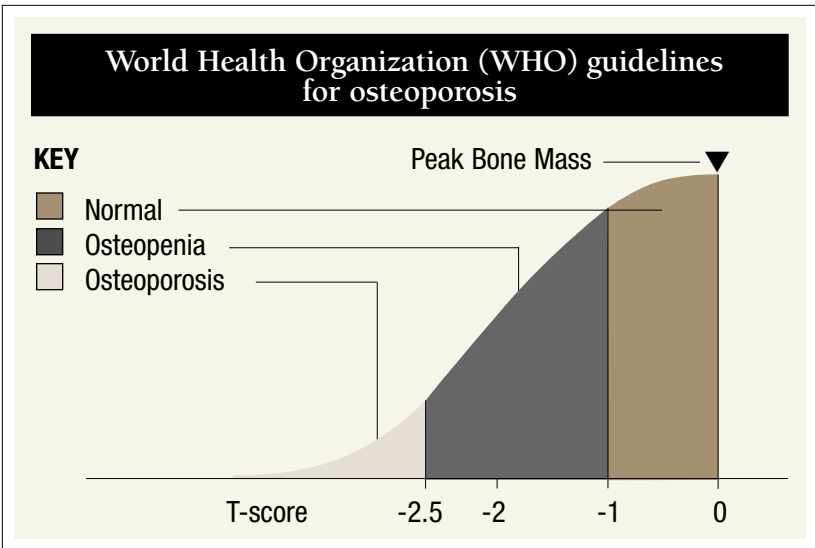


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The slide kit is supplemental to the CME material and is not included in the material designated for AMA category 1 credit.

Contents

- I. WHO diagnostic guidelines
- II. Treatment goals and therapeutic options
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Osteoporosis is generally defined as having a BMD ≥ 2.5 standard deviations (SD) below the mean for young adults.¹ A BMD between 1 and 2.5 SDs is defined as osteopenia, or low bone mass. The number of SDs above or below the mean is defined as the T-score. Treatment is currently recommended for women with BMD T-scores < -2 if no additional risk factors are present and < -1.5 if one or more additional risk factors (especially prior fractures) are present. Women with osteopenia who do not meet these criteria may also be candidates for treatment if they have several risk factors. For example, a patient with osteopenia who is on corticosteroid therapy should be considered at risk. However, these are recommendations only; the decision to treat should be a joint one between physician and patient.

1. Kanis J, WHO Study Group. Assessment of fracture risk and its application to screening for osteoporosis: Synopsis of a WHO report. *Osteoporosis Int.* 1994;4:368-381.

Current treatment options for osteoporosis	
Treatment	Dosage form
Calcium and vitamin D	Oral (daily)
Hormone replacement therapy (HRT)	Oral, transdermal
Calcitonin	Nasal spray (daily)
Selective estrogen receptor modulators (SERMs)	Oral (daily)
Bisphosphonate: alendronate	Oral (daily or weekly)
Bisphosphonate: risedronate	Oral (daily or weekly)
Parathyroid hormone: (PTH) (teriparatide)	Daily subcutaneous

The goal of osteoporosis treatment is to increase BMD; the end point of treatment is a reduction in overall fracture risk. The ideal therapy should reduce risk not only for spinal fractures, but also for fractures of the hip, tibia, fibula, and wrist. Treatment should be effective across all age groups and different degrees of low bone density. Efficacy should be rapid and sustained for the duration of therapy. The treatment should also be safe and well tolerated. Current treatment options for osteoporosis and their dosage forms are listed in this slide. Recombinant parathyroid hormone has recently been approved as a daily subcutaneous injection. The number of available treatment options for osteoporosis has complicated the decision-making process. The results of the Women's Health Initiative (WHI) trial have recently added a further complication, suggesting that long-term (> 4 years) hormone replacement therapy (HRT) may not be appropriate for most women.¹

1. Lacey JV Jr, Mink PJ, Lubin JH. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA*. 2002;288:334-341.

Calcium and vitamin D

- Used as adjunctive therapies to the more potent antiresorptives
- Benefits of calcium are modest:
 - Meta-analysis shows small positive effect on BMD
 - Trend toward vertebral fracture reduction
 - No conclusions about nonvertebral fractures
- Chapuy et al:
 - Hip fractures reduced by 43% ($p=0.043$)
 - Nonvertebral fractures reduced by 32% ($p=0.015$)

Calcium and vitamin D are essential as adjunctive therapies to the more potent antiresorptive therapies. Calcium is the simplest and least costly preventive therapy for osteoporosis, but its benefits on BMD are modest. Shea et al conducted a meta-analysis of controlled trials of the effects of calcium supplementation on bone density and fractures in postmenopausal women.¹ They found that calcium supplementation had a small positive effect on BMD, and there was a trend toward reduction in vertebral fractures. However, conclusions could not be drawn about the effect of calcium on nonvertebral fractures.

In one of the studies summarized by Shea et al, Chapuy et al studied the effects of vitamin D and calcium supplementation on the frequency of hip and other nonvertebral fractures in 3270 healthy, ambulatory elderly women.² Each day for 18 months 1634 women received 1.2 g of elemental calcium and 20 μg (800 IU) of vitamin D. The control group ($n=1636$) received a double placebo. The number of hip fractures was 43% lower ($p=0.043$), and the number of nonvertebral fractures was 32% lower ($p=0.015$) among women who received the supplements, compared with those who received placebo. The bone density of the proximal femur increased 2.7% in the treatment group and decreased 4.6% in the placebo group ($p<0.001$).

1. Shea B, Wells G, Cranney A, et al. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocrine Rev.* 2002;23(4):552-559.
2. Chapuy MC, Arlot ME, Delmas PD, et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *Br J Med.* 1994; 308(6936): 1081-1082.

Hormone replacement therapy (HRT)

- WHI study halted when risk of HRT exceeded benefits
 - Hip and vertebral fractures reduced by 34%
 - All osteoporotic fractures reduced by 24%
 - Slight increases in risk of heart attacks, strokes, and blood clots
 - Risk of invasive breast cancer increased by 25%
 - No increase in all-cause mortality

The recent publication of the Women's Health Initiative (WHI) study has led to a reexamination of the indications for HRT.¹ The study was halted in 2001 when the risk-benefit ratio for treatment began to favor the risk. The study showed that women receiving HRT had a 34% decrease in hip and vertebral fractures and a reduction in risk of all osteoporotic fractures of approximately 24%. However, there were also slight increases in the risk of heart attacks, strokes, blood clots, and breast cancer in the treatment group. The risk of invasive breast cancer was increased by approximately 25%, but HRT did not increase all-cause mortality.

Clinicians can no longer routinely recommend long-term therapy with HRT. The WHI study suggests that two to four years may be a reasonable limit on therapy duration, because results started to diverge significantly between the two WHI groups during this interval. A general rule is to use HRT for the shortest possible time at the lowest possible dose. After stopping HRT, an antiresorptive therapy, such as a bisphosphonate, should be considered to stop the rapid bone loss seen when HRT is withdrawn.

1. Lacey JV Jr, Mink PJ, Lubin JH. Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA*. 2002;288:334-341.

Selective estrogen receptor modulators (SERMs)

- Raloxifene is the first SERM approved for osteoporosis
 - Produces estrogen-agonist effects on bone and estrogen-antagonist effects on endometrial and breast tissue
 - Minimizes undesirable effects of estrogen
- Meta-analysis shows positive effects on bone density; these increased over time and were independent of dose
- Significant increases in BMD for total body, lumbar spine, combined forearm, and combined hip BMDs ($p < 0.01$)

Raloxifene is a nonhormonal agent that binds with high affinity to estrogen receptors, producing estrogen-agonist effects on bone and estrogen-antagonist effects on endometrial and breast tissue.¹ The rationale for using SERMs is to obtain the beneficial effects of estrogen on bone while avoiding or minimizing undesirable effects on the breast and uterus.

In a meta-analysis of seven trials of raloxifene, investigators found positive effects on bone density in the group receiving raloxifene; these increased over time and were independent of dose.² The differences between raloxifene and placebo were statistically significant for total body, lumbar spine, combined forearm, and combined hip BMDs ($p < 0.01$).

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1. Khovidhunkit W, Shoback DM. Clinical effects of raloxifene hydrochloride in women. *Ann Intern Med.* 1999;130:431-439.
 2. Cranney A, Tugewell P, Zytaruk N, et al. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocrine Rev.* 2002;23(4): 524-528.
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Calcitonin

- A polypeptide hormone that inhibits bone resorption by osteoclasts
- Recommended as an alternative to HRT or alendronate
- Results of meta-analysis of randomized studies:
 - 54% reduction in vertebral fractures
 - No effect on nonvertebral fractures
 - Results of largest study in meta-analysis (PROOF) compromised by large dropout rate

Calcitonin is a polypeptide hormone secreted by the C cells of the parafollicular tissue of the thyroid gland; it acts on bone by inhibiting bone resorption by osteoclasts. It also appears to have an analgesic effect in women with vertebral fractures.¹ Currently, the National Osteoporosis Foundation (NOF) recommends calcitonin as an alternative to HRT or alendronate when patients cannot tolerate or fail therapeutically on these agents.²

A meta-analysis was conducted of 30 studies that randomized women to calcitonin or placebo.³ The pooled analysis of the four studies reporting vertebral fractures showed that calcitonin reduced the risk of vertebral fractures by 54% ($p=0.02$). For nonvertebral fractures the results were not significant. The largest trial in the meta-analysis was the Prevent Recurrence of Osteoporotic Fractures (PROOF) study.⁴ In this study, the risk of vertebral fractures was reduced by 33% ($p=0.03$) in women taking a 200-IU dose of calcitonin. However, results of the PROOF study are rendered problematic by the fact that 59% of the subjects were discontinued early from the trial, which casts some doubt on the validity of the statistical analysis.

1. Plosker GL, McTavish D. Intranasal calcitonin: a review of its pharmacological properties and role in the management of postmenopausal osteoporosis. *Drugs Aging*. 1996;8:378-400.
2. Eddy DM. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. *Osteoporosis Int*. 1998;S1-S88.
3. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. *Endocrine Rev*. 2002;23(4):540-551.
4. Chesnut CH III, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The Prevent Recurrence of Osteoporotic Fractures Study. *Am J Med*. 2000;109:267-276.

**FIT: Risk reduction of alendronate vs. placebo
(n=3658)**

Fracture class	Risk reduction	p-value
Radiologic vertebral	48%	< 0.001
Multiple vertebral (radiologic)	87%	< 0.001
Clinical vertebral	45%	0.003
Any clinical	30%	< 0.001
Nonvertebral	27%	< 0.001
Nonvertebral (osteoporotic)	36%	0.002
Hip	53%	0.005
Wrist	30%	0.038

Bisphosphonates act by decreasing bone turnover, and therefore bone loss, and by increasing bone mineralization and density. The two available bisphosphonates, alendronate and risedronate, represent major additions to the therapeutic armamentarium for the prevention and treatment of osteoporosis.

Cranney et al conducted a meta-analysis of 11 trials of alendronate.¹ The pooled risk reduction for vertebral fractures in patients given alendronate was 48%. For nonvertebral fractures in patients given 10 mg of alendronate or more, the risk reduction was 49%. The investigators found similar risk reductions across all nonvertebral fracture types. Alendronate also demonstrated significant increases in BMD that were directly proportional with dose and length of treatment.

The largest study included in the above meta-analysis was the Fracture Intervention Trial (FIT).² This slide shows the results from this trial of a combined analysis of women with and without existing vertebral fractures.

1. Cranney A, Wells G, Willan LG, et al. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocrine Rev.* 2002;23(4):508-516.
2. Black DM, Thompson DE, Bauer DC. Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial. *J Clin Endocrinol Metab.* 2000;85(11):4118-4124.

FIT: Number of patients needed to treat with alendronate for five years to prevent selected types of fractures

Fracture class	Women with existing vertebral fractures	Women without vertebral fractures and T-score < -2.5
Any radiologic fracture	8	29
Any clinical	13	11
Any nonvertebral	21	12
Hip	46	66

The results of FIT also showed that the benefits of treatment with alendronate are apparent fairly soon after initiating treatment, with reductions in fracture risk becoming statistically significant as early as 12-18 months after initiation of treatment.¹

As this slide shows, only a modest number of women with osteoporosis need to be treated to prevent fractures. Alendronate can be given in a once-weekly dose of 70 mg, since FIT demonstrated the equivalency of the weekly dose to the 10 mg daily dose in increasing BMD and suppressing bone markers.

1. Black DM, Thompson DE, Bauer DC. Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial. *J Clin Endocrinol Metab.* 2000;85(11):4118-4124

Results of meta-analysis of risedronate trials

- Vertebral fractures reduced by 35%
- Nonvertebral fractures reduced by 27%
- Pooled estimate of difference in percent change in BMD (risedronate vs. placebo):
 - 4.54% for the lumbar spine
 - 2.75% for the femoral spine

Risedronate recently received FDA approval for the prevention and treatment of osteoporosis in postmenopausal women. A meta-analysis was conducted of eight randomized, placebo-controlled trials of postmenopausal women receiving either risedronate or placebo who were followed for at least one year.¹ In patients receiving 2.5 mg/day or more of risedronate, the reduction in risk of vertebral fractures was 35% compared with placebo; for nonvertebral fractures, the risk reduction was 27%. Risedronate also had positive effects on the percentage change in BMD of the lumbar spine, combined forearm, and femoral neck.

1. Cranney A, Tugwell P, Adachi J, et al. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocrine Rev.* 2002;23(4):517-523.

Results of VERT trial (risedronate 5 mg/day)

- New vertebral fractures reduced by 41% ($p=0.003$)
- Nonvertebral fractures reduced by 39% ($p=0.02$)
- BMD increased significantly
- Results compromised by high dropout rate

Two large-scale studies included in the above meta-analysis were the basis for the FDA approval of risedronate. Both trials studied postmenopausal women with severe osteoporosis (two or more vertebral fractures at baseline or one vertebral fracture and a BMD score < -2.0). The VERT (Vertebral Efficacy with Risedronate Therapy) trial studied the effects of risedronate in 2458 postmenopausal women less than 85 years of age.¹ Treatment with 5 mg/day of risedronate decreased the incidence of new vertebral fractures over three years by 41% compared with placebo ($p = 0.003$). The cumulative incidence of nonvertebral fractures over three years was reduced by 39% in the risedronate group ($p = 0.02$). Bone mineral density increased significantly at the lumbar spine, femoral neck, femoral trochanter, and midshaft of the radius. The overall safety profile of risedronate was similar to placebo. However, the results of the VERT trial are compromised by the high dropout rate.

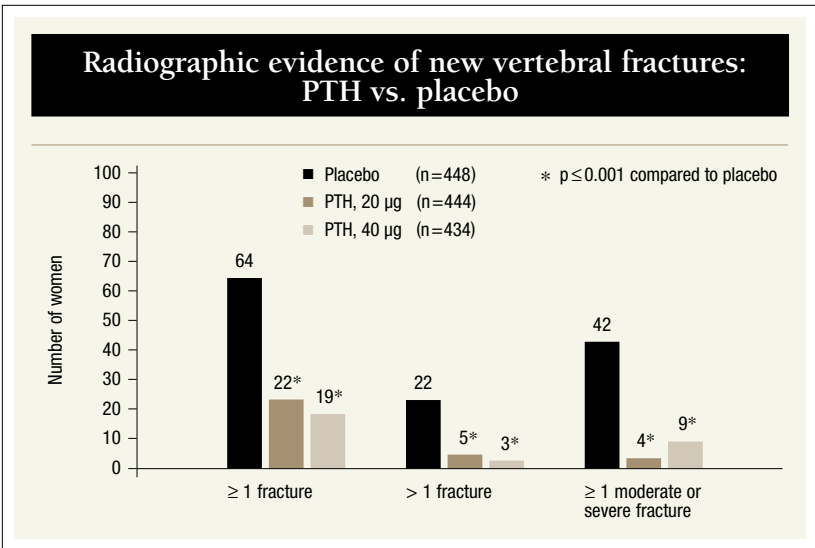
1. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: A randomized controlled trial. *JAMA*. 1999;282(14):1344-1352.

Effect of risedronate on hip fracture

- Overall reduction in hip fracture: 30% ($p=0.02$)
- Reduction in hip fracture among women aged 70-79 with osteoporosis: 40% ($p=0.009$)
- No reduction seen in women over age 80 with nonskeletal risk factors
- Results compromised by lack of follow-up in 36% of patients

The effect of risedronate on the risk of hip fracture was studied in 5445 women aged 70 to 79 with osteoporosis.¹ Patients were randomly assigned to receive risedronate 2.5 mg/day, 5 mg/day, or placebo. The overall incidence of hip fracture among women assigned to risedronate was 2.8%, compared with 3.9% among those assigned to placebo; this represents a 30% risk reduction ($p = 0.02$). In the group aged 70 to 79 with osteoporosis, the reduction in risk of hip fracture was 40% ($p=0.009$). In the group of women over age 80 selected primarily on the basis of nonskeletal risk factors, the reduction in hip fracture risk was not significant compared to placebo. The low number of fractures in the placebo group may not have allowed the treatment to show a significant result. The overall results of this trial are also compromised by a lack of follow-up in 36% of enrolled patients. Risedronate is now available as a once-weekly, 35-mg dose.

1. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med.* 2001;344(5):333-340.



Human recombinant 1,34 N-terminal parathyroid hormone (PTH) has recently received FDA approval for the treatment for osteoporosis. PTH is a potent stimulator of bone formation and resorption and, depending on its administration route (continuous IV or daily subcutaneous injections), it can increase or decrease bone mass.¹ Neer et al conducted a randomized controlled study of PTH to determine its effects on fracture risk in postmenopausal women with prior vertebral fractures. Of the 1326 women for whom radiographs were available, 105 had one or more new vertebral fractures. Compared with placebo, PTH 20 µg and 40 µg reduced the risk of one or more new vertebral fractures by 65% and 69%, respectively, while the risk of two or more new vertebral fractures was reduced by 77% and 86%, respectively. Nonvertebral fragility fractures were reduced by 53% and 54%, respectively. Treatment with PTH also produced significant, dose-dependent increases in BMD of the spine and hip, as well as total-body bone mineral.

1. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344(19):1434-1441.

Estimate of relative risk reduction of available osteoporosis agents				
Intervention	Vertebral fractures		Nonvertebral fractures	
	Risk reduction (95% CI)	p-value	Risk reduction	p-value
Calcium	33%	0.14	14%	0.66
Vitamin D	37%	<0.01	23%	0.09
HRT*	34%	0.12	13%	0.10
Raloxifene	40%	0.01	9%	0.24
Calcitonin [†]	21%	0.05	20%	0.16
Alendronate	48%	<0.01	49%**	<0.01
Risedronate	46%	0.01	27%	<0.01

* Does not include WHI results † Estimate obtained from PROOF trial ** Alendronate doses of 10-40 mg

This slide is an estimate of the relative efficacy of available agents in reducing vertebral and nonvertebral fractures based on the meta-analysis of controlled studies by Cranney et al.¹ The authors caution that, for a variety of reasons, direct comparisons between trials are unreliable. They also note that confidence intervals around the magnitude of treatment effect sometimes overlap, so that apparent differences in the point estimates may not reliably reflect actual differences in treatment effect. The quality of the available data appears strongest for alendronate, risedronate and, to a lesser degree, for vitamin D. Results for these agents tend to be consistent from one study to the next.

Thus, while there are a number of factors besides efficacy that affect the choice of an agent to prevent or treat osteoporosis, the weight of the evidence clearly justifies the current role of bisphosphonates as first-line therapy.

1. Cranney A, Guyatt G, Griffith L, et al. Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocrine Rev.* 2002;23(4):570-578.

P A R T T W O

14 PowerPoint slides on enclosed CD

