

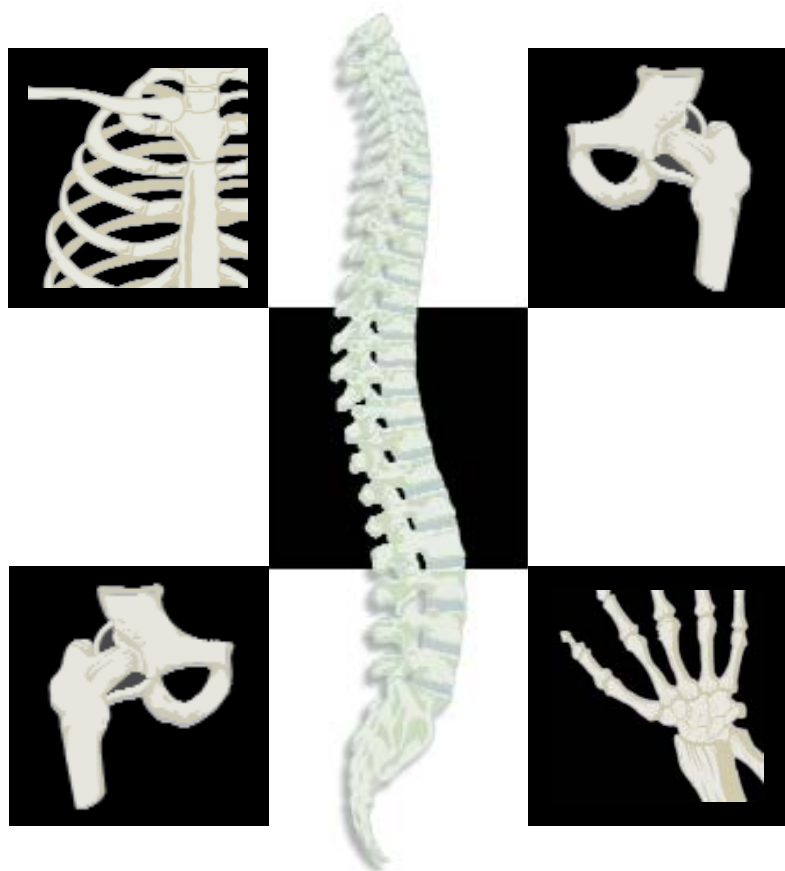
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# OSTEOPOROSIS: THE ERA OF THE BISPHOSPHONATES

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## P A R T T H R E E

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*This slide kit with lecture notes is based on Part 3 of a continuing medical education program sponsored by the School of Medicine, Virginia Commonwealth University, Medical College of Virginia (VCU Campus) and supported by an educational grant from Merck & Co., Inc.*

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

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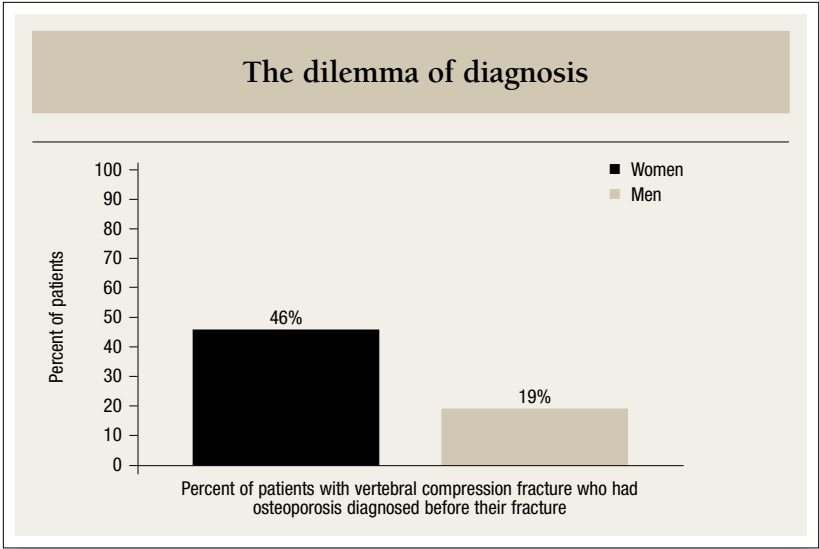
- I. Recent developments affecting treatment of osteoporosis
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### The Women's Health Initiative study results

- HT increased BMD and reduced fracture risk
- Data from estrogen/progestin arm showed increased risk of breast cancer and stroke with little or no CV benefit
- With exception of breast cancer risk, these results are confirmed by estrogen-alone arm

As expected, initial and continuing results from the WHI showed that hormone therapy (HT) significantly increased bone mineral density (BMD) and reduced the risk of fracture compared to placebo.<sup>1</sup> However, data that began to appear from the estrogen/progestin arm of the WHI in 2002 also showed an increased risk of breast cancer and stroke, with little or no cardiovascular benefit from long-term HT.<sup>2-4</sup> With the exception of increased breast cancer risk, these results were recently confirmed in the estrogen-alone arm of the study<sup>5</sup>, which also suggested increased risk of dementia and cognitive impairment associated with HT in a subgroup of women over age 65.<sup>6,7</sup>

1. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003;290(13):1729-1738.
2. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289(24):3243-3253.
3. Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. *JAMA*. 2003;289(20):2673-2684.
4. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med*. 2003;349(6):523-534.
5. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701-1712.
6. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291(24):2947-2958.
7. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*. 2004;291(24):2959-2968.



**A**nother current issue in osteoporosis is low rates of BMD screening and diagnosis of osteoporosis in postmenopausal women. A recent alarming study of patients who had already suffered vertebral compression fractures showed that only 38%, including 46% of women and 19% of men, had received a diagnosis of osteoporosis before the fracture, and only 69% of the women who had been diagnosed were receiving osteoporosis prescription medications.<sup>1</sup>

1. Neuner JM, Zimmer JK, Hamel MB. Diagnosis and treatment of osteoporosis in patients with vertebral compression fractures. *J Am Geriatr Soc.* 2003;51(4):483-491.

**Who should be treated? New NOF guidelines:**

- BMD T-scores less than -2.0 and no other risk factors
  - BMD T-scores below -1.5 and one or more other risk factors
  - Patients with prior vertebral or hip fractures
- 

In view of increased awareness of the need for close monitoring of BMD in postmenopausal women who may have discontinued HT or changed to low doses of HT, the National Osteoporosis Foundation recently revised its guidelines for determining who should be treated. Hip and spine dual-energy x-ray absorptiometry should be used to measure BMD. The number of standard deviations from the average BMD of young adults is the T-score. In addition, the contribution of risk factors, such as history of fractures, a family history of osteoporotic fractures, smoking, a thin build, and frequent falls, is evaluated for each patient. Patients with BMD T-scores less than -2.0 and no other risk factors, patients with BMD T-scores below -1.5 and one or more other risk factors, and patients who have had a prior vertebral or hip fracture should receive osteoporosis therapy.<sup>1</sup>

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1. National Osteoporosis Foundation. *Physician's Guide to Prevention and Treatment of Osteoporosis*. Available at <http://www.nof.org/physguide> Accessed July 6, 2004.

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### Ten-year alendronate study (*N Engl J Med*)

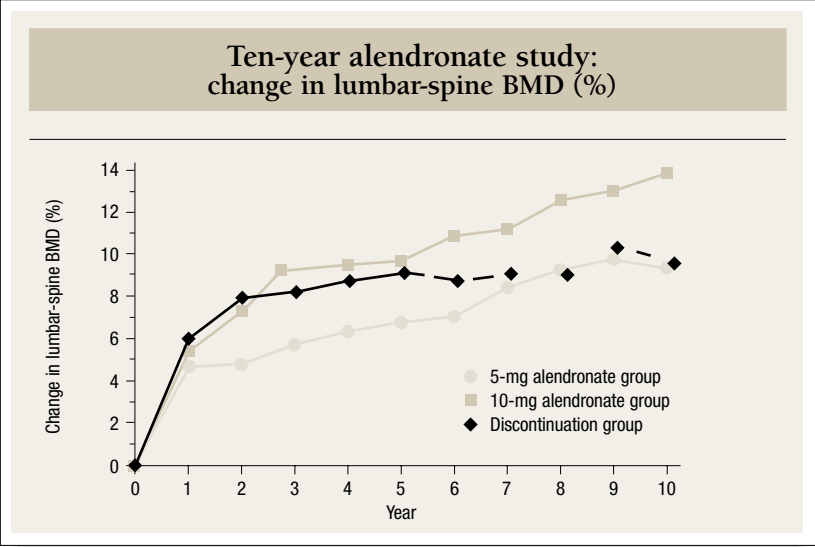
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- 247 postmenopausal women with osteoporosis
  - Subjects received alendronate for up to 10 years
  - Study design: randomized, double-blind, placebo-controlled
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**A**lendronate has been available in the United States since 1995 and is associated with the most extensive clinical experience of any non-hormonal therapy for prevention of osteoporosis. A recent publication in the *New England Journal of Medicine* reports results for 247 postmenopausal women with osteoporosis who received alendronate for up to 10 years in a randomized, double-blind, placebo-controlled study.<sup>1</sup>

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1. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med*. 2004;350(12):1189-1199.



In patients who received 5 mg/d or 10 mg/d alendronate for up to 10 years, BMD at the lumbar spine continued to increase during years 6 through 10 and years 8 through 10. The alendronate groups had no decreases in BMD at any skeletal site during years 6 through 10. Markers of bone remodeling were reduced to low levels that were stable throughout the study. In patients who discontinued active treatment and began to receive placebo after 5 years, decreases in BMD occurred at several sites but remained above baseline at the 10-year follow-up measurement. Also, bone markers increased in patients who discontinued active treatment but remained below baseline measurements.<sup>1</sup>

1. Bone HG, Hosking D, Devogelaer JP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med.* 2004;350(12):1189-1199.

**Preliminary results of EFFECT  
(the Efficacy of Fosamax vs Evista Comparison Trial)**

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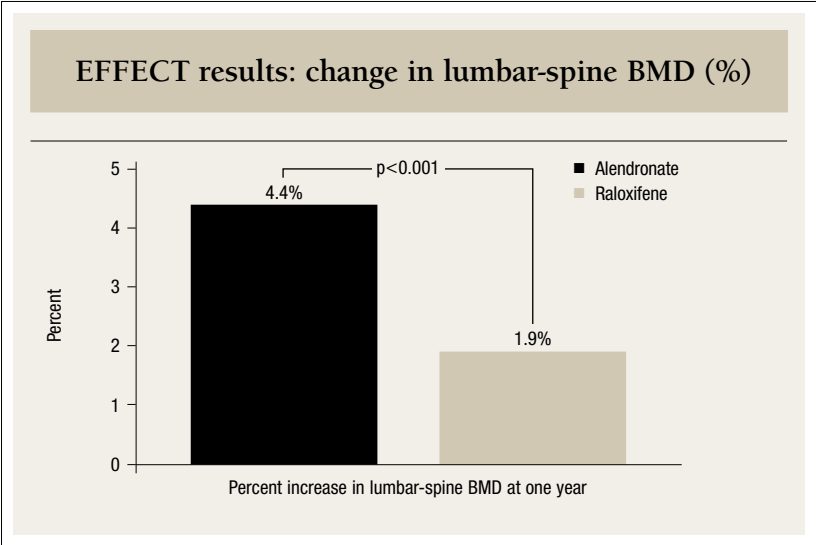
- 456 women with osteoporosis
  - Randomized to alendronate 70 mg once weekly or raloxifene 60 mg/day
  - BMD measured at baseline, at 6 months, and at 12 months
  - Primary end point: % change in lumbar-spine BMD at one year
- 

**P**reliminary results are also available from a year-long study (the Efficacy of Fosamax® vs Evista® Comparison Trial, or EFFECT) that compared increases in BMD in 456 women with osteoporosis. The patients were randomized to receive alendronate 70 mg once weekly or raloxifene 60 mg per day and BMD was measured at baseline, after 6 months of treatment, and after 12 months of treatment. The primary end point was percent change in BMD at the lumbar spine at the one-year time point.<sup>1</sup>

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1. Luckey M, Kagan R, Greenspan S, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. *Menopause*. 2004;11(4):405-415.

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**A**fter one year, increases in lumbar-spine BMD in patients who received alendronate were more than 2-fold higher than increases in patients who received raloxifene (4.4% vs 1.9%;  $p < 0.001$ ). Total hip BMD increased 2.0% for patients who received alendronate and 1.0% for patients who received raloxifene at the one-year time point ( $p < 0.001$ ). The response rate, defined as the percentage of patients who increased or maintained BMD, was 94% for the alendronate group and 75% for the raloxifene group.<sup>1</sup> There were no clinically apparent vertebral or hip fractures in either treatment arm.

1. Luckey M, Kagan R, Greenspan S, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. *Menopause*. 2004;11(4):405-415.

### Current treatment options: Estrogen

- Ultralow-dose formulation recently approved for prevention of osteoporosis
- Results of a controlled trial of very-low-dose transdermal estradiol in 417 women aged 60-80:
  - Lumbar-spine BMD increased 2.6% in estradiol group and 0.6% in the placebo group ( $p < 0.001$ )
  - Mean total hip BMD increased 0.4% in the estradiol group and decreased 0.8% in the placebo group ( $p < 0.001$ )

Estrogen therapy is now recommended, in low doses and for short periods of time, only for treatment of urogenital or vasomotor symptoms in peri- or postmenopausal women.<sup>1</sup> However, ultralow-dose formulations of estrogen are under investigation, and one of these was recently approved for the prevention of osteoporosis in postmenopausal women (Menostar®; Berlex). *Ettinger et al* conducted a placebo-controlled, double-blind trial of very-low-dose transdermal estradiol (0.014 mg/d) in 417 women aged 60-80, with bone mineral density z-scores of -2.0 or higher.<sup>2</sup> Median plasma estradiol levels in the treated group (n=208) increased from 4.8 pg/mL at baseline to 8.5 pg/mL at one year and 8.6 pg/mL at two years ( $p < 0.001$ ). Lumbar-spine bone mineral density increased 2.6% in the estradiol group and 0.6% in the placebo group (between-group difference 2.0%,  $p < 0.001$ ). Mean total hip bone mineral density increased 0.4% in the estradiol group and decreased 0.8% in the placebo group (between-group difference 1.2%,  $p < 0.001$ ).

1. The American College of Obstetricians and Gynecologists. Response to Women's Health Initiative study results. Available at: [www.acog.org](http://www.acog.org)
2. Ettinger B, Ensrud KE, Wallace R, et al. Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol.* 2004;104(3):443-451.

### Current treatment options: SERMs

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■ Results of MORE trial:

- Modest benefits on BMD
  - Reductions in bone turnover markers
  - Reduction in risk of vertebral fractures
  - Significant reductions seen in incidence of breast cancer and cardiovascular and cerebrovascular disease
- 

**R**aloxifene is the only SERM indicated to prevent or treat osteoporosis. Raloxifene is a non-hormonal agent that binds selectively to estrogen receptors on many cells, producing activation of some estrogen pathways and blockage of others. Raloxifene interactions with the estrogen receptor inhibit bone resorption. Raloxifene does not have estrogen-like adverse effects on endometrial and breast tissue.<sup>1</sup>

The efficacy of raloxifene for prevention and treatment of osteoporosis was shown in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial.<sup>2</sup> Raloxifene treatment was associated with modest effects on bone density and was shown to produce reductions in bone turnover markers. In addition, the risk of vertebral fractures was reduced. There were no data for nonvertebral fractures from this trial. The MORE trial also showed that raloxifene treatment produced significant reductions in the incidence of breast cancer as well as cardiovascular and cerebrovascular disease.

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1. Evista® (raloxifene hydrochloride) package insert, Eli Lilly and Company.

2. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA*. 1999;282(7):637-645.

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### Current treatment options: Calcitonin

- Results of PROOF trial:
  - 200 IU/day reduced risk of vertebral fractures by 33% overall and by 36% in patients with existing vertebral fractures
  - 100 IU/day and 400 IU/day did not reach statistical significance
- Results problematic because of 59% dropout rate and lack of blinding

**C**alcitonin (Miacalcin®; Novartis) interacts directly with receptors on osteoclasts, inhibiting bone resorption.<sup>1</sup> There are two dosage forms of salmon calcitonin, injectable (rarely used) and a nasal spray. The nasal spray form was evaluated in the Prevent Recurrence of Osteoporotic Fractures (PROOF) trial. In this large, double-blind, randomized, placebo-controlled trial, postmenopausal women with established osteoporosis received 100, 200, or 400 IU calcitonin daily by nasal spray. Lumbar-spine BMD was increased and markers of bone turnover were decreased in all treatment groups compared with placebo ( $p < 0.01$  for all comparisons). In this study, 200 IU per day significantly reduced the risk of new vertebral fractures by 33% overall and by 36% in patients with existing vertebral fractures. However, 100 IU and 400 IU per day reductions in fractures did not reach significance.<sup>2</sup> Results from this trial are problematic, due to the dropout of 59% of the patients before the end of the trial and an absence of dose response in fracture reduction. In addition, the PROOF study was only partially blinded.

1. Hardman JG, Limbird LL. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th edition. New York: The McGraw-Hill Companies, Inc., 1996.
2. 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 Study Group. *Am J Med*. 2000;109(4):267-276.

### Current treatment options: Bisphosphonates

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- Bind to sites where active bone resorption is taking place
  - Bone resorption is inhibited while bone formation continues, resulting in net increases in bone mass
  - Two available bisphosphonates: alendronate and risedronate
- 

**B**isphosphonates are synthetic analogues of pyrophosphate that work by binding preferentially to hydroxyapatite in bone where active bone resorption is taking place under osteoclasts. Bone resorption is inhibited at the sites where bisphosphonates are bound and bone formation continues, resulting in net increases in bone mass at those sites.<sup>1</sup> Two bisphosphonates are indicated for osteoporosis prevention and treatment in the United States, alendronate (Fosamax®; Merck & Co.) and risedronate (Actonel®; Procter & Gamble). To maximize absorption of bisphosphonates, they must be taken on an empty stomach first thing in the morning with water only, and cannot be followed by any food or drink for at least 30 minutes.

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1. Fosamax® (alendronate sodium) prescribing information. Merck & Co., Inc.

**Current treatment options: Bisphosphonates (cont.)**

## ■ Results of FIT:

- Alendronate increased spine BMD by 7-9% and hip BMD by 5-8%
- By year 4, the risk of fracture in women with osteoporosis but no prior hip fractures was reduced by 56%

## ■ Results of VERT trial:

- Approximately 40% reductions in risk of vertebral fractures with risedronate
- These reductions were sustained for at least five years

**A**lendronate, the most potent available agent for prevention and treatment of osteoporosis, was studied in the Fracture Intervention Trial (FIT), a large, randomized, double-blind, placebo-controlled study in patients with low BMD measurements. Patients who received alendronate (5 mg/day, increased to 10 mg/day two years into the study) had increases in BMD (average 7% to 9% at the spine and 5% to 8% at the hip compared to placebo). By year 4, the risk of fracture in women with osteoporosis but no prior hip fractures was reduced by 56%.<sup>1</sup>

Risedronate produces moderate effects on BMD in the spine and hip and reduces the risk of osteoporotic fractures. The Vertebral Efficacy with Risedronate Therapy (VERT) trials<sup>2,3</sup> documented approximately 40% reductions in the risk of vertebral fractures. These reductions were sustained for at least five years.

1. Black DM, Thompson DE, Bauer DC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. *J Clin Endocrinol Metab.* 2000;85(11):4118-4124.
2. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA.* 1999;282(14):1344-1352.
3. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int.* 2000;11(1):83-91.

### Anabolic therapy (PTH)

- Stimulates osteoblastic activity, resulting in increases in bone mass and strength
- Results of a randomized, controlled study:
  - BMD increased overall and in lumbar spine and vertebral neck
  - New vertebral fractures in 14% (placebo), in 5% (20- $\mu$ g group), and 4% (40- $\mu$ g group)

**A** recent addition to the armamentarium of non-estrogen therapies for osteoporosis is a derivative of human parathyroid hormone (PTH). The recombinant form of PTH, teriparatide, was approved in 2002 (Forteo®; Lilly), a subcutaneously administered injection. Once-daily administration of PTH stimulates osteoblastic activity resulting in increases in bone mass and strength.<sup>1</sup>

This agent was evaluated in 1637 postmenopausal women with prior vertebral fractures in a randomized placebo-controlled trial. Patients who received 20  $\mu$ g/d and 40  $\mu$ g/d doses of PTH had increased BMD overall, and in the lumbar spine and femoral neck specifically, relative to placebo. New vertebral fractures occurred in 14% of women in the placebo group and in 5% and 4%, respectively, of the women in the 20- $\mu$ g group and the 40- $\mu$ g group. The risk of nonvertebral fractures was reduced by more than 50% in the two treatment groups.<sup>2</sup>

1. Forteo™ teriparatide (rDNA origin) package insert, Eli Lilly and Company.

2. 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.

### Summary

- Evidence supports the bisphosphonates as first-line therapy for the prevention and treatment of osteoporosis.
  - Comparison across trials of antiresorptive therapies suggested that alendronate is more effective than risedronate, calcitonin, raloxifene, or hormone therapy.
- 

**A** meta-analysis of controlled trials provides an estimate of the comparative efficacy of these therapies (with the exception of PTH) for prevention and treatment of osteoporosis.<sup>1</sup> Although direct comparisons between trials are unreliable, strong data are apparent for alendronate and risedronate as first-line therapy.<sup>1</sup> In addition, a recent comparison across trials of antiresorptive therapies suggested that alendronate was more effective than risedronate, calcitonin, raloxifene, and hormone therapy for reducing the risk of vertebral and nonvertebral fractures. Significant differences were found between alendronate and calcitonin for vertebral fractures and between alendronate and risedronate, calcitonin, estrogen, and raloxifene for nonvertebral fractures.<sup>2</sup>

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1. Cranney A, Guyatt G, Griffith L, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev.* 2002;23(4):570-578.
  2. Wehren LE, Hosking D, Hochberg MC. Putting evidence-based medicine into clinical practice: comparing anti-resorptive agents for the treatment of osteoporosis. *Curr Med Res Opinion.* 2003;20:P1-P6.
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*15 PowerPoint slides on enclosed CD*

