosis/public and professionals	Foundation for Osteoporosis Research and Education	<a href="http://www.fore.org">http://www.fore.org</a>
International organization site	Osteoporosis/public and professionals	International Osteoporosis Foundation	<a href="http://www.osteofound.org">http://www.osteofound.org</a>
Professional organization site	Public and professionals	International Society of Clinical Densitometry	<a href="http://www.iscd.org">http://www.iscd.org</a>
Women's health information	Women's health/ public	Mayo Health Oasis Women's Health Resource	<a href="http://www.mayoclinic.org">http://www.mayoclinic.org</a>
General information about osteoporosis prevention and treatment	Osteoporosis/public and professionals	National Osteoporosis Foundation	<a href="http://www.nof.org">http://www.nof.org</a>
Current information about osteoporosis and research	Osteoporosis and bone diseases/public and professionals	NIH - Osteoporosis and Related Bone Diseases Resources Center	<a href="http://www.osteoporosis.nih.gov">http://www.osteoporosis.nih.gov</a>
Professional organization site	Menopause-related topics/ public and professionals	North American Menopause Society	<a href="http://www.menopause.org">http://www.menopause.org</a>
Professional journal	Professionals	North American Menopause Society	<a href="http://www.menopausejournal.com">http://www.menopausejournal.com</a>
Be Bone Wise - Exercise; Video on weight-bearing and strength-training exercises	Public and professionals	National Osteoporosis Foundation	National Osteoporosis Foundation 202/223-2226
The Osteoporosis Book (1999); book on prevention and treatment of osteoporosis	Public and professionals	Nancy E. Lane, MD	Oxford University Press
Boning Up On Osteoporosis	Public	National Osteoporosis Foundation	National Osteoporosis Foundation 202/223-2226

**Other Resources Available**

<b>Title/Description</b>	<b>Audience</b>	<b>Author/Organization</b>	<b>Websites/Order Information</b>
Osteoporosis Handbook (2000); book on prevention and treatment of osteoporosis	Public	Sydney Bonnick, MD	Taylor Publishing
Strong Women, Strong Bones (2000); book on prevention of osteoporosis	Public	Miriam Nelson, PhD	Putnam Publishing Group
Men with Osteoporosis (2000); pamphlet on osteoporosis treatment for men	Public	National Osteoporosis Foundation	National Osteoporosis Foundation #B111 202/223-2226
Tiene sus huesos sanos?; Spanish language pamphlet on risk factors, prevention, diagnosis and treatment of osteoporosis	Public	National Osteoporosis Foundation	National Osteoporosis Foundation #B141 202/223-2226
How Strong Are Your Bones? (2000); booklet on bone health assessment	Public	National Osteoporosis Foundation	National Osteoporosis Foundation #B108 202/223-2226
Skeletal Changes; 14-page booklet describing the role of the skeletal system and possible complications that can occur including osteoporosis	Public	Mayo Clinic	Mayo Clinic Order #MC2151-46