ICSI

Institute for Clinical Systems Improvement

Health Care Guideline

The information contained in this *ICSI Health Care Guideline* is intended primarily for health professionals and the following expert audiences:

- physicians, nurses, and other health care professional and provider organizations;
- health plans, health systems, health care organizations, hospitals and integrated health care delivery systems;
- medical specialty and professional societies;
- researchers;
- federal, state and local government health care policy makers and specialists; and
- employee benefit managers.

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This *ICSI Health Care Guideline* is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. An *ICSI Health Care Guideline* rarely will establish the only approach to a problem.

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INSTITUTE FOR CLINICAL SYSTEMS IMPROVEMENT

Health Care Guideline:

Diagnosis and Treatment of Osteoporosis

BONE HEALTH ALGORITHM

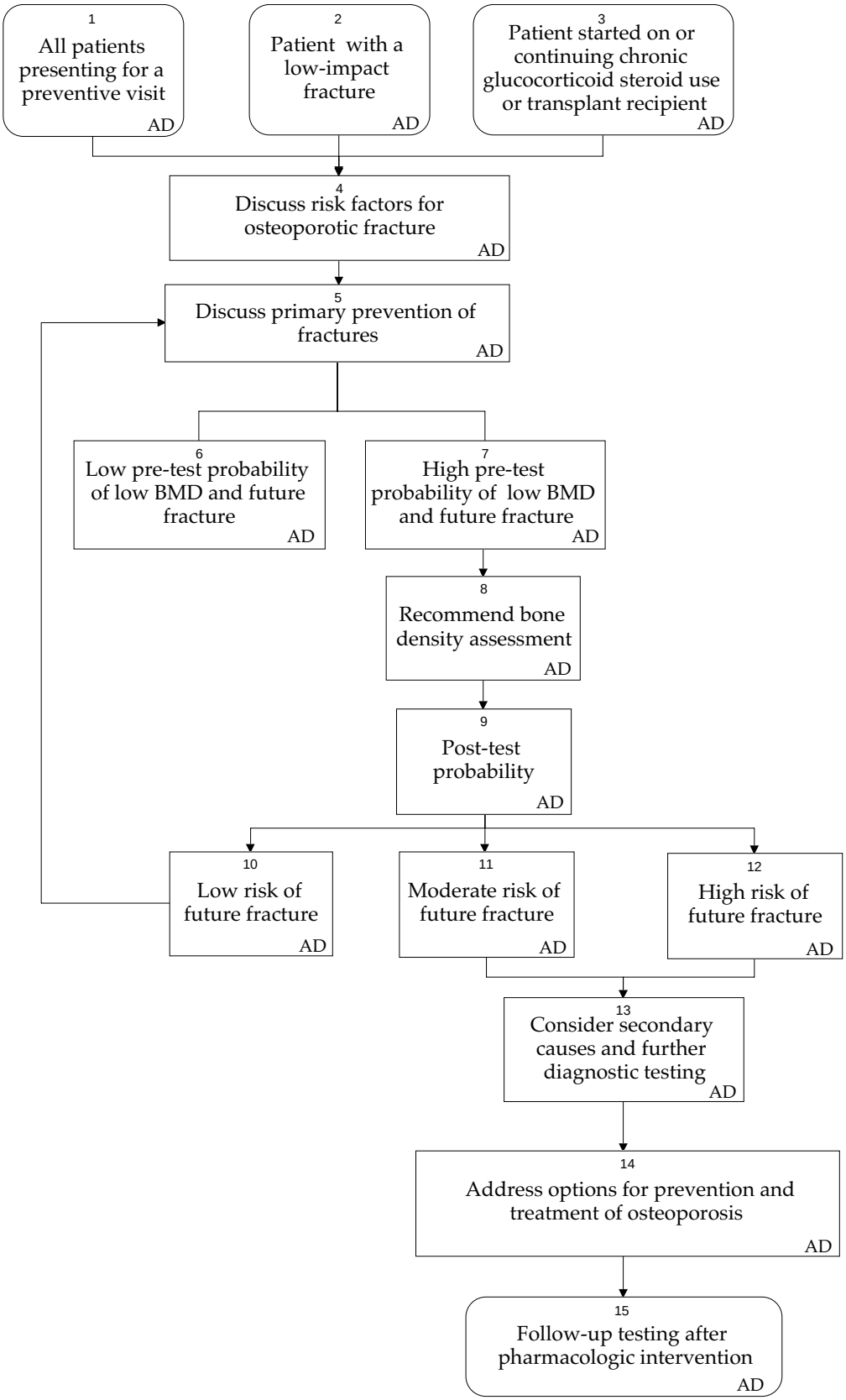

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Table of Contents

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.

Related ICSI Scientific Documents

Another ICSI guideline whose scope and/or recommendations are closely related to the content of this guideline is:

1. Hormone Replacement Therapy: Collaborative Decision Making and Management

Technology Assessment Reports related to the content of this guideline:

1. Report #53 "Biochemical Markers for Bone Turnover in Osteoporosis"
2. Report #31 "Densitometry as a Diagnostic Tool for the Identification and Treatment of Osteoporosis in Women"

Clinical Highlights for Individual Clinicians

1. Discuss risk factors for osteoporosis, and primary prevention with all patients presenting for preventive health visits. (*Annotations #4, 5*)
2. Patients with a high pretest probability of low BMD and future fracture should have bone density testing to further define their fracture risk. (*Annotations #7,8,13,15)*
3. 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 #14)*

Priority Aims and Suggested Measures for Health Care Systems

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 identified as having low bone mass offered treatment for osteoporosis.

   c. Percentage of adults with a history of low impact fracture offered treatment for osteoporosis.

   d. Percentage of adults with a history of low impact fracture with documentation of discussion with a health care provider of osteoporosis risk.

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 who have had bone densitometry.

3. Increase follow-up testing of patients on long-term hormone replacement therapy (HRT).

   Possible measure for accomplishing this aim:

   a. Percentage of patients on long-term HRT who have had follow-up bone densitometry.

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, IV.

A full explanation of these designators is found in the Discussion and References section of the guideline.

ALGORITHM ANNOTATIONS

1. All Patients Presenting for a Preventive Visit

Osteoporosis is the consequence of continued bone loss throughout adulthood. We recommend maintaining peak bone mass for all patients. To achieve this, patients should have risks for osteoporosis reviewed when they present to their provider offices. In addition to reviewing historical risk factors (discussed in Annotation #4), 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 thoracic and lumbar spine radiographs and bone density testing.

Evidence supporting this recommendation is of class: R

2. Patient With a Low-Impact Fracture

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, including fragility fractures occurring 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 and may be an indication for bone density testing. This historical risk factor provides information that may be additive to bone mineral density information. There are three possible hypotheses to explain this increased risk. First, risk factors for the development of one fracture are still operative to increase susceptibility to a second and subsequent event. Second, the occurrence of a fracture, particularly in the limbs, is followed by bone loss, not completely reversible, which could lead to an increased risk of subsequent fracture. Finally, there may be mechanical influences caused by having had one fracture, and it may be these mechanical effects that increase this subsequent risk.

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, and fall prevention;
- Consider bone density testing in fracture patients willing to accept treatment;
- Consider all men* and postmenopausal women with low impact fracture as candidates for osteoporosis treatment;
- Adults 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 LJ III, Atkinson EJ, O'Connor MK, et al. "Bone density and fracture risk in men." *J Bone Mineral Res* 13:1915-23,1998.]

Evidence supporting this recommendation is of classes: A, B, C, D, M, R

3. Patient Started On or Continuing Chronic Glucocorticoid Steroid Use or Transplant Recipient

Glucocorticoid Steroid Use

Osteoporosis prevention and treatment measures and bone mineral density testing should be considered for anyone who is started on or has been on exogenous systemic glucocorticoid therapy (at a dose of more than 7 mg of prednisone per day or equivalent per day for 3 or more months). 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 at the time glucocorticoids are commenced, because the greatest amount of bone is lost during the first several months of glucocorticoid use. Osteoporosis prevention measures should also be considered for those who have been or can be expected to be on daily use high-dose inhaled glucocorticoids for several years.

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.

Evidence supporting this recommendation is of classes: C, D

4. Discuss Risk Factors for Osteoporotic Fracture

The following are risk factors for osteoporotic fracture:

- Female
- Advanced age (greater than 65)
- Body habitus (weight less than 127 pounds; or BMI ≤ 20)
- Caucasian or Asian race
- Family history of osteoporosis
- Hypogonadism (estrogen or testosterone deficiency)
- Sedentary lifestyle
- Smoking (greater than or equal to than one pack per day)
- Excessive alcohol intake (greater 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 Annotation Appendix A, "Secondary Causes of Osteoporosis".

Evidence supporting this recommendation is of classes: A, B, M, R

5. Discuss Primary Prevention of Fractures

Body Habitus

Patients should be counseled that a BMI of less than 20, or weight less than 127 pounds increases their risk of osteoporotic fractures.

Evidence supporting this recommendation is of class: B

Gonadal Hormonal Status

Patients who are deficient in estrogen or testosterone are at increased risk for fracture and should be offered replacement therapy. For further information, please see Discussion #13, "Consider Secondary Causes and Further Diagnostic Testing" as well as Discussion #14, "Address Options for Prevention or 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.

Evidence supporting this recommendation is of classes: 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.

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.

Evidence supporting this recommendation is of class: R

Calcium

Adequate calcium intakes from food sources and supplements promote bone health. Calcium also supports estrogen's positive effect on 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 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 use, pregnant or nursing women, or persons over the age of 65, it may be more appropriate to recommend 1500 mg.

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

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

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

Prevention of Falls

Preventing falls reduces fractures and fracture risk. Modifying environmental and personal risk factors can be effective in reducing falls. Home visits may help with this. Soft hip protector pads have been shown to reduce hip fractures in frail, elderly adults in community-based health care centers.

Evidence supporting this recommendation is of classes: A, 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

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

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 7.5 mg prednisone per day

3. Radiographic osteopenia, or vertebral deformity consistent with fracture
4. All women greater than 65 years of age
5. Postmenopausal women less than age 65 with one of the following additional risk factors:
    a. Body weight less than 127 lbs or BMI ≤ 20
    b. History of fracture after age 45 in a first degree relative
    c. Current smoker (one pack or more per day)
    d. Not using hormone replacement therapy
    e. Surgical menopause, or natural menopause before age 40
    f. On hormone replacement therapy greater than 10-15 years
6. Chronic diseases known to be associated with bone loss (see Annotation 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. Transplant recipient

Evidence supporting this recommendation is of classes: C, D, M, R

8. Recommend Bone Density Assessment

Measurements of BMD 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 increases in BMD with therapy for osteoporosis lead to substantial reductions in fracture incidence. Therefore, densitometry offers an objective measurement of a patient's response to treatment over time.

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 young adult healthy population. A T-score is calculated from the following equation:

[(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 an age- and sex-matched healthy population. A Z-score is calculated from the following equation:

[(measured BMD - age-matched population mean BMD) / age-matched population SD]

Normal, osteopenia, and osteoporosis are defined by the T-score, according to the World Health Organization. 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.
- 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 both a fragility fracture(s) *and* a T-score less than or equal to -2.5.

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.

Evidence supporting this recommendation is of classes: C, M, R

9. Post-Test Probability

The result of the bone mineral density test is the best single predictor of future fracture risk.

Evidence supporting this recommendation is of classes: B, C

10. 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).

Evidence supporting this recommendation is of classes: B, R

11. Moderate Risk of Future Fracture

Moderate fracture risk is clinically defined by a bone mineral density T-score below -1.0 and above -2.5 (osteopenia by the WHO definition).

Evidence supporting this recommendation is of classes: B, R

12. High Risk of Future Fracture

High fracture risk is clinically defined by a bone mineral density T-score below -2.5 (osteoporosis density by the WHO definition).

Evidence supporting this recommendation is of classes: B, R

13. Consider Secondary Causes and Further Diagnostic Testing

A minimum screening laboratory profile should be considered in all patients with osteoporosis. Expert opinion in the literature varies regarding the degree of laboratory investigation indicated in the osteoporotic patient with a bone density at the age-matched value, but it is agreed that a more extensive evaluation is indicated to look for a potentially reversible cause of lower than expected bone density (Z-score less than or equal to -1). See discussion section for additional information on lab testing.

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 Annotation Appendix A, "Secondary Causes of Osteoporosis." In broad categories, these include chronic inflammatory autoimmune conditions, endocrinopathies, malignancies, and malabsorptive states.

Evidence supporting this recommendation is of class: R

14. Address Options for Prevention and Treatment of Osteoporosis

Please see the medication tables in Annotation Appendix B, "Recommended Pharmacologic Agents" and Discussion #14 for specific information on pharmacologic agents for treatment and prevention of osteoporosis.

In addition to pharmacological agents for osteoporosis all patients should supplement their dietary intake of calcium and vitamin D if it is not adequate (see Annotation #5). Physical therapy may also be considered.

Osteoporosis Prevention

Estrogen is considered first line therapy for prevention of osteoporosis in postmenopausal women. 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 and calcitonin.

Excellent clinical trial data supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal osteopenia or osteoporosis. The best clinical trials have been done with alendronate (Fosamax®) and risedronate (Actonel®). *[Conclusion Grade I: See Discussion Appendix B, Conclusion Grading Worksheet – Annotation #14 (Bisphosphonates for Primary Osteoporosis)].*

Good clinical trial data support the use of alendronate for preventing bone loss in men diagnosed with osteoporosis. *[Conclusion Grade I: See Discussion Appendix B, Conclusion Grading Worksheet – Annotation #14 (Bisphosphonates for Primary Osteoporosis)].*

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 Discussion Appendix C, Conclusion Grading Worksheet – Annotation #14 (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 Discussion Appendix C, Conclusion Grading Worksheet – Annotation #14 (Bisphosphonates for Glucocorticoid-Induced Bone Loss)].*

Post-transplantation Bone Loss

Antiresorptive therapy may be effective at preventing bone density loss after transplantation. Considering the rates of bone loss after transplantation described in Annotation #3, bone mineral density testing should be performed every 6 months 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 pamidronate or oral alendronate are more likely to prevent bone loss after transplantation.

Alternative and Complementary Agents for Prevention and Treatment of Osteoporosis

There is preliminary 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 eicosopentanoic 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.

Evidence supporting this recommendation is of classes: A, B, C, D, M

15. Follow-Up Testing After Pharmacologic Intervention

Sequential bone density testing may be used to monitor antiresorptive therapy. The key factor is understanding that this tool is limited by the calculated precision of the machine and operator at a particular body site. It is imperative that a central site (lumbar spine and/or total hip) be used for follow-up testing to provide information about a change in BMD. There is not adequate data to recommend using any peripheral site for follow-up bone density testing, including forearm DXA, calcaneal DXA or calcaneal ultrasound. The best follow-up evaluation will be done on the same or similar bone density machine by the same trained bone density technologist.

Despite its limitations, bone density testing with DXA, with coefficients of variation in the range of 1%-2%, remains one of the most precise measurements used in medical practice. Controversy exists as to whether follow-up testing is necessary in all patients, but if it is performed, it should be done after one to two years of therapy. In patients at particularly high risk for accelerated bone loss, such as the glucocorticoid-treated patient or a woman in early menopause who is not using estrogen replacement, follow-up bone density testing may be indicated annually.

Evidence supporting this recommendation is of classes: A, C, D, M, R

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

Secondary Causes of Osteoporosis

I. Endocrine Disorders

- **A. Cushing's syndrome**
- **B. Male or female hypogonadism**
  1. Hyperprolactinemia
  2. Turner's syndrome
  3. Klinefelter's syndrome
  4. Surgical menopause
  5. Other causes of hypogonadism
- **C. Hyperthyroidism**
- **D. Primary hyperparathyroidism**
- E. Type 1 diabetes mellitus
- F. Growth hormone deficiency
- G. Addison's disease
- H. Acromegaly

II. Rheumatologic Disorders

- **A. Rheumatoid arthritis**
- **B. Systemic lupus erythematosus**
- **C. Ankylosing spondylitis**
- **D. Juvenile polyarticular arthritis**

III. Malignancy

- A. Multiple myeloma
- B. Leukemia
- C. Systemic mastocytosis

IV. Pharmacotherapy

- **A. Glucocorticoid excess**
- **B. L-thyroxine over-replacement**
- **C. Anticonvulsants (phenytoin or phenobarbital)**

D. Intravenous heparin

E. Drugs causing hypogonadism

1. Chemotherapy (methotrexate or other antimetabolites)
2. Gonadotropin-releasing hormone (GnRH) agonists (buserelin, leuprolide, nafarelin)
3. Depot progesterone injections

F. Chronic lithium therapy

G. Chronic phosphate binding (aluminum-containing) antacids

H. 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:

A. (Primary biliary cirrhosis)

VI. Gastrointestinal disease

A. Inflammatory bowel disease (Crohn's disease in particular)

B. Celiac disease

C. Gastrectomy or intestinal bypass surgery

D. Pernicious anemia

VII. Renal insufficiency or failure

VIII. Miscellaneous causes

A. Vitamin D deficiency of any cause

B. Alcohol abuse

C. Anorexia nervosa

D. Movement disorders (Parkinson's disease)

E. Chronic obstructive pulmonary disease

F. Sarcoidosis

G. Amyloidosis

H. Hemophilia

I. Hemochromatosis

J. Idiopathic scoliosis

K. Pregnancy and lactation (reversible)

L. Endometriosis

M. Epidermolysis bullosa

N. Prolonged parenteral nutrition

O. Lactose intolerance

P. Lacto-Vegetarian dieting

IX. Immobilization

A. Spinal cord syndromes

B. Space flight

C. Prolonged bedrest or wheelchair bound from any cause

X. Genetic Diseases

A. Osteogenesis imperfecta

B. Ehlers-Danlos syndrome

C. Marfan's syndrome

D. Homocystinuria

E. Menkes' syndrome

F. Riley-Day syndrome (familial dysautonomia)

G. Multiple sclerosis

H. Gaucher's disease and other glycogen storage diseases

I. Sickle-cell anemia

J. Thalassemia

K. Hypophosphatasia

L. Congenital porphyria

M. Mitochondrial myopathies

XI. Idiopathic causes

A. Juvenile osteoporosis

B. Idiopathic osteoporosis of young adults

C. Regional osteoporosis: reflex sympathetic dystrophy, transient osteoporosis of the hip, or regional migratory osteoporosis

RECOMMENDED PHARMACOLOGIC AGENTS FOR OSTEOPOROSIS

Medication	Indications	Dose/Administration	Reduction in Fracture Risk[2]	AWP[3] Cost for 30 Days
Bisphosphonates				
Alendronate (Fosamax®)	TREATMENT • Postmenopausal osteoporosis • Increase bone mass in men with osteoporosis • Glucocorticoid-induced osteoporosis in men and women PREVENTION • Postmenopausal osteoporosis	TREATMENT • 10 mg once daily or one 70 mg tablet weekly • Glucocorticoid-induced osteoporosis is 5 mg once daily. For postmenopausal women not receiving estrogen the dose is one 10 mg once daily. PREVENTION • Postmenopausal osteoporosis is 5 mg once daily or one 35 mg tablet weekly *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.*	Vertebral: +++ Nonvertebral: ++ Hip: +++	• 5 mg: $70 • 10 mg: $70 • 35 mg: $65 (4 tablets) • 70 mg: $65 (4 tablets)
Risedronate (Actonel®)	TREATMENT • Postmenopausal osteoporosis • Glucocorticoid-induced osteoporosis PREVENTION • Postmenopausal osteoporosis •Glucocorticoid-induced osteoporosis	TREATMENT and PREVENTION • 5 mg daily *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.*	Vertebral: +++ Nonvertebral: ++ Hip: +++	• 5 mg: $59
Selective Estrogen Receptor Modulator (SERM)				
Raloxifene (Evista®)	TREATMENT • Postmenopausal osteoporosis PREVENTION • Postmenopausal osteoporosis	TREATMENT and PREVENTION • 60 mg daily	Vertebral: ++ Nonvertebral: - Hip: -	• 60 mg: $66
Calcitonin				
Calcitonin-salmon (Miacalcin® injection and nasal spray, Calcimar® injection, Salmonine® injection, Osteocalcin® injection)	TREATMENT • Postmenopausal osteoporosis	• Injection: 100 IU IM or SC every other day • Nasal spray: 200 IU intranasally daily, alternate nostrils daily	Vertebral: + Nonvertebral: - Hip: -	• Injection: $155 • Nasal spray: $64
Estrogens[4]	**Please refer to the ICSI HRT and Management of Menopause guideline for more brand specific information on estrogens**			
Estrogens	PREVENTION • Postmenopausal osteoporosis	• Varies by manufacturer	Vertebral: N/A Nonvertebral: N/A	• Varies by manufacturer

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

3 AWP = average wholesale price (* indicates a generic is available) Prices current as of 4/02

4 Women with a uterus must also take a progestin to prevent endometrial cancer

TREATMENTS NOT FDA APPROVED FOR OSTEOPOROSIS

Medication	Comments
Bisphosphonates	
Etidronate (Didronel®)	Low oral absorption. Inconvenient dosing cycle but is the least expensive bisphosphonate.
Pamidronate (Aredia®)	Available only as an injectable dosage form.
Zoledronic Acid (Zometa®)	A potent bisphosphonate indicated for hypercalcemia of malignancy.
Others	
Calcitriol (Rocaltrol®)	Insufficient data.
Ergocalciferol (Calciferol®)	Insufficient data. Increase in bone mineral density.
Nandrolene deconoate	Insufficient data. Adverse effects would limit use.
Parathyroid hormone (PTH)	Studies completed. Pending FDA approval.
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.

RALOXIFENE FOR OSTEOPOROSIS

A new group of medications, SERMs (Selective Estrogen Receptor Modulators), has been developed to prevent osteoporosis in women after menopause. The first SERM to be approved by the FDA for this purpose is raloxifene (Evista®).

What are the effects?

Raloxifene has estrogen-like effects in different areas of the body, but does not appear to have some of the serious risks as estrogen. These effects include:

- reducing bone loss and improving bone mineral density, i.e., "bone-building
- prevention of osteoporosis-related vertebral fractures
- possible protection against heart disease
- decreased risk of breast cancer
- improving serum lipid profiles: decreases total and LDL ("bad") cholesterol as well as oral estrogen does; does not increase HDL ("good") cholesterol, but does not increase serum triglycerides as oral estrogen does
- Raloxifene will not treat hot flashes, and may worsen them. It is not effective to treat vaginal atrophy or spotting.

What are the indications?

The indication for raloxifene is for the prevention and treatment of osteoporosis.

What are the contraindications?

Women should not take raloxifene if:

- they are premenopausal or perimenopausal
- they have a history of certain types of blood clots

What are the possible side effects?

Hot flashes may worsen and leg cramps are reported side effects of raloxifene. There have been no reports of breast pain or breast enlargement.

What is the recommended dosage?

The usual dose is a 60 mg tablet of raloxifene (Evista®) to be taken every day. This tablet can be taken at any time of the day, with or without meals. It is also recommended that all postmenopausal women get enough calcium (1500 mg) and Vitamin D (400-800 I*u*) through diet and supplements.

Please discuss individual questions with your health care staff.

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In the interest of full disclosure, ICSI has adopted a policy of revealing relationships work group members have with companies that sell products or services that are relevant to this guideline topic.

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All other work group members: none declared

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-benefit analysis
Cost-effectiveness study

Class R: Narrative review
Consensus statement
Consensus report

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 ø 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 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 uncertainty attached to the conclusion because of inconsistencies among the results from different 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.

Grade IV: The support for the conclusion consists solely of the statements of informed medical commentators based on their clinical experience, unsubstantiated by the results of any research studies.

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

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

– indicates that these issues have not been adequately addressed;

ø indicates that the report is neither exceptionally strong or exceptionally weak;

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

1. All Patients Presenting for a Preventive Visit

Osteoporosis is the consequence of continued bone loss throughout adulthood. We recommend maintaining peak bone mass for all patients. To achieve this patients should have risks for osteoporosis reviewed when they present to their provider offices. In addition to reviewing historical risk factors (discussed in Annotation #4), standing height should be measured using an accurate stadiometer for initial and repeat measurements and posture should be observed for kyphosis. Patients with significant acquired kyphosis and/or a height loss of one inch (or two inches based on patient recollection) should have thoracic and lumbar spine radiographs and BMD testing.

"Osteoporosis prevention, diagnosis, and therapy: NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy." *JAMA* 285:785-95, 2001. (Class R)

2. Patient With a Low-Impact Fracture

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. 25% 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. Published clinical guidelines specify that patients with the presence of a vertebral compression facture have an increased risk for subsequent fracture.

Kanis JA, Delmas P, Burckhardt P, et al on behalf of the European Foundation for Osteoporosis and Bone Disease. "Guidelines for diagnosis and management of osteoporosis." *Osteoporos Int* 7:390-406, 1997. (Class R)

Lindsay R, Silverman SL, Cooper C, et al. "Risk of new vertebral fracture in the year following a fracture." *JAMA* 285:320-23, 2001. (Class B)

National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Washington DC: National Osteoporosis Foundation, 1999. (Class R)

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. Other studies support this observation.

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)

Black DM, Arden NK, Palermo L, et al for the Study of Osteoporotic Fractures Research Group. "Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures." *J Bone Miner Res* 14:821-28, 1999. (Class B)

Davis JW, Grove JS, Wasnich RD, Ross PD. "Spatial relationships between prevalent and incident spine fractures." *Bone* 24:261-64, 1999. (Class B)

Huopio J, Kroger H, Honkanen R, et al. "Risk factors for perimenopausal fractures: a prospective study." *Osteoporos Int* 11:219-27, 2000. (Class B)

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.

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. 92% 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 1,0000 women.

Schroder HM, Petersen KK, Erlandsen M. "Occurrence and incidence of the second hip fracture." *Clin Orthop* 289:166-69, 1993. (Class C)

Fractures of the wrist (Colles' fractures) can also be indicators of significant risk for osteoporosis or future fractures. 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. A retrospective case-control study of patients in Sweden who sustained non-osteoporotic fractures early in life was reported by Karlsson, et al. 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.

Earnshaw DA, Cawte SA, Worley A, Hosking DJ. "Colles' fracture of the wrist as an indicator of underlying osteoporosis in postmenopausal women: a prospective study of bone mineral density and bone turnover rate." *Osteoporos Int* 8:53-60, 1998. (Class D)

Gunnes M, Mellstrom D, Johnell O. "How well can a previous fracture indicate a new fracture? A questionnaire study of 29,802 postmenopausal women." *Acta Orthop Scand* 69:508-12, 1998. (Class C)

Wigderowitz CA, Rowley DI, Mole PA, et al. "Bone mineral density of the radius in patients with a Colles' fracture." *J Bone Joint Surg* 82:87-89, 2000. (Class C)

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 both alendronate and risedronate. The largest therapy-induced BMD increase is observed in patients with the lowest BMD and vertebral fractures, the population at highest risk.

Ettinger B, Black DM, Mitlak BH, et al. for the Multiple Outcomes Raloxifene Evaluation (MORE) Investigators. "Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial." *JAMA* 282:637-45, 1999. (Class A)

Hochberg MC, Ross PD, Black D, et al for the Fracture Intervention Trial Research Group. "Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis." *Arthritis Rheum* 42:1246-54, 1999. (Class C)

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 CM, Ross PD, Landsman PB, et al. "Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis." *J Bone Miner Res* 15:721-39, 2000. (Class M)

3. Patient Started On or Continuing Chronic Glucocorticoid Steroid Use or Transplant Recipient

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 AM, Bouquet J, Krenning EP, et. al. "Bone mineral density and nutritional status in children with inflammatory bowel disease." *Gut* 42:188-94, 1998. (Class D)

Lane NE, Lukert B. "The science and therapy of glucocorticoid-induced bone loss." *Endocrinol Metab Clin N Am* 27:465-481, 1998. (Class R)

Reid IR, Heap SW. "Determinants of vertebral mineral density in patients receiving long-term glucocorticoid therapy." *Arch Intern Med* 150:2545-48, 1990. (Class C)

Ruegsegger P, Medici TC, Anliker M. "Corticosteroid-induced bone loss. A longitudinal study of alternate day therapy in patients with bronchial asthma using quantitative computed tomography." *Eur J Clin Pharmacol* 25:615-20, 1983. (Class D)

Sinigaglia L, Nervetti A, Mela Q. "A multicenter cross-sectional study on bone mineral density in rheumatoid arthritis." *J Rheumatol* 27:2582-89, 2000. (Class D)

Varanos S, Ansell BM, Reeve J. "Vertebral collapse in juvenile chronic arthritis; its relationship with glucocorticoid therapy." *Calcif Tissue Int* 41:75-78, 1987. (Class C)

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 BJ. "Systemic adverse effects of inhaled corticosteroid therapy. A systematic review and meta-analysis." *Arch Int Med* 159:941-55, 1999. (Class M)

Lung Health Study Research Group, The. "Effect of inhaled triamcinolone on the decline of pulmonary function in chronic obstructive pulmonary disease." *N Engl J Med* 343:1902-09, 2000. (Class A)

Wong CA, Walsh LJ, Smith JP, et. al. "Inhaled corticosteroid use and bone mineral density in patients with asthma." *Lancet* 355:1399-1403, 2000. (Class D)

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 increased urinary calcium loss. Glucocorticoids reduce testosterone levels in men, and adrenal androgens in post-menopausal women.

The microanatomy and histomorphometry of glucocorticoid-osteoporosis differs from that of post-menopausal 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 post-menopausal osteoporosis, and greater decreases of indices of bone formation.

Aaron JE, Francis RM, Peacock M, Makins NM. "Contrasting microanatomy of idiopathic and corticosteroid-induced osteoporosis." *Clin Orthop Rel Res* 243:294-305, 1989. (Class C)

Dempster DW, Arlot MA, Meunier PJ. "Mean wall thickness and formation periods of trabecular bone packets in corticoid-induced osteoporosis." *Calcif Tissue Int* 35:401-17, 1983. (Class C)

Weinstein RS, Jilka RL, Parfitt AM, Manalagos SC. "Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids." *J Clin Invest* 102:274-82, 1998. (Class C)

Pretransplantation Bone Loss

Patients accepted for solid organ or allogenic 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.

Cardiac Transplantation

Leidig-Bruckner et al. followed 235 consecutive patients who underwent cardiac transplantation (105 patients, 88 men, 17 women) or liver transplantation (130 patients, 75 men, 55 women) for 4 years. Vertebral fractures were assessed by spinal radiographs at baseline and yearly after transplantation. Fifty-nine percent of the men who underwent cardiac transplantation, and 27% of the women, had normal lumbar spine bone mineral density at baseline. Fifty-one percent of the men who underwent liver transplantation, and 24% of the women, had normal lumbar spine bone mineral density at baseline. Vertebral fracture analysis showed that 21% of cardiac patients, and 14% of liver patients, had incident fractures in their first year after transplant, and that 27% of cardiac patients, and 21% of liver patients, had incident fractures by the second year after transplant. By the end of the fourth year, one-third of patients in both groups had one or more vertebral fractures. Non-vertebral fractures occurred in 9 liver transplant patients and hip avascular necrosis in 3 cardiac transplant patients. Fractures did not correlate with cumulative doses of immunosuppressive therapies. Predictors of vertebral fracture in cardiac transplant patients included age and baseline lumbar spine bone mineral density. The only predictor of vertebral fracture in liver transplant patients was pre-transplant vertebral fracture. The authors concluded that vertebral fractures are common after transplantation, and that reliable fracture risk predictors are limited, and suggested that preventive strategies need investigation.

Leidig-Bruckner G, Hosch S, Dodidou P, et al. "Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study." *Lancet* 357:342-47, 2001. (Class B)

Shane et al. followed 70 patients (52 men, 18 women) for 3 years after cardiac transplantation. All patients received supplementation with calcium 1,000 mg/day and vitamin D 400 IU/day. Patients lost 7.3% ± 0.9% of their lumbar spine bone mineral density and 10.5% ± 1.1% of their femoral neck bone mineral density during the first year after transplant. Lumbar spine bone mineral density decreased rapidly during the first 6 months, without further subsequent loss from 6-12 months, whereas femoral neck bone mineral density continued to decrease at an annualized rate of 8.2% ± 1.3% during the second half of the year. The rate of lumbar spine loss slowed to 0.9% ± 0.5%, and femoral neck to 0.1% ± 1.0%, during the second year posttransplant. Lumbar spine bone mineral density increased 2.4% ± 0.8%, whereas the femoral neck remained stable, during the third year after transplant. This paper describes the time course of bone loss after cardiac transplantation.

Shane E, Rivas M, McMahon DJ, et al. "Bone loss and turnover after cardiac transplantation." *J Clin Endocrinol Metab* 82:1497-1506, 1997. (Class D)

4. Discuss Risk Factors for Osteoporotic Fracture

Risk factors for osteoporosis and fractures are fixed or modifiable. They may or may not contribute independently to the risk of having low bone mass and fractures and they are not necessarily cumulative. 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 have been shown to be independent risk factors for osteoporosis and related fractures. 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.

Bohannon AD, Hanlon JT, Landerman R, Gold DT. "Association of race and other potential risk factors with nonvertebral fractures in community-dwelling elderly women." *Am J Epidemiol* 149:1002-09, 1999. (Class B)

Hannan MT, Felson DT, Dawson-Hughes B, et al. "Risk factors for longitudinal bone loss in elderly men and women: The Framingham Osteoporosis Study." *J Bone Miner Res* 15:710-20, 2000. (Class B)

Melton LJ III, Atkinson EJ, Khosla S, et al. "Secondary osteoporosis and the risk of vertebral deformities in women." *Bone* 24:49-55, 1999. (Class B)

Body Habitus

Low body mass index (BMI, less than 20) or thinness (weight less than 127 pounds) has been identified as a predictor for hip fractures and other osteoporotic fractures. BMD at the lumbar spine and hip have been correlated with weight, height, and BMI. During the Framingham Osteoporosis Study, women who gained weight, gained BMD or had little change, while women who had a lower baseline weight or weight loss, lost BMD. Low BMI has been classified as an independent risk factor and a modifiable factor.

Hannan MT, Felson DT, Dawson-Hughes B, et al. "Risk factors for longitudinal bone loss in elderly men and women: The Framingham Osteoporosis Study." *J Bone Miner Res* 15:710-20, 2000. (Class B)

Melton LJ III, Atkinson EJ, Khosla S, et al. "Secondary osteoporosis and the risk of vertebral deformities in women." *Bone* 24:49-55, 1999. (Class B)

Ravn P, Cizza G, Bjarnason NH, et al. "Low body mass index is an important risk factor for low bone mass and increased bone loss in early postmenopausal women." *J Bone Miner Res* 14:1622-27, 1999. (Class B)

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 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.

Fox KM, Cummings SR, Powell-Threets K, et al. "Family history and risk of osteoporotic fracture." *Osteoporos Int* 8:557-62, 1998. (Class B)

Omland LM, Tell GS, Ofjord S, Skag A. "Risk factors for low bone mineral density among a large group of Norwegian women with fractures." *Eur J Epidemiol* 16:223-29, 2000. (Class D)

Cigarette Smoking

Cigarette use has been identified as a risk factor for BMD and osteoporotic fracture. 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 (greater than one pack/day) 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 J, Feskanich D, Willett WC, Colditz GA. "Smoking, smoking cessation, and risk of hip fracture in women." *Am J Med* 106:311-14, 1999. (Class B)

Hannan MT, Felson DT, Dawson-Hughes B, et al. "Risk factors for longitudinal bone loss in elderly men and women: The Framingham Osteoporosis Study." *J Bone Miner Res* 15:710-20, 2000. (Class B)

Huopio J, Kroger H, Honkanen R, et al. "Risk factors for perimenopausal fractures: a prospective study." *Osteoporos Int* 11:219-27, 2000. (Class B)

Sedentary Lifestyle

Sedentary life-style is a risk factor for osteoporosis. The type of physical activity and what optimal age period is most beneficial 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. Absence of gravity, such as during space flight or prolonged bed rest, can lead to bone loss of 0.3%-0.4% of total bone calcium per month. 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.

Bemben DA. "Exercise interventions for osteoporosis prevention in postmenopausal women." *J Oklahoma State Med Assoc* 92:66-70, 1999. (Class R)

Branca F. "Physical activity, diet and skeletal health." *Public Health Nutr* 2:391-96, 1999. (Class R)

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 RF. "Alcohol-induced bone disease: impact of ethanol on osteoblast proliferation." *Alcohol Clin Exp Res* 21:392-99, 1997. (Class R)

A high level of alcohol intake is associated with both decreased bone mineral density and increased risk of hip fractures. 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 of 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.

Hannan MT, Felson DT, Dawson-Hughes B, et al. "Risk factors for longitudinal bone loss in elderly men and women: The Framingham Osteoporosis Study." *J Bone Miner Res* 15:710-20, 2000. (Class B)

Hoidrup S, Gornbaek M, Gottschau A, et al. "Alcohol intake, beverage preference, and risk of hip fracture in men and women." *Am J Epidemiol* 149:993-1001, 1999. (Class B)

Low Calcium Intake

Comprehensive reviews of the relationship of calcium intake and bone health reported that calcium 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 Discussion Appendix A, Conclusion Grading Worksheet - Annotations #4 & 5 (Calcium)]*

Chapuy MC, Arlot ME, Duboeuf F, et al. "Vitamin D and calcium to prevent hip fractures in elderly women." *N Engl J Med* 327:1637-42, 1992. (Class A)

Cumming RG, Nevitt MC. "Calcium for prevention of osteoporotic fractures in postmenopausal women." *J Bone Miner Res* 12:1321-29, 1993. (Class M)

Dawson-Hughes B, Dallal GE, Krall EA, et al. "A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women." *N Engl J Med* 323:878-83, 1990. (Class A)

Heaney RP. "Calcium, dairy products and osteoporosis." *J Am Coll Nutr* 19(2 Suppl):83S-99S, 2000. (Class R)

Recker RR, Hinders S, Davies KM, et al. "Correcting calcium nutritional deficiency prevents spine fractures in elderly women." *J Bone Miner Res* 11:1961-66, 1996. (Class A)

Riggs BL, O'Fallon WM, Muhs J, et al. "Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women." *J Bone Miner Res* 13:168-74, 1998. (Class A)

Inadequate Vitamin D

Vitamin D is essential for calcium absorption and bone metabolism. Aging is associated with decreasing 1,25 dihydroxyvitamin D_3 levels, progressive renal insufficiency, reduced sun exposure and reduced skin capacity for vitamin D production. Vitamin D insufficiency and overt deficiency can both 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 fractures. This supplement-induced benefit on bone mass can be lost when the calcium and vitamin D are discontinued.

Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. "Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older." *N Eng J Med* 337:670-76, 1997. (Class A)

LeBoff MS, Kohlmeier L, Hurwitz S, et al. "Occult vitamin D deficiency in postmenopausal US women with acute hip fracture." *JAMA* 281:1505-11, 1999. (Class C)

Increased Likelihood of Falling

Many factors increase the likelihood of falling, and falling increases fracture risk. Included in these factors are impaired eyesight, poor health, frailty, low physical function - such as slow gait and speed and decreased quadriceps strength - dementia, and history of past falls. 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, soft hip protector pads have been shown to reduce hip fractures in frail, elderly adults in community-based health care centers.

Kannus P, Parkkari J, Niemi S, et al. "Prevention of hip fracture in elderly people with use of a hip protector." *N Engl J Med* 343:1506-13, 2000. (Class A)

NHS Centre for Reviews and Dissemination. "Preventing falls and subsequent injury in older people." *Eff Health Care* 2:2-16, 1996. (Class R)

5. Discuss Primary Prevention of Fractures

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 MT, Felson DT, Dawson-Hughes B, et al. "Risk factors for longitudinal bone loss in elderly men and women: The Framingham Osteoporosis Study." *J Bone Miner Res* 15:710-20, 2000. (Class B)

Hoidrup S, Gronbaek M, Pedersen AT, et al. "Hormone replacement therapy and hip fracture risk: Effect modification by tobacco smoking, alcohol intake, physical activity, and body mass index." *Am J Epidemiol* 150:1085-93, 1999. (Class B)

Gonadal Hormonal Status

Please see Discussion #14, "Address Options for Prevention and Treatment of Osteoporosis."

Exercise

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 periods 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 CM, Georgiou CC, Gillis DE, Snow CM. "Lifetime physical activity is associated with bone mineral density in postmenopausal women." *J Women Health* 8:365-75, 1999. (Class D)

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 (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.

Randomized clinical trials have shown exercise to decrease the risk of falls by approximately 25%, but there is no experimental evidence that exercise affects fracture. Those who exercise may fall differently and decrease their risks as a result. 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.

Layne JE, Nelson ME. "The effects of progressive resistance training on bone density: a review." *Med Sci Sports Exerc* 31:25-30, 1999. (Class R)

"Osteoporosis prevention, diagnosis, and therapy: NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy." *JAMA* 285:785-95, 2001. (Class R)

Weaver CM. "Calcium requirements of physically active people." *Am J Clin Nutr* 72:579S-84S, 2000. (Class R)

Our responsibility is to encourage and assist our patients 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.

Smoking Cessation

Please see Discussion #4, "Discuss Risk Factors for Osteoporotic Fracture."

Alcohol Restriction

Please see Discussion #4, "Discuss Risk Factors for Osteoporotic Fracture."

Calcium

Daily elemental calcium recommendations for healthy individuals 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 use, pregnant or nursing women, or persons over the age of 65, it may be more important to recommend 1500 mg.

Institute of Medicine. "Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride." Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu/books/0309071836/html/ (Class R)

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.

"Osteoporosis prevention, diagnosis, and therapy: NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy." *JAMA* 285:785-95, 2001. (Class R)

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 supplements on an empty stomach may increase the risk of kidney stones. A recent study suggested that calcium citrate is better absorbed than calcium carbonate in supplement form. Lead levels in calcium supplements vary, with some supplements exceeding the acceptable level.

Heller HJ, Stewart A, Haynes S, Pak CYC. "Pharmacokinetics of calcium absorption from two commercial calcium supplements." *J Clin Pharmacol* 39:1151-54, 1999. (Class A)

Institute of Medicine. "Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride." Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu/books/0309071836/html/ (Class R)

Ross EA, Szabo NJ, Tebbett IR. "Lead content of calcium supplements." *JAMA* 284:1425-29, 2000. (Class D)

Vitamin D

Vitamin D levels are affected by a variety of factors. Vitamin D synthesis through sunlight exposure is significantly affected by skin pigmentation, latitude, time of day, season of the year, weather conditions and the amount of skin surface covered with clothing and sunscreen. It is very difficult to estimate or assume sunlight-mediated vitamin D synthesis. It is also unknown what level of vitamin D may be stored in fat from spring or summer sunlight exposure or whether it is adequate.

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. "Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride." Washington, DC: National Academy Press, 1997. Available at: http://www.nap.edu/books/0309071836/html/ (Class R)

Prevention of Falls

Please see Discussion #4, "Discuss Risk Factors for Osteoporotic Fracture."

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

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 post-menopausal women is neither cost-effective nor appropriate. Many professional organizations, including the National Osteoporosis Foundation, the North American Menopause Society, National Institute of Health and the American Association of Clinical Endocrinologists have published their own guidelines describing whom to select for bone densitometry.

The National Osteoporosis Foundation (NOF) conducted a cost-effectiveness analysis (Eddy et. al., 1998) regarding the prevention, detection and treatment of osteoporosis. They concluded that bone densitometry was reasonable for all women over age 65, and for post-menopausal 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 post-menopausal woman under age 65.

The American Association of Clinical Endocrinologists guidelines are less comprehensive than the aforementioned ones. This guideline recommends bone densitometry for estrogen deficient women for whom the decision as to whether or not to use hormone replacement therapy will be influenced by

a bone density test. Prior fractures, radiographic osteopenia, glucocorticoid therapy, and primary hyperparathyroidism are also considered to be indications for bone densitometry in this guideline.

Eddy DM, Johnston CC, Cummings SR, et al. "Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis." *Osteoporos Int* Suppl4:S1-S88, 1998. (Class M)

Hodgson SF, Johnston CC Jr. "AACE Clinical practice guidelines for the prevention and treatment of postmenopausal osteoporosis." *Endocrinol Prac* 2:155-71, 1996. (Class R)

National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Washington DC: National Osteoporosis Foundation, 1999. (Class R)

North American Menopause Society. "Management of post menopausal osteoporosis: position statement of the North American Menopause Society." *Menopause* 9:84-101, 2002. (Class R)

"Osteoporosis prevention, diagnosis and therapy: NIH consensus development panel on osteoporosis prevention, diagnosis and therapy." *JAMA* 285:785-95, 2001. (Class R)

Two groups have developed simple questionnaires to determine an individual's risk for low bone mass. The Simple Calculated Osteoporosis Risk Estimation (SCORE) of Lydick et. al. (1998) uses five items to predict low bone density: age, weight, history of fracture, history of rheumatoid arthritis, and use of estrogen replacement therapy to determine the likelihood of low bone mass. Cadarette et. al. (2000) found that three factors in post-menopausal women (age, weight, and use of estrogen replacement therapy) could be combined in a questionnaire (Osteoporosis Risk Assessment Instrument – ORAI) to predict the presence or absence of low bone mass. Both of these questionnaires have high sensitivity for detection of those with low bone mass, but low specificity. Compared to mass screening of all post-menopausal women, the ORAI could eliminate the need for bone densitometry in almost half of post-menopausal women, yet detect those with low bone mass with as high sensitivity as the National Osteoporosis Foundation guidelines.

In the development and validation cohorts for both of these questionnaires, lack of estrogen replacement therapy in post-menopausal women was noted to be a significant risk factor for low bone mass. Neither of these studies found physical activity or cigarette smoking sufficiently predictive of bone loss independent of age, body weight, and estrogen status to be included in their final model for predicting bone mineral density.

Cadarette SM, Jaglal SB, Krieger N, et al. "Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry." *CMAJ* 162:1289-94, 2000. (Class C)

Cadarette SM, Jaglal SB, Murray TM. "Validation of the Simple Calculated Osteoporosis Risk Estimation (SCORE) for patient selection for bone densitometry." *Osteoporos Int* 10:85-90, 1999. (Class C)

Lydick E, Cook K, Turpin J, et al. "Development and validation of a simple questionnaire to facilitate identification of women likely to have low bone density." *Am J Manag* Care 4:37-48, 1998. (Class C)

Our guideline is based on the National Osteoporosis Foundation 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 radiographs of the thoracic and lumbar spines. 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 far majority of these individuals will be over age 65 anyway. 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 et. al. 1998, Cadarette et. al. 2000, Bauer et. al. 1993). Severe loss of mobility (prolonged immobilization) however, is a risk factor for osteoporosis and is included.

Bauer DC, Browner WS, Cauley JA, et al. "Factors associated with appendicular bone mass in older women." *Ann Intern Med* 118:657-65, 1993. (Class D)

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

It should be noted that for men and pre-menopausal women, there are far fewer indications for bone densitometry. Pre-menopausal women without amenorrhea, prior fracture or radiographic osteopenia, glucocorticoid therapy, or another chronic illness that specifically predisposes to osteoporosis are in fact at low risk for osteoporosis. Similarly, eugonadal men without any of these chronic illnesses, radiographic osteopenia or prior fractures, and who are not being treated with glucocorticoids are at low risk for osteoporosis.

8. Recommend Bone Density Assessment

Measurements of BMD 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 increases in BMD with therapy for osteoporosis lead to substantial reductions in fracture incidence. These data will be discussed in the treatment section.

Hailey D, Sampietro-Colom L, Marshall D, et al. "The effectiveness of bone density measurement and associated treatments for prevention of fractures: an international collaborative review." *Int J Tech Assess Health Care* 14:237-54, 1998. (Class M)

Miller PD, Zapalowski C, Kulak CAM, Bilezikian JP. "Bone densitometry: the best way to detect osteoporosis and to monitor therapy." *J Clin Endocrin Metab* 84:1867-71, 1999. (Class R)

Ringertz H, Marshall D, Johansson C, et al. "Bone density measurement: a systematic review." *J Intern Med* 241:1-60, 1997. (Class M)

Owing to a lack of standardization of techniques in the past, 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 young adult healthy population. A T-score is calculated from the following equation:

[(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 an age- and sex-matched healthy population. A Z-score is calculated from the following equation:

[(measured BMD - age-matched population mean BMD) / age-matched population SD]

Normal, osteopenia, and osteoporosis are defined by the T-score, according to the World Health Organization:

- Normal: A T-score greater than or equal to -1.
- Osteopenia: A T-score between -1 and -2.5.

- Osteoporosis: A T-score less than or equal to -2.5.
- Severe osteoporosis: Reserved for patients with a fragility fracture(s) *and* a T-score less than or equal to -2.5.

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. Low Z-scores (less than -1.0) should prompt a search for secondary causes of osteoporosis (see box #13, "Consider Secondary Causes").

WHO Study Group. "Assessment of fracture risk and its application to screening for postmenopausal osteoporosis." Geneva, Switzerland: World Health Organization, 1994. (Class R)

Selective screening for osteoporosis, targeting populations at risk, is accepted as the standard of care. The National Osteoporosis Foundation recommends BMD measurements for:

- All postmenopausal women under age 65 who have one or more additional risk factor for osteoporosis.
- All women aged 65 and older, regardless of additional risk factors.
- Postmenopausal women who present with fractures (to confirm diagnosis and determine disease severity).
- Women who are considering therapy for osteoporosis, if BMD testing would facilitate the decision.
- Women who have been on hormone replacement therapy for prolonged periods.

Of note, these recommendations are for white postmenopausal women only. They are not for women of other races, women who have not yet reached menopause, or men.

National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. Washington DC: National Osteoporosis Foundation, 1999. (Class R)

The Bone Measurement Act of 1998 broadened the selective screening by mandating 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).
- An individual with primary hyperparathyroidism.
- An individual being monitored to assess the response to or the efficacy of a FDA-approved drug for osteoporosis therapy.

DHHS. Medicare coverage of and payment for bone mass measurements. *Federal Register* 63:34320-28, 1998. Washington DC: US Government Printing Office. (Class not assignable)

There have been no scientific trials to assess the effectiveness of population-based bone density screening. The predictive power of bone density screening is low. It is estimated that a bone density screening program may lead to the prevention of 1% to 7% of fractures in elderly women. 197 women would need to be screened to prevent one fracture. An estimate of the annual cost of a population-based bone density screening program is 1.1 million dollars for HRT and follow-up. A routine population-based bone screening program would be inadvisable.

Marshall D, Johnell O, Wedel H. "Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures." *BMJ* 312:1254-59, 1996. (Class M)

"Screening for osteoporosis to prevent fractures." Bulletin on the Effectiveness of Health Service Interventions for Decision Makers. Bulletin #1, 1992. (Class R)

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. 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 HK, Engelke K, Fuerst T, et al. "Noninvasive assessment of bone mineral and structure: state of the art." *J Bone Miner Res* 11: 707-30, 1996. (Class R)

Institute for Clinical Systems Improvement. "Densitometry as a diagnostic tool for the identification and treatment of osteoporosis in women." Technology Assessment Report #31, 2000. (Class R)

Miller PD, Zapalowski C, Kulak CAM, Bilezikian JP. "Bone densitometry: the best way to detect osteoporosis and to monitor therapy." *J Clin Endocrin Metab* 84:1867-71, 1999. (Class R)

Historically, the field of bone densitometry developed without any oversight. 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. 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 www.iscd.org.

To emphasize the importance of appropriate training in densitometry interpretation, the Minnesota Medical Association adopted at its September 2000 meeting, a resolution that calls for densitometry interpretation to be done only by properly trained physicians. This should result in legislation that removes densitometry from non-certified sites, such as drug stores, by limiting payments to certified physicians or facilities. There will be a need for physicians who have not yet met the standards of certification, to do so.

Limitations of Densitometry

BMD represents a continuous variable. There is overlap in BMD values between individuals with and without fragility fractures. Thus, fracture risk is multifactorial and not solely defined by BMD.

There are other limitations to the use of T-score to diagnose osteoporosis. Each vendor of densitometry machines uses a different young normal reference database. For this reason, the same bone mineral density may yield T-scores that may differ between different instruments. Additionally, the database used to determine the normal range of bone mineral densities may not reflect the population being tested, since most data have been generated for Caucasian women. The Third National Health and Nutrition Examination Survey (NHANES III) included hip BMD measurements for a representative

sample of men and women aged 20 years or older. Data included non-Hispanic Whites, non-Hispanic Blacks, and Mexican-Americans. The use of the NHANES III BMD database by all manufacturers of densitometry equipment, should help to eliminate discrepancies based on different normative values.

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 in the future.

Hanson J. for the International Committee for the Standards in Bone Measurement. "Standardization of femur BMD." *J Bone Miner Res* 12:1316-17, 1997. (Class not assignable)

Looker AC, Orwoll ES, Johnston CC Jr, et al. "Prevalence of low femoral bone density in older US adults from NHANES III." *J Bone Miner Res* 12:1761-68, 1997. (Class C)

Steiger P for the Committee for Standards in DXA. "Standardization of spine BMD measurements." *J Bone Miner Res* 10:1602-03, 2000. (Class not assignable)

9. Post-Test Probability

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 LJ III, Atkinson EJ, O'Connor MK, et al. "Bone density and fracture risk in men." *J Bone Miner Res* 13:1915-23, 1998. (Class C)

Melton LJ III, Atkinson EJ, O'Fallon WM, et al. "Long-term fracture prediction by bone mineral assessed at different skeletal sites." *J Bone Miner Res* 8:1227-33, 1993. (Class B)

10. Low Risk of Future Fracture
11. Moderate Risk of Future Fracture
12. High Risk of Future Fracture

Risk of osteoporotic fracture depends on skeletal bone strength, and fracture risk is therefore determined by many factors that affect bone strength. These include, in the broadest sense, the genetic influences on bone strength modified by all superimposed factors affecting bone strength during the lifetime of the patient. Risk factors for osteoporosis and osteoporotic fracture are discussed elsewhere in these guidelines.

Hannan MT, Felson DT, Dawson-Hughes B, et al. "Risk factors for longitudinal bone loss in elderly men and women: The Framingham Osteoporosis Study." *J Bone Miner Res* 15:710-20, 2000. (Class B)

Ross PD. "Risk factors for osteoporotic fracture." *Endocrinol Metab Clin North Am* 27:289-301, 1998. (Class R)

Some of these risk factors are modifiable, and some are not. However, none of these factors, singly or in combination, predict likelihood of future osteoporotic fracture as well as measurement of bone mineral density. 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 JM, Zimmerman SI, Girman CJ, et al. "Low bone mineral density and risk of fracture in white female nursing home residents." *JAMA* 284:972-77, 2000. (Class B)

Cummings SR, Nevitt MC, Browner WS, et al. "Risk factors for hip fracture in white women." *N Engl J Med* 332:767-73, 1995. (Class B)

Duppe H, Gardsell P, Nilsson B, Johnell O. "A single bone density measurement can predict fracture over 25 years." *Calcif Tissue Int* 60:171-74, 1997. (Class B)

For the purposes of these guidelines, risk of fracture is mainly determined by the bone mineral density T-score, using the World Health Organization definition.

WHO Study Group. "Assessment of fracture risk and its application to screening for postmenopausal osteoporosis." Geneva, Switzerland: World Health Organization, 1994. (Class R)

Low fracture risk is defined as a bone mineral density T-score above -1.0. Patients with T-scores above -1.0 have normal bone density, and are therefore at low risk of fracture. Moderate fracture risk is defined as a bone mineral density T-score below -1.0 and above -2.5. Patients with T-scores below -1.0 and above -2.5 have osteopenia, and are therefore at mildly increased risk of fracture. High fracture risk is defined as a bone mineral density T-score below -2.5. Patients with T-scores below -2.5 have osteoporosis, and are therefore at high risk of fracture. It should be noted that the normal range for T-scores is between +1.0 and -1.0, that is, within 1.0 standard deviation above or below the mean for young adults of the same gender and ethnicity. Technically, a T-score of -1.0 means that a patient's bone mineral density is 1.0 standard deviation below the mean for young adults of the same gender and ethnicity. Fracture risk increases with age for the same level of bone mineral density.

Hui SL, Slemenda CW, Johnston CC Jr. "Age and bone mass as predictors of fracture in a prospective study." *J Clin Invest* 81:1804-09, 1988. (Class B)

Despite the clinical utility of bone mineral density T-score for categorizing fracture risk, it is important to remember that bone mineral density T-score is not the only factor determining fracture risk. 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 P, Hausherr E, Chapuy M-C, et al. "Markers of bone resorption predict hip fracture in elderly women: The EPIDOS Prospective Study." *J Bone Miner Res* 11:1531-38, 1996. (Class B)

Riis BJ, Hansen MA, Jensen AM, et al. "Low bone mass and fast rate of bone loss at menopause: equal risk factors for future fracture: a 15-year follow-up study." *Bone* 19:9-12, 1996. (Class B)

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

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. 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 one to two years 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 five to ten years after the initial measurement, in order to detect patients who lose significant bone density over time.

13. Consider Secondary Causes and Further Diagnostic Testing

Consider the following for the low risk patient: *Osteoporosis but an average age-matched bone density (Z-score >-1.0):*

- A biochemical profile that provides information on:
  - renal function
  - hepatic function
  - calcium (important if starting an antiresorptive 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 may indicate an inflammatory process or monoclonal gammopathy
- TSH and thyroxine for primary hyperthyroidism which may be apathetic
- The 24-hour urinary calcium excretion on a high calcium intake screens for malabsorption and hypercalciuria, a correctable cause of bone loss. Low 24-urine calcium suggests vitamin D deficiency, osteomalacia or malabsorption due to small bowel diseases such as celiac sprue.

Consider adding the following tests for the high-risk patient: *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 Annotation Appendix A, "Secondary Causes of Osteoporosis" for a comprehensive list of secondary causes of osteoporosis.)**

- Testosterone (total and free) in men and estradiol in women; LH and FSH and prolactin if evidence of hypogonadotropic hypogonadism

- Intact parathyroid hormone
- 25-hydroxycalciferol evaluates vitamin D status
- Antigliadin and endomyoseal antibodies if clinical suspicion for gluten enteropathy
- 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

Harper, KD, Weber TJ. Secondary osteoporosis, diagnostic considerations. *In* Endocrinology and Metabolism Clinics of North America, Nelson B. Watts, editor. WB Saunders Company, Philadelphia. 27(2)325-348, 1998. (Class R)

At this time there is no consensus about the routine usefulness of serum and/or urinary markers of bone turnover in the evaluation of patients with osteoporosis.

Institute for Clinical Systems Improvement. "Biochemical markers for bone turnover in osteoporosis." Technology Assessment Report #53, 2001. (Class R)

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

14. Address Options for Prevention and Treatment of Osteoporosis

In addition to calcium, vitamin D, physical therapy, surgical repair, and radiologic intervention as appropriate, the following therapies may be used:

Gonadal Hormone Replacement Therapy

Female gonadal hormone replacement 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 M, Tuppurainen MT, Kroger H, et al. "Vitamin D and HRT: no benefit additional to that of HRT alone in prevention of bone loss in early postmenopausal women: a 2.5 year randomized placebo-controlled study." *Osteoporos Int* 7:126-32, 1997. (Class A)

Prince RL, Smith M, Dick IM, et al. "Prevention of postmenopausal osteoporosis: a comparative study of exercise, calcium supplementation, and hormone-replacement therapy." *N Engl J Med* 325:1189-95, 1991. (Class A)

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 P, Kolthoff N, Nielsen SP. "Effect of 10 years hormone replacement therapy on bone mineral content in postmenopausal women." *Bone* 19:191S-93S, 1996. (Class A)

Writing Group for the PEPI Trial, The. "Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial." *JAMA* 276:1389-96, 1996. (Class A)

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 R, Tohme JF. "Estrogen treatment of patients with established postmenopausal osteoporosis." *Obstet Gynecol* 76:290-95, 1990. (Class A)

Quigley ME, Martin PL, Burnier AM, Brooks P. "Estrogen therapy arrests bone loss in elderly women." *Am J Obstet Gynecol* 156:1516-23, 1987. (Class C)

The effects of estrogen therapy on bone metabolism cannot only be documented by measurements of bone density, but also markers of bone turnover show positive effects.

Rosen CJ, Chesnut CH III, Mallinak NJS. "The predictive value of biochemical markers of bone turnover for bone mineral density in early postmenopausal women treated with hormone replacement or calcium supplementation." *J Clin Endocrinol Metab* 82:1904-10, 1997. (Class A)

The protective effects of estrogen on bone density is lost quickly after estrogen is discontinued. Since most osteoporotic related fractures occur in the 7th and 8th decades of life, it would be anticipated that long term use of hormone replacement therapy would be necessary to protect against those fractures.

Lindsay R, MacLean A, Kraszewski A, et al. "Bone response to termination of estrogen treatment." *Lancet* 7:1325-27, 1978. (Class D)

Dose response effectiveness of hormone replacement therapy on bone mass had gone under a lot of recent scrutiny. Traditionally, estradiol blood levels of 40-60 pg/mL, provided by exogenous estrogen supplementation in the equivalent of 0.625 mg of conjugated estrogens were felt to be necessary to provide adequate protection. It has been shown that among women 65 years or older, those who have serum estradiol levels of 5-20 pg/mL have higher bone density and fewer fractures than those whose level is below 5 pg/mL. A clinical trial using low dosage estrogen combined with calcium and vitamin D 5 pg/mL. A clinical trial using low dosage estrogen combined with calcium and vitamin D in women over 65 years of age could achieve significant gains in spinal and hip bone density over 3.5 years. It is possible to expect that women with the lowest endogenous estrogen levels might expect the best gains from exogenous estrogen therapy.

Cummings SR, Browner WS, Bauer D, et al. "Endogenous hormones and the risk of hip and vertebral fractures among older women: Study of Osteoporotic Fractures Research Group." *N Engl J Med* 339: 733-38, 1998. (Class B)

Ettinger B, Pressman A, Sklarin P, et al. "Associations between low levels of serum estradiol, bone density and fractures among elderly women: the study of osteoporotic fractures." *J Clin Endocrinol Metab* 83:2239-43, 1998. (Class B)

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

Other individual covariables may also affect which individual may expect the most advantage of hormone replacement therapy on bone mass and future fracture risk. Several studies have shown that hormone treatment might be most optimal in women with low body weight, are inactive, or are smokers.

Hoidrup S, Gronbaek M, Pedersen AT, et al. "Hormone replacement therapy and hip fracture risk: Effect modification by tobacco smoking, alcohol intake, physical activity, and body mass index." *Am J Epidemiol* 150:1085-93, 1999. (Class B)

Michaelsson K, Baron JA, Johnell O, et al. "Variation in the efficacy of hormone replacement therapy in the prevention of hip fracture." *Osteoporos Int* 8:540-46, 1998. (Class C)

The combination of estrogen with other bone protecting agents may offer more value in protection of bone mass and future fracture risk. Even though all currently available approaches to osteoporosis prevention suppress bone remodeling, different agents may interact at different points in the remodeling cycle. Several uncontrolled trials have addressed the possibility of a synergistic effect between calcium and estrogen on bone mass but the data thus far are inconclusive. 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 C, Riis BJ. "17-Beta estradiol and continuous norethisterone: a unique treatment for established osteoporosis in elderly women." *J Clin Endocrinol Metab* 71:836-41, 1990. (Class A)

Marcus R, PEPI Trial Investigators. "Effects of hormone replacement therapies on bone mineral density results from the Postmenopausal Estrogen/Progestin Intervention trial." *J Bone Miner Res* 10:S30, 1995. (Abstract) (Class A)

Riis BJ, Thomsen K, Christianson C. "Does calcium supplementation prevent postmenopausal bone loss? A double-blind controlled clinical study." *N Engl J Med* 316:173-77, 1987. (Class B)

Understanding the effect of estrogen on future fracture risk is complicated by a lack of published controlled trials. Present data come mainly from observational and epidemiological trials. The lack of randomization or placebo controls limits the usefulness of these results. 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. Controlled trials are now underway, such as Women's Health Initiative, that will hopefully answer these questions.

Torgerson DJ, Bell-Syer SEM. "Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials." *JAMA* 285:2891-97, 2001. (Class M)

Male gonadal hormone replacement therapy

The bone loss associated with male hypogonadism is reversed by testosterone replacement therapy. Testosterone replacement therapy, although not FDA-approved for osteoporosis, seems a reasonable first therapeutic intervention in men symptomatic with hypogonadism.

Behre HM, Kliesch S, Leifke E, et al. "Long-term effect of testosterone therapy on bone mineral density in hypogonadal men." *J Clin Endocrinol Metab* 82:2386-90, 1997. (Class D)

Katznelson L, Finkelstein JS, Schoenfeld DA, et al. "Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism." *J Clin Endocrinol Metab* 81:4358-65, 1996. (Class C)

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) 2027 postmenopausal women with low BMD and at least one vertebral fracture at baseline were randomized to alendronate or placebo. This arm of the study 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 DM et al for the Fracture Intervention Trial Research Group. "Randomized trial of effect of alendronate on risk of fracture in women with existing vertebral fractures." *Lancet* 348:1535-41, 1996. (Class A)

Liberman VA, Weiss SR, et al. "Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis." *N Engl J Med* 333:1437-43, 1995. (Class A)

Risedronate has shown a 41% risk reduction in the number of new vertebral fractures after 3 years with risedronate 5 mg 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.

Folgelman I, Ribot C, Smith R, et al. "Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial." *J Clin Endocrinol Metab* 85:1895-1900, 2000. (Class A)

Harris ST, Watts NB, Genant HK, et al for the Vertebral Efficacy with Risedronate Therapy (VERT) study group. "Effects of risedronate treatment on vertebral and non-vertebral fractures in women with postmenopausal osteoporosis." *JAMA* 282:1344-52, 1999. (Class A)

McClung et al showed that risedronate reduced the risk of hip fracture in elderly women with osteoporosis.

McClung MR, Geusens P, Miller PD, et al. "Effect of risedronate on the risk of hip fracture in elderly women." *N Engl J Med* 344:333-40, 2001. (Class A)

Excellent clinical trial data supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal osteopenia or osteoporosis. The best clinical trials have been done with alendronate (Fosamax®) and risedronate (Actonel®). *[Conclusion Grade I: See Discussion Appendix B, Conclusion Grading Worksheet – Annotation #14 (Bisphosphonates for Primary Osteoporosis)].*

Etidronate is an oral bisphosphonate that has not achieved FDA approval in this country for the treatment of osteoporosis. There is no prospective trial showing that etidronate reduces the risk of vertebral or non-vertebral fracture. A meta-analysis recently published suggests there may be some vertebral fracture reduction from etidronate, but we do not consider this evidence strong enough to recommend its use in the treatment or prevention of osteoporosis.

Cranney A, Guyatt G, Krolicki N, et al. "A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis." *Osteoporos Int* 12:140-51, 2001. (Class M)

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 decreases in height for men with osteoporosis.

Orwoll E et al. "Alendronate for the treatment of osteoporosis in men." *N Engl J Med* 343:604-10, 2000. (Class A)

Good clinical trial data support the use of alendronate for preventing bone loss in men diagnosed with osteoporosis. *[Conclusion Grade I: See Discussion Appendix B, Conclusion Grading Worksheet – Annotation #14 (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 KG et al. "Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis." *N Engl J Med* 339:292-99, 1998. (Class A)

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

Cohen S, Levy RM, Keller M, et al. "Risedronate therapy prevents corticosteroid induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study." *Arthritis Rheum* 42:2309-18, 1999. (Class A)

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 Discussion Appendix C, Conclusion Grading Worksheet – Annotation #14 (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 Discussion Appendix C, Conclusion Grading Worksheet – Annotation #14 (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 small studies have shown that intravenous pamidronate may prevent bone loss after organ transplantation. No studies using oral bisphosphonates in transplantation patients are available.

Aris RM, Lester GE, Renner JB, et al. "Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation." *Am J Respir Crit Care Med* 162:941-46, 2000. (Class A)

Shane E, Rodino MA, McMahon DJ, et al. "Prevention of bone loss after heart transplantation with antiresorptive therapy: a pilot study." *J Heart Lung Transplant* 17:1089-96, 1998. (Class C)

Bisphosphonate Side Effects

Oral bisphosphonate preparations have the potential to cause upper gastrointestinal erosions and ulcerations on rare occasions. Endoscopy trials and rechallenge trials have not shown significant increases in esophageal ulceration relative to placebo and significantly less erosive disease than aspirin when taken properly.

Lanza FL, Hunt RH, Thomson AB, et al. "Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women." *Gastroenterology* 119:631-38, 2000. (Class A)

Lowe CE, Depew WT, Vanner SJ, et al. "Upper gastrointestinal toxicity of alendronate." *Am J Gastroenterol* 95:634-40, 2000. (Class A)

Miller PD, Woodson G, Licata AA, et al. "Rechallenge of patients who had discontinued alendronate therapy because of upper gastrointestinal symptoms." *Clin Ther* 22:1433-42, 2000. (Class A)

Selective Estrogen Receptor Modulator (SERM)

The only SERM approved for the prevention and treatment of 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. The risk of non-vertebral fractures did not differ between placebo and raloxifene. There was an increased risk of venous thromboembolus compared with placebo (RR 3.1, 95% CI 1.5-6.2).

Ettinger B, Black DM, Mitlak BH, et al for the Multiple Outcomes Raloxifene Evaluation (MORE) investigators. "Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene." *JAMA* 282:637-45, 1999. (Class A)

Calcitonin

Treatment of osteoporosis in postmenopausal women

Calcitonin has shown a 33% risk reduction in new vertebral fractures with calcitonin 200 IU daily 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.

Chesnut CH III, Silverman S, Andriano K, et al. "A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The prevent recurrence of osteoporotic fractures study (PROOF)." *Am J Med* 109:267-76, 2000. (Class A)

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 MJ, Kinnunen K, Volin L, et al. "A prospective study of bone loss and turnover after cardiac transplantation: effect of calcium supplementation with or without calcitonin." *Osteoporosis Int* 10:128-36, 1999. (Class A)

Valimaki MJ, Kinnunen K, Volin L, et al. "A prospective study of bone loss and turnover after allogenic bone marrow transplantation: effect of calcium supplementation with or without calcitonin." *Bone Marrow Transplant* 23:355-61, 1999. (Class A)

Combination Therapy

Estrogen and alendronate

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. Most combination therapy trials have been with estrogen and bisphosphonates. Combination therapy would be appropriate in patients who continue to lose bone mineral density on estrogen and those who initially present with very low bone density.

Bone HG, Greenspan SL, McKeever C, et al. "Alendronate and estrogen effects in postmenopausal women with low bone mineral density." *J Clin Endocrinol Metab* 85:720-26, 2000. (Class A)

Lindsay R, Cosman F, Lobo RA, et al. "Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial." *J Clin Endocrinol Metab* 84:3076-81, 1999. (Class A)

Estrogen and risedronate

Harris ST, Eriksen EF, Davidson M, et al. "Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women." *J Clin Endocrinol Metab* 86:1890-97, 2001. (Class A)

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 RW, Bell NH, Ettinger MP. "Comparison of alendronate and intranasal calcitonin for treatment of osteoporosis in postmenopausal women." *J Clin Endocrinol Metab* 85:1783-88, 2000. (Class A)

Calcitriol-Vitamin D3

Post-transplantation

Stempfle et al randomized 132 patients (111 men, 21 women) with a mean age of 51 ± 25 months after cardiac transplantation to receive elemental calcium 1000 mg daily, hormone replacement (if hypogonadal), and calcitriol 0.25 mg daily, or calcium hormone replacement, and placebo for 36 months. They found that lumbar spine bone mineral density increased by 5.7% ± 4.4% in the calcitriol group and by 6.1% ± 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 HU, Werner C, Echtler S, et al. "Prevention of osteoporosis after cardiac transplantation: a prospective, longitudinal, randomized, double-blind trial with calcitriol." *Transplantation* 68:523-30, 1999. (Class A)

Parathyroid Hormone

Daily subcutaneous injections of recombinant human PTH has been studied alone, and in combination with other agents. It has been studied in both men and women, and in glucocorticoid-induced osteoporosis and postmenopausal osteoporosis. It is universally effective at building bone and decreasing fractures. Its metabolic effects seem to continue even after discontinuation of the drug. The impressive data backing PTH makes FDA approval seem likely in the near future. PTH is an anabolic agent, in distinction to other antiresorptive agents.

Neer RM, Arnaud CD, Zanchetta JR, et al. "Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis." *N Engl J Med* 344:1434-41, 2001. (Class A)

Alternative and Complementary Agents

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 DL, St Germain A, Peterson CT, et al. "Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women." *Am J Clin Nutr* 72:844-52, 2000. (Class A)

Horiuchi T, Onouchi T, Takahashi M, et al. "Effect of soy protein on bone metabolism in postmenopausal Japanese women." *Osteoporos Int* 11:721-24, 2000. (Class D)

Potter SM, Baum JA, Teng H, et al. "Soy protein and isoflavones: their effects on blood lipids and bone density in postmenopausal women." *Am J Clin Nutr* 68(suppl):1375S-79S, 1998. (Class A)

Ipriflavone

Ipriflavone is a synthetic isoflavone derivative, currently available as a dietary supplement. Over 60 human studies, involving a total of 2,769 patients, have been conducted in Italy, Japan, and Hungary.

A multicenter European study, in which 474 postmenopausal women aged 45-75 were randomly assigned to treatment with ipriflavone 200 mg t.i.d. plus calcium versus placebo plus calcium over three years, found no statistically significant difference in bone loss, biochemical markers of bone metabolism or number of vertebral factures, between the two groups. Women treated with ipriflavone had a significant decrease in blood lymphocyte concentrations, in some cases to the point of subclinical lymphopenia.

Alexandersen P, Toussaint A, Christiansen, et al for the Ipriflavone Multicenter European Fracture Study. "Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial." *JAMA* 285:1482-88, 2001. (Class A)

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 HB, Longo S, Anasti JN. "Transdermal progesterone cream for vasomotor symptoms and postmenopausal bone loss." *Obstet Gynecol* 94:225-28, 1999. (Class A)

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 GS, Tepper R, Leichter I, et al. "Trabecular bone density in a two-year controlled trial of peroral magnesium in osteoporosis." *Magnesium Res* 6:155-63, 1993. (Class C)

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 D, Weber P, Willett WC, et al. "Vitamin K intake and hip fractures in women: a prospective study." *Am J Clin Nutr* 69:74-79, 1999. (Class B)

Shiraki M, Shiraki Y, Aoki C, Miura M. "Vitamin K2 (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis." *J Bone Miner Res* 15:515-21, 2000. (Class A)

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 MC, Coetzer H, de Winter R, et al. "Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis." *Aging Clin Exp Res* 10:385-94, 1998. (Class A)

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 H, Miyahara T, Tezuka Y, et al. "The effect of Kampo formulae on bone resorption in vitro and in vivo. I. Active constituents of Tsu-kan-gan." *Biol Pharm Bull* 21:1322-26, 1998. (Class C)

15. Follow-Up Testing After Pharmacologic Intervention

Understanding that the spine, which is primarily trabecular bone, will demonstrate response to antiresorptive therapy earlier than the more cortical site of the hip, we can develop realistic expectations for change in bone density due to therapy. In a patient with a measurable spine, i.e., no prior lumbar vertebral fracture or significant dystrophic calcifications, a follow-up AP lumbar spine scan should be done using the greatest number of lumbar vertebrae. In general, the precision of the AP spine is at least as great as any other skeletal site using DXA. A bone density change that is 2.6 times the precision error of the instrument used is necessary to be sure the change observed is real. If you are uncertain if a change is significant, you should request the precision error at the center performing bone density testing. Typically a change of 3-5% is statistically significant.

Bonnick SL. Bone Densitometry in Clinical Medicine. Chapter 9: Clinical Indications for Bone Densitometry, Totowa NJ: Humana Press, 1998, pp 197-210. (Class R)

Faulkner KG, VonStetten E, Miller P. "Discordance in patient classification using T-scores." *J Clin Densitometry* 2:343-50, 1999. (Class C)

Miller PD, Bonnick SL. "Clinical application of bone densitometry." *In* Primer on the metabolic bone diseases and disorders of mineral metabolism. Philadelphia: Lippincott Williams and Wilkins, 1999: pp 152-59. (Class R)

Follow-up DXA at the hip site should use the total hip value, which affords the least precision error because of its larger area than the femoral neck. An anti-resorptive agent may not demonstrate a statistically significant change in hip bone density for two to three or more years at this more cortical, less metabolically active site. Lack of bone density response at the hip should not be interpreted as a failure of therapy if done one to two years after therapy is started.

Bonnick SL. Bone Densitometry in Clinical Medicine. Chapter 9: Clinical Indications for Bone Densitometry, Totowa NJ: Humana Press, 1998, pp 197-210. (Class R)

There has been considerable controversy about the necessity of follow-up bone density testing in patients on specific osteoporosis therapy. Although the science of bone densitometry is imperfect and we are limited by technologic deficiencies, operator error and bone biology that is not completely understood, follow-up bone density testing can be useful in clinical practice. If we understand that bone density at all sites decreases with aging and this decrease in bone density is associated with an increased risk for fracture in populations studied, we have an implied but not proven causal relationship.

Miller PD, Zapalowski C, Kulak CAM, Bilezikian JP. "Bone densitometry: the best way to detect osteoporosis and to monitor therapy." *J Clin Endocrin Metab* 84:1867-71, 1999. (Class R)

Evaluating this relationship from the direction of post-treatment, Drs. Wasnich and Miller looked at increasing bone density with antiresorptive therapy and its correlation with reduced risk for fracture. They pooled data from the 13 randomized, placebo-controlled trials of antiresorptive agents (alendronate, calcitonin, estrogen, etidronate and tiludronate) and performed a Poisson regression to examine this association. Although the confidence intervals for this relationship are large for indi-

vidual trials, the studies that reported greater increases in BMD tended to report greater reductions in vertebral fracture risk. In this model, treatments that increased spine bone density 8% would reduce risk of vertebral fracture 54%. There remained a small effect of treatment that was unexplained by BMD that might be related to technology limitations, measurement errors or bias. For hip BMD, the model suggests an increase of 5% predicts a 50% risk reduction of vertebral fracture.

Wasnich RD, Miller PD. "Antifracture efficacy of antiresorptive agents are related to changes in bone density." *J Clin Endocrinol Metab* 85:231-36, 2000. (Class M)

Looking at the Fracture Intervention Trial, Hochberg found a similar relationship with the sub-population of patients experiencing the greatest bone density improvement having the greatest fracture risk reduction.

Hochberg MC, Ross PD, Black D, et al for the Fracture Intervention Trial Research Group. "Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis." *Arthritis Rheum* 42:1246-54, 1999. (Class C)

As noted above, although improvement with bone density is the greatest indicator of fracture risk reduction, there is an element of fracture risk reduction that cannot be quantitated by densitometry. This intercept in the regression model is estimated to be about 20% from the Wasnick and Miller analysis. This is most evident when fracture risk reduction is related to bone density response from raloxifene in the MORE trial and nasal calcitonin in the PROOF trial. Bone turnover response may afford an additional and independent fracture risk reduction and unmeasurable effects related to lifestyle changes that may accompany a patient's pharmacological therapy.

Chesnut CH III, Silverman S, Andriano K, et al. "A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The prevent recurrence of osteoporotic fractures study (PROOF)." *Am J Med* 109:267-76, 2000. (Class A)

Ettinger B, Black DM, Mitlak BH, et al. for the Multiple Outcomes Raloxifene Evaluation (MORE) Investigators. "Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial." *JAMA* 282:637-45, 1999. (Class A)

Miller PD, Zapalowski C, Kulak CAM, Bilezikian JP. "Bone densitometry: the best way to detect osteoporosis and to monitor therapy." *J Clin Endocrin Metab* 84:1867-71, 1999. (Class R)

Other considerations include skeletal fragility and aging which can increase the slope of the fracture relationship curve increasing fracture risk for a given decrease in bone density. The fracture risk relationship may not be bi-directional (a phenomenon known as "hysteresis").

*Hysteresis is the phenomenon defined by an alteration in response on a reversal of the effect. It is often applied in engineering systems to the force/deformation relationship, which may depend on the direction of the testing (tension or compression).

Faulkner KG. "Bone matters: are density increases necessary to reduce fracture risk?" *J Bone Miner Res* 15:183-87, 2000. (Class R)

Controversy has been raised about applying the statistical phenomenon of 'regression toward the mean' to individuals being tested serially with DXA, rather than to populations. This law states that the further a patient's bone density value is from the mean of the population, the more likely subsequent examinations will tend toward the population mean. Cummings et al reported that patients in the Fracture Intervention Trial who lost bone on therapy initially were statistically more likely to improve on subsequent testing and vice versa. Since almost all patients will eventually have improved bone densities on alendronate therapy, the need for sequential bone density testing was challenged.

Cummings SR, Palermo L, Browner W, et al. for the Fracture Intervention Trial Research Group. "Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean." *JAMA* 283:1318-21, 2000. (Class D)

The counter-argument by Bonnick, in an eloquent editorial, is that "regression to the mean relates to the experience of the whole group and not to any defined individual". It is the precision of the instrument, whether it is a densitometer or sphygmomanometer that is of statistical importance. Bonnick further points out that if we applied Cummings' argument to other areas in medicine, we would not repeat any test in clinical practice and this would be a disservice to our patients.

Bonnick SL. "Monitoring osteoporosis therapy with bone densitometry: a vital tool or regression toward mediocrity?" *J Clin Endocrinol Metab* 85:3493-95, 2000. (Class R)

It is the conclusion of this work group that follow-up bone density testing with central DXA may be considered after two years* to monitor the response to antiresorptive therapy. Certain conditions of particularly high rates of bone loss, such as patients receiving glucocorticoids, patients on suppressive doses of thyroid hormone, women in early menopause, or women who have discontinued estrogen replacement and are not on another antiresorptive agent, may warrant more frequent testing. It is important that follow-up densitometry be performed on the same machine with the same technologist to achieve the least precision error and greatest accuracy in predicting significance of change. It is difficult to decide if a second agent should be used on the basis of a follow-up bone density because there is currently no fracture data available demonstrating reduced fractures with dual antiresorptive therapy although modest bone density increases have been shown.

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

Conclusion Grading Worksheet – 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 +, –, ø	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/ *Work Group's Comments (italicized)*
Dawson-Hughes, et al. (1990)	RCT	A	ø	-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 ≥2 SD below age-matched mean -Analyzed separately those who had undergone menopause ≤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 **Early Postmenopausal Women (n=67)** -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 **Late Postmenopausal Women (n=169)** -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 (≥1.6% at 2 yrs) was observed in all groups except low calcium intake receiving calcium citrate malate; significant bone loss from femoral neck (≥2.4% at 2 yrs) and radius (≥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 *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*

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

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/ *Work Group's Comments (italicized)*
Chapuy, et al. (1992)	RCT	A	0	-Women ages 69 to 106 yrs old; ambulatory; no serious medical conditions; life expectancy ≥18 mos -Excluded: drugs known to alter bone metabolism in past year; fluoride salts for >3 mos; vit D or calcium in past 6 mos or for >1 yr in past 5 yrs -Randomized to vit D_3+calcium (1.2 g calcium, 800 IU vit D_3) or placebo -Baseline assessment of calcium intake and frequency of falls -Assessed for fractures at 6, 12, & 18 mos; subset of 142 had serum analysis at baseline & every 6 mos; subset of 56 had BMD at baseline & 18 months	-1634 in vit D_3+calcium group; 1636 in placebo; no differences in age, wt, ht, dietary calcium or % with ≥1 fall in 3 months before study; dietary calcium was low (mean of 513 mg/day); vit D intake estimated at 123 IU/day -54% (1765) treated and followed for 18 mos; drop-out rates similar in 2 groups -For those 1765: 32% fewer non-vertebral fractures (p=0.02); 43% fewer hip fractures (p=0.04) in the vit D_3+calcium group (vs. placebo) -Active tx analysis (treatment for varying lengths of time): 28% fewer non-vertebral fractures (p=0.02); 31% fewer hip fractures (p=0.04) -Intention-to-treat analysis: 25% fewer non-vertebral fractures (p<0.001); 27% fewer hip fractures (p=0.004) -Odds ratio=1.7 (95%CI: 1.0-2.8) for hip fractures in placebo group vs. vit D_3+calcium group; for non-vertebral fractures OR=1.4 (95%CI: 1.4-2.1) -Treatment reduced age-related risk of fracture at 18 mos (p=0.007 for hip fractures; p=0.009 for all non-vertebral fractures) -In BMD subgroup, total proximal femoral BMD increased 2.7% in vit D_3+calcium group and decreased 4.6% in placebo group (p<0.001) -40 in vit D_3+calcium group and 28 in placebo group had gastrointestinal symptoms that led to discontinuation of treatment	-Vit D_3+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. NOTES: women with past fractures or who had taken or were taking estrogen or thiazide diuretics were eligible; <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 *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% withdrawal in each group*

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

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/ *Work Group's Comments (italicized)*
Recker, et al. (1996)	RCT	A	–	-Healthy white women volunteers; 60 yrs (mean 73.5±7.1 yrs); ambulatory; living independently; calcium intake estimated at <1g/day -2 groups: those with prevalent spine fractures (PF) & those without (NPF) -Excluded: other diagnoses or treatments that affect skeleton -Randomized to calcium (600 mg BID) or placebo -Bone mineral content (BMC) of radius every 6 mos (SPA) -Spine x-rays every yr -Mean follow-up of 4.3 years	-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 ($p<0.002$) -36 in PF group had 86 incident vertebral deformities; 25 in NPF group had 59 incident vertebral deformities -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 ($p=0.002$) -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 -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) -Calcium prevented bone loss in PF group ($p<0.001$) but not NPF group ($p<0.2$); rate of bone loss greater in PF placebo group than NPF placebo group ($p=0.03$)	-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. NOTES: 750 screened, 499 didn't enroll because of calcium intake >1g/day (50%) or personal choice (50%); 54 more excluded from analysis (< 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 *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*

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

Author/Year	Design Type	Class	Quality +,–,ø	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/ *Work Group's Comments (italicized)*
Riggs et al. (1998)	RCT	A	ø	-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 (>800 IU/d) or calcium (>500 mg/d), or other drugs that affect bone; no history of use of fluoride or bisphosphonates -Excluded: renal lithiasis, impaired renal function, hypercalcemia, hypercalciuria; disease known to affect bone or calcium metabolism -Randomized to 1600 mg/day calcium or placebo -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	-236 women randomized (119 calcium, 117 placebo); no differences between groups at baseline -177 (75%) completed 4 yrs of study (88 calcium, 89 placebo); 16 discontinued because of side effects (10 calcium, 6 placebo) -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 -Mean dose of calcium in tx group was 1,234 mg/d; no change in dietary calcium over course of study for either group -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<0.02) -Serum calcium (p<0.001), parathyroid hormone (p=0.001), & osteocalcin (p=0.04) and urinary calcium & free pyridinoline (p=0.001) differed between groups at 4 yrs -Intention-to-treat analysis and analysis of those completing 4 yrs of study produced similar results for BMD and biochemical measures	-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. NOTES: to maintain urinary calcium at <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 *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*

Conclusion Grading Worksheet – Annotation # 14 (Bisphosphonates for Primary Osteoporosis)

Work Group's Conclusion: Excellent clinical trial data supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal osteopenia or osteoporosis. The best clinical trials have been done with alendronate (Fosamax) and risedronate (Actonel).

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/ *Work Group's Comments (italicized)*
Liberman, et al. (1995)	RCT	A	0	-Women ages 45-80 years old; ≥5 yrs postmenopausal; lumbar spine BMD ≥2.5 SD below mean for premenopausal women -Excluded: other causes of osteoporosis; other disorders of bone & 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 -Randomized to receive placebo or 5, 10, or 20 mg alendronate per day for 2 years; in 3rd year women receiving 20 mg were switched to 5 mg; all received 500 mg calcium/day -BMD of lumbar spine, femoral neck, trochanter, forearm, and total body with DXA -Lateral spine films for vertebral fractures at baseline and after 1, 2, & 3 yrs of treatment	-Paired spine films of 881 women (355 in placebo group, 526 in alendronate groups combined) -Groups similar at baseline in age, years since menopause, body-mass index, % with vertebral fractures, % with no vertebral deformities, Spine Deformity Index, BMD -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 -10 mg group had significantly greater BMD than placebo at all sites ($p<0.001$) -6.2% of placebo group and 3.2% of treatment groups had ≥1 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 -Spine Deformity Index increased in 33% of alendronate group and 41% of placebo group (p=0.03) -Mean loss of height at 36 mos was 3.0mm in alendronate group and 4.6mm in placebo (p=0.005) -Non-vertebral fractures occurred in 83 women; trend toward fewer in treatment group (7.5% of women vs. 9.6%) -Adverse effects comparable in treatment and placebo groups	-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. NOTES: Pooled data from 2 identical multicenter studies (pooling was planned); study was originally intended to be open-label in 3rd 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 ≥1 yr of study *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*

Conclusion Grading Worksheet – Annotation # 14 (Bisphosphonates for Primary Osteoporosis) (cont)

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/ *Work Group's Comments (italicized)*
Black, et al. (1996)	RCT	A	+	-Women 55 to 81 yrs old; postmenopausal for ≥2 yrs; femoral neck BMD ≤0.68g/cm^2 (about 2.1 SDs below peak); at least 1 vertebral fracture at baseline -Excluded: peptic-ulcer disease, dyspepsia requiring treatment, abnormal renal function, major medical problems, severe malabsorption syndrome, uncontrolled hypertension, MI in past 6 mos, unstable angina, disturbed thyroid or parathyroid function; estrogen or calcitonin in past 6 mos; prior use of bisphosphonates or fluoride -Randomized to placebo or alendronate (initial dose of 5 mg/day increased to 10 mg at 24-month visit) -BMD of hip, spine, & whole body (plus forearm in 20%) -Lateral spine x-rays at baseline, 24 mos, and 36 mos; also clinical fractures	-2,027 women (1,022 in alendronate group, 1,005 in placebo group); groups were comparable at baseline -Alendronate group had increased BMD relative to placebo at femoral neck, trochanter, total hip, posterior-anterior lumbar spine, lateral spine, whole body, & forearm (relative to placebo, all p<0.001) -1,946 had follow-up x-rays; 8% of placebo group and 15% of alendronate group had 1 or more new fractures; risk of new vertebral fracture was 47% lower in alendronate group (RR=0.53; 95%CI:0.41-0.68); risk of multiple fractures was also reduced (RR=0.10; 95%CI:0.05-0.22) -Fewer in alendronate group had clinical vertebral fractures (2% vs. 5%; Rel Hazard=0.45; 95%CI:0.27-0.72) -Cumulative proportions with hip or wrist fractures were significantly lower in alendronate group -Average height loss in 36 months was lower in alendronate group (6.1 mm vs. 9.3 mm; p<0.001) -Proportions of women reporting upper-GI problems were similar for the two groups -Proportions of women who permanently discontinued treatment because of adverse effects were similar	-Postmenopausal women with low BMD and pre-existing vertebral fracture who received alendronate had a lower incidence of several types of fractures than women who received placebo. The alendronate dose was well tolerated. NOTES: all received 500 mg supplemental calcium if intake <1000 mg/day; study was designed to have 99% power to detect a 40% reduction in risk of vertebral fractures (90% power to detect 32% reduction) assuming 6.5% annual incidence; because of positive results, the follow-up period was shortened by an average of 0.1 yrs (to 2.9 yrs); analysis was based on numbers of women with fractures rather than number of fractures; 97% of women enrolled were Caucasian; study was conducted at 11 sites in the United States *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*

Conclusion Grading Worksheet – Annotation # 14 (Bisphosphonates for Primary Osteoporosis) (cont)

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/ *Work Group's Comments (italicized)*
Harris, et al. (1999)	RCT	A	0	-Ambulatory women ≤ 85 yrs; ≥5 yrs postmenopausal; either ≥2 vertebral fractures on x-ray or 1 vertebral fracture and low lumbar spine BMD (2 SDs below young adult mean) -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 -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 -Lateral thoracic and lumbar spine x-rays at baseline and annually -BMD of lumbar spine and femoral neck at baseline and 6 month intervals	-2,458 women were enrolled (815 in placebo group, 811 to 2.5 mg group, 813 to 5 mg group with 19 not treated after randomization) -55% of placebo group and 60% of 5 mg group completed 3 years of treatment -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) -Cumulative incidence of non-vertebral fractures was lower by 39% in the 5 mg group vs. placebo (p=0.02) -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 $p<0.05$) -Overall incidence of adverse events and withdrawals for adverse events was similar across treatment groups	-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. NOTES: study designed to have ≥90% 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 *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*

Conclusion Grading Worksheet – Annotation # 14 (Bisphosphonates for Primary Osteoporosis) (cont)

Author/Year	Design Type	Class	Quality +,–,ø	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/ *Work Group's Comments (italicized)*
Fogelman, et al. (2000)	RCT	A	ø	-Women up to 80 yrs old; postmenopausal for ≥1 yr; lumbar spine T-score of ≤-2 -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 -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 1g/d calcium -BMD of lumbar spine, femoral neck, and trochanter at baseline, 6, 12, 18, & 24 mos -Spine x-rays at baseline and end of study	-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) -Groups were comparable at baseline -BMD of lumbar spine increased from baseline by 4% at 24 months in 5 mg group vs. no change in placebo group ($p<0.001$ for difference between groups); comparable increase in BMD of lumbar spine in subgroups postmenopausal ≤5 yrs or >5 yrs -BMD of femoral neck increased by 1.3% at 24 mos in 5 mg group and decreased by 1% in placebo group ($p<0.001$ between groups) -BMD of trochanter increased by 2.7% in 5 mg group and decreased by –0.6% in placebo group ($p<0.001$ between groups) -At 24 months, vertebral fractures were present in 14% of patients with known fracture status in placebo group vs 7% of 5 mg group -No difference in overall incidence of adverse events among groups; no difference in withdrawals due to adverse events	-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. 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 *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*

Conclusion Grading Worksheet – Annotation # 14 (Bisphosphonates for Primary Osteoporosis) (cont)

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/ *Work Group's Comments (italicized)*
McClung, et al. (2001)	RCT	A	0	-2 parallel groups of ambulatory postmenopausal women **Group A**: 70-79 yrs old; osteoporosis (femoral neck BMD T-score of -4 or lower or T-score of -3 with with ≥1 nonskeletal risk factor for hip fracture) **Group B**: ≥80 yrs; at least 1 nonskeletal risk factor, femoral neck T-score of lower than –4, or T-score lower than -3 with hip-axis length of ≥11.1 cm -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)	-Total of 9,331 enrolled and received ≥1 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 **Group A (70-79 yrs old with osteoporosis)** -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 **Group B (≥80 yrs old with ≥ 1 risk factor)** -Of 3,886 in ≥80 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	-Risedronate prevented hip fracture in women who had osteoporosis (as indicated by a low BMD - **Group A**) but not in those with clinical risk factors for hip fracture (but not necessarily osteoporosis - **Group 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 *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)*

Conclusion Grading Worksheet – Annotation # 14 (Bisphosphonates for Primary Osteoporosis) (cont)

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/ *Work Group's Comments (italicized)*
Orwoll, et al. (2000)	RCT	A	0	-Men age 31 to 87 years; femoral neck BMD ≥2 SDs below mean for normal young men and lumbar spine BMD ≥1 SD below mean or femoral neck BMD ≥1 Sd below mean and at least 1 vertebral deformity or a history of osteoporotic fracture -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 -Randomized to 10 mg alendronate or placebo (3:2); all received calcium (500 mg/d) and vitamin D (400-450 IU/d) -Spine x-rays at baseline and 2 years -BMD at baseline and 6, 12, 18, & 24 mos	-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 -BMD changes from baseline at 2 years: *p<0.001 vs. baseline and vs. placebo -Changes in lumbar spine BMD with alendronate treatment were similar regardless of serum-free testosterone concentrations and regardless of serum estradiol concentrations -Effect of alendronate was independent of age -Height decreased 2.4mm in placebo group vs. 0.6 in alendronate group (p=0.02 for difference between groups); decrease in height was greater in those with new vertebral fractures during the study -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 -11% of placebo group and 3% of alendronate group withdrew because of adverse effects (p=0.02)	-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. 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 *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*

	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 – Annotation #14 (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 +,–,ø	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/ *Work Group's Comments (italicized)*
Saag, et al. (1998)	RCT	A	ø	-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) *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*

Conclusion Grading Worksheet – Annotation #14 (Bisphosphonates for Glucocorticoid-Induced Bone Loss) (cont)

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/ *Work Group's Comments (italicized)*
Cohen, et al. (1999)	RCT	A	–	-Ambulatory patients; 18-85 yrs of age; began taking corticosteroids (≥7.5 mg/day prednisone or equivalent) for underlying disease within past 3 mos & expected to continue for another 12 mos; women at least 1 yr postmenopausal, surgically sterile, or using birth control -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 -Randomized to receive risedronate (2.5 mg/d or 5 mg/d) or placebo for 12 mos; all received 500 mg/d calcium -BMD of lumbar spine, femoral neck, and trochanter, at baseline, 3, 6, and 12 mos; radius at baseline and 12 mos -Spine x-rays baseline, 12 mos	-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) -150 completed 12 mos (57 placebo, 31 2.5 mg/d risedronate, 62 5 mg/d risedronate) -Lumbar spine, femoral neck, and trochanter BMD decreased at 12 mos in placebo group ($p<0.05$ at each site vs. baseline) -Lumbar spine and femoral neck BMD maintained at 12 mos and trochanter BMD increased ($p<0.05$ vs. baseline) at 12 mos in 5 mg/d risedronate group (all $p<0.001$ vs. placebo) -In 2.5 mg/d risedronate group, BMD did not increase from baseline; 12 month values at lumbar spine and trochanter differed from placebo ($p<0.005$) -BMD of radius did not change in any treatment group at 12 mos -Adjustment for mean dose and duration of therapy did not affect results -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 -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) -Percentages reporting adverse events, serious adverse events, and dropout due to adverse events were similar in the 3 groups	-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. NOTES: 2.5 mg/d dose discontinued based on other studies (majority completed 6 mos of treatment and >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 *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*

Support for Implemenation:

Diagnosis and Treatment of Osteoporosis

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

OVERVIEW

The following aims were identified by the guideline work group as key areas in which medical groups may receive benefits in implementing this guideline.

The measures associated with these aims are presented as suggested measures. Measures of aim help medical groups determine progress in achieving a particular aim. However, additional approaches may be customized by individual medical groups to ferret out improvement information important to the medical group's individual practice.

PRIORITY AIMS AND SUGGESTED MEASURES FOR HEALTH CARE SYSTEMS

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 low impact fracture identified as having low bone mass offered treatment for osteoporosis.

   c. Percentage of adults with a history of low impact fracture offered treatment for osteoporosis.

   d. Percentage of adults with a history of low impact fracture with documentation of discussion with a health care provider of osteoporosis risk.

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 who have had bone densitometry.

3. Increase follow-up testing of patients on long term hormone replacement therapy (HRT).

   Possible measure for accomplishing this aim:

   a. Percentage of patients on long term HRT who have had follow-up bone densitometry.

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, one or two measurement specifications may be included.

*RECOMMENDED WEBSITE RESOURCES**

Note: Websites are listed in alphabetical order, not in order of work group preference.

Website Sponsor	Target Audience	Description	Website Address
American Academy of Orthopedic Surgeons	Professionals and public	Professional organization site	www.aaos.org
American Association of Clinical Endocrinologists	Endocrinology/ professionals	Professional organization site	www.aace.com
American College of Rheumatology	Arthritis and related disorders/ professionals	Professional organization site	www.rheumatology.org
American Medical Association	General medical/ professionals	Professional organization site	www.ama-assn.org
Foundation for Osteoporosis Research and Education	Osteoporosis/public and professionals	Current information about osteoporosis and research	www.fore.org
International Osteoporosis Foundation	Osteoporosis/public and professionals	International organization site	www.osteofound.org
International Society of Clinical Densitometry	Densitometry professionals	professional organization site	www.iscd.org
Mayo Health Oasis Women's Health Resource	women's health/public	women's health information	www.mayoclinic.org
National Osteoporosis Foundation	Osteoporosis/public and professionals	General information about osteoporosis prevention and treatment	www.nof.org
NIH - Osteoporosis and Related Bone Diseases Resources Center	Osteoporosis and bone diseases/public and professionals	Current information about osteoporosis and research	www.osteo.org
North American Menopause Society	Menopause- related topics/ public and professionals	Professional organization site	www.menopause.org
North American Menopause Society	Professionals	Professional journal	www.menopausejournal.com

These websites were reviewed by the ICSI *Diagnosis and Treatment of Osteoporosis* guideline work group as credible resources. ICSI does not have the authority to monitor the content of these sites. Any health-related information offered from these sites should not be interpreted as giving a diagnosis or treatment.

*** Criteria for Selecting Websites**

The preceding websites were selected by the *Diagnosis and Treatment of Osteoporosis* guideline work group as additional resources for practitioners and the public. The following criteria were considered in selecting these sites.

- The site contains information specific to the particular disease or condition addressed in the guideline.
- The site contains information that does not conflict with the guideline's recommendations.
- The information is accurate and/or factual. The author of the material or the sponsor of the site can be contacted by means other than e-mail. For example, a nurse line or other support is provided.
- The material includes the source/author, date and whether the information has been edited in any way. The site clearly states revision dates or the date the information was placed on the Internet.
- The site sponsor is an objective group without an obvious or possible bias. For example, the site does not promote a product, service or other provider.
- The coverage of the topic is appropriate for the guideline's target audience. It is clearly written, well-organized and easy to read. The site is easy to navigate.