The Prevention and Treatment of Postmenopausal Osteoporosis

Educational Partner:
Session 3: The Prevention and Treatment of Postmenopausal Osteoporosis

Learning Objectives
- Identify 3 risk factors for osteoporosis and osteoporotic fractures.
- Review at least 2 pharmacologic interventions available in the treatment of postmenopausal osteoporosis and the effect of therapeutic agents on bone density and fracture risk.

Faculty

**Joseph M. Grisanti, MD**
Assistant Clinical Professor of Medicine
State University of New York at Buffalo
Chief of Rheumatology
Mercy Hospital of Buffalo
Medical Director
Buffalo Rheumatology Associates
Buffalo, New York

Dr Joseph Grisanti is an assistant clinical professor of medicine in the Division of Rheumatology at the State University of New York (SUNY) at Buffalo and Chief of Rheumatology at the Mercy Hospital of Buffalo. He is the medical director of Buffalo Rheumatology Associates in Orchard Park, New York and President of the Buffalo Osteoporosis Institute. Dr Grisanti received a bachelor’s degree in biology from Canisius College in 1980, where he received the coveted 7ri-Bela Award for having the highest grade-point average in the Sciences in his graduating class. He attended medical school at the University of Rochester, graduating in 1984. Dr Grisanti completed a medical residency program at SUNY at Buffalo. He went on to complete a fellowship in rheumatology at the Cleveland Clinic Foundation in 1989. Board Certified in both internal medicine and rheumatology, Dr Grisanti also holds certification with the International Society for Clinical Densitometry.

Dr Grisanti was voted “Teacher of the Year” by the medical staff at Millard Fillmore Hospitals in Buffalo, New York in 1987. Dr Grisanti has published extensively in such journals as the *Journal of Rheumatology*, the *Journal of Clinical Densitometry*, and the *American Family Physician* and has a national reputation as a lecturer in both arthritis and metabolic bone diseases.

**Ellen Hirschman Miller, MD**
Clinical Associate Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York

Ellen Hirschman Miller, MD, is clinical associate professor of medicine at the Albert Einstein College of Medicine and the vice president of academic affairs at Southside Hospital in Bay Shore, New York. She also has a private practice in internal medicine, endocrinology, and reproductive endocrinology in Hewlett, New York.

Dr Miller received her medical degree from New Jersey Medical School in 1980 and completed her post-graduate work at Beth Israel Medical Center and Columbia University. She is on the editorial board of the *International Journal of Fertility and Women's Medicine* and is a fellow of the American Association of Clinical Endocrinologists, as well as a member of the Steering and Scientific Committee for the World Foundation for Medical Studies in Female Health.

Dr Miller has conducted extensive research in the areas of endocrinology and women's health, and has authored articles that have been published in numerous medical journals.

Faculty Financial Disclosure Statements
The presenting faculty reported the following:
Dr Grisanti receives honorarium as a member of the speakers bureau and consultant for Abbott; Amgen; Bristol-Myers Squibb; Centocor; Eli Lilly and Company; GlaxoSmithKline; Genentech; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer, Inc.; Proctor and Gamble; Roche; sanofi-aventis U.S.; Wyeth Pharmaceuticals; and E.C.B. (United Chemicals of Belgium)
Dr Miller receives honorarium from and is a speaker for Novartis Pharmaceuticals Corporation, GlaxoSmithKline, Roche, and Merck & Co., Inc.

Content Collaborator Financial Disclosure Statements
The content collaborators at Potomac Center for Medical Education, A Rockpointe Company have reported the following:

Laurie Frueh, MD, medical science liaison, has no relationships to disclose. Kathy Merlo, medical writer, has no relationships to disclose. Donna Fucello, vice president, has no relationships to disclose. Debra Minnick, program coordinator, has no relationships to disclose.

Drug List

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Suggested Reading List


The Prevention and Treatment of Postmenopausal Osteoporosis

JOSEPH M. GRISANTI, MD

Identification and Evaluation of Postmenopausal Osteoporosis

NIH Consensus Conference Defines ‘Osteoporosis’

A skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture

BONE STRENGTH = BONE DENSITY + BONE QUALITY

Osteoporosis in the US

Epidemiology

1. 40-50% of women ≥ age 50 will suffer an osteoporosis-related fracture within their lifetime
2. Approximately 700,000 vertebral fractures and 300,000 hip fractures occur annually
3. Fewer than half of hospitalized hip-fracture patients recover pre-fracture competence in activities


Normal
Osteoporosis

Osteoporosis in the US

Epidemiology

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Hip Fractures Are Common

Numbers Are Projected to Increase

Increased Morbidity and Mortality

1 Year After Hip Fracture

ADL = activity of daily living


Cooper C. Am J Med. 1997;103:12S-17S.
Case Study 1

History
- Mrs. Brown, a 70-year-old white female, presents for a physical exam
  - HTN x 12 years
  - Mild COPD (last exacerbation requiring oral steroids >1-year prior)
  - Continues to smoke ½ pack/day
  - Depression x 2 years

Medications
- Amlodipine
- Albuterol prn
- Sertraline
- Tiotropium

Physical Exam/Study Findings
- 5'3", 118 pounds, healthy appearing Caucasian female
- BP 122/78, NAD
- T-scores: -1.3 at lumbar spine (LS) and -1.5 at the femoral neck (FN)

Indications for BMD Testing
- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Men age 50-70 and younger postmenopausal women about whom you have concern, based on their clinical risk factor profile

What is Mrs. Brown’s chance of fracture in the next 10 years?
1. Pretty low because her T-scores are not osteoporotic
2. About the same as a 50-year-old who has the same T-scores
3. Higher than a 50-year-old who has a femoral neck T-score of -3.0
4. The same as a 50-year-old with a femoral neck T-score of -3.0

10-year Probability of Fracture in Women

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<th>Age (years)</th>
<th>T-Score 0</th>
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<td>15.2</td>
<td>19.4</td>
<td>24.5</td>
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Indications for BMD Testing, cont’d: Risk Factor Profiles
- Perimenopausal women with a specific risk factor associated with increased fracture risk (e.g. smoking, family history)
- Fracture after age 50
- Adults with a condition (e.g. rheumatoid arthritis) or taking a medication (e.g. glucocorticoids) associated with bone loss
- Individuals with primary hyperparathyroidism
- Anyone being considered for pharmacologic therapy for osteoporosis
- Anyone being treated for osteoporosis, to monitor treatment effect
- Postmenopausal women discontinuing estrogen


ARS

Hip Fracture

Age and BMD Are Independent Risk Factors

Fracture Risk Assessment

- The use of clinical factors can improve identification of people at higher fracture risk
- The WHO Fracture Probability approach will determine an individual’s 10-year hip and major osteoporotic fracture risk based on BMD and other important risk factors

WHO Risk Assessment Tool (FRAX)

- Current age
- Use of oral glucocorticoid therapy
- Gender
- Secondary osteoporosis (e.g. rheumatoid arthritis)
- Personal history of a fracture
- Parental history of hip fracture
- Femoral neck BMD
- Current smoking
- Low body mass index (kg/m2)
- Alcohol intake of 3 or more drinks/day

Summary of Mrs. Brown’s Fracture Risk

- 70-year-old postmenopausal female with a femoral neck T-score of -1.5
- Based on other major risk factors her 10-year probability of:
  - Hip fracture: 4.3%
  - Major osteoporotic fracture: 22%
- Should she be treated?

National Osteoporosis Foundation (NOF) 2008 Additions to Treatment Guidelines

- Initiate treatment in postmenopausal women and in men age 50 and older with:
  - Low bone mass (T-score -1 to -2.5, osteopenia) at the femoral neck, total hip, or spine and 10-year hip fracture probability ≥3%
  - 10-yr all major osteoporosis-related fracture probability of ≥20%, based on the US-adapted WHO absolute fracture risk model.
- FRAX tool calculates probability for major osteoporotic fracture and hip fracture

Take Home Messages

- BMD should be completed on all women over 65, or younger postmenopausal women with risk factors for osteoporosis
- T-scores don’t tell the whole story
- Age and BMD are independent risks for fracture
- The WHO FRAX tool will help clinicians identify patients who should receive treatment by incorporating other risk factors into a 10-year fracture risk determinant
- The WHO FRAX tool should ONLY be used in treatment naïve patients
Identifying Others at Risk for Osteoporotic Fractures

Risk Factors for Fracture

- Low BMD
- Advanced age
- History of fracture as an adult
- History of a low trauma fracture in a first-degree relative
- Low body weight (<127 lbs)
- Smoker
- Use of oral corticosteroid therapy for >3 months
- Excessive alcohol intake (>2 drinks per day)
- Medications (narcotics, sedatives, diuretics)
- Impaired vision
- Weakness
- Estrogen deficiency at an early age (<45 yrs)
- Hypogonadism
- Discontinuation of estrogen therapy
- Dementia
- Poor health status/frailty
- Low physical activity
- Recent falls
- Poor mobility
- Lifelong low calcium intake/low vitamin D

Risk Factors for Falls

- Prior falls
- Age, female, white
- Low mobility or poor neuromuscular control, neurological disease or cognitive deficit
- Use of eye meds, impaired vision
- Use of psychotropic drugs, diuretics, laxatives
- Dependency in ADLs, chronic medical conditions, DJD, HBP
- Low systolic blood pressure
- Low BMI

FALL EVALUATION

- Observe patient walking to exam room
- Have patient do “get up and go” test
- Assess vision
- If any of above are impaired, arrange for in-home evaluation to assess hazards/minimize risks

Medical Conditions Contributing to Osteoporotic Fracture Risk

- Endocrine Diseases
  - Hyperthyroidism
  - Hyperparathyroidism
  - Hypogonadism
  - Diabetes Mellitus
- GI Diseases
  - Malabsorption syndromes
  - Chronic liver disease
  - Gastric operations
- Organ Transplant
- Other Chronic Diseases
  - Rheumatoid arthritis
  - Chronic lung disease
  - Malignancy
  - Renal Insufficiency
- Dietary Disorders
  - Vitamin D deficiency/insufficiency
  - Excess alcohol intake
  - Anorexia nervosa

Medications Contributing to Osteoporotic Fracture Risk

- Glucocorticoids
- Long-acting progestin
- Aromatase inhibitors
- Gonadotropin-releasing hormone agonists
- Anticonvulsants
- Cytotoxic drugs
- Long-term heparin
- Lithium
- Proton pump inhibitors
- Selective serotonin receptor inhibitors
- Glitazones


How Often Do “Healthy” Women with Osteoporosis Have Underlying Disorders?

- 173 “healthy” women age 46-87
- T-score < -2.5
- No prior lab abnormalities
- Evaluated for secondary osteoporosis:
  - CBC, chemistry, 24-hr urine for calcium, PTH, 25(OH) Vitamin D
  - Most also had TSH, SPEP
- Result: 44% had at least one unexpected new diagnosis

Data recalculated from Tannenbaum C et al. J Clin Endocrinol Metab. 2002;87:4431-4437.

All of the following should be considered in the routine evaluation of someone found to be osteoporotic EXCEPT…

1. Complete blood cell count
2. Renal/liver function
3. Serum chemistries
4. TSH
5. 1,25(OH)2D
6. 24-hour urine for calcium and creatinine

Laboratory Assessment

Consider the following:

- Complete blood cell count
- Renal/liver function
- Serum chemistries
- TSH
- 25(OH)D
- 24-hour urine for calcium and creatinine

Laboratory Assessment

Specialized Testing for Secondary Osteoporosis

- Intact PTH
- Urine-free cortisol or overnight dexamethasone suppression test (if considering Cushing’s syndrome)
- SPEP, UPEP, and IEP (if anemia, high ESR, protein or calcium)
- Tissue transglutaminase AB IgA and small bowel Bx (if malabsorption, low iron, or low 25(OH) vitamin D with suggestive Hx)
- Serum iron and ferritin (if malabsorption or hemachromatosis)
- Transiliac bone biopsy (very selected cases)

Take Home Messages

- Fracture risk includes both risk factors for osteoporosis and risk factors for fall
- When evaluating patients with osteoporosis, consider secondary causes
- Check calcium and vitamin D levels

Case Study, continued:

- Mrs. Brown’s lab work all came back within normal limits
- Her femoral neck BMD is –1.5
- Based on other risk factors and using the WHO FRAX tool, her 10-year probability of:
  - Hip fracture: 4.3%
  - Major osteoporotic fracture: 22%
What treatment options should we consider for Mrs. Brown?

1. No need to treat, her BMD is not osteoporotic
2. Lifestyle modifications at this time; recheck BMD in 1-2 years
3. Pharmacotherapy only
4. Lifestyle modifications and pharmacotherapy

**NOF 2008 Updated Treatment Recommendations**

- Postmenopausal women and men age 50 and older presenting with the following should be treated:
  - Hip or vertebral fracture
  - Other prior fractures and low bone mass (T-score between -1.0 and -2.5 at the femoral neck, total hip, or spine)
  - T-score < -2.5 at the femoral neck, total hip, or spine after appropriate evaluation to exclude secondary causes
  - Low bone mass and secondary causes associated with high risk of fracture (e.g. glucocorticoid use or total immobilization)
  - Low bone mass + 10-yr probability of hip fracture ≥3% or 10-yr probability of any major osteoporosis related fracture ≥20%

**Prevention Measures**

**Nonpharmacologic**

- Fall prevention strategies
- Regular weight-bearing exercise
  - Strength training maintains or increases BMD, improves muscle mass, strength, and balance
  - Nurses Health Study: active women with 24 metabolic equivalent task (MET)-h/wk had 55% lower risk of hip fracture (linear relationship)
- Avoid tobacco & excessive use of alcohol

**Vitamin D**

- Actually a hormone (not really a vitamin)
- UVB rays convert 7-dehydrocholesterol to vitamin D₃ in the skin
- By age 65, 75% reduction in vitamin D production in skin
- Few dietary sources
- Fat soluble
- Supplements differ in type and quantity
  - Ergocalciferol (vitamin D₂)
  - Cholecalciferol (vitamin D₃)

**Recent Emphasis on Vitamin D**

In Search of the Sun…

Vitamin D Supplementation Decreases Fall and Fracture Risk

Change in Vitamin D Recommendation

Old Guideline
- Vitamin D 400 IU/d for women under age 70
- Vitamin D 600 IU/d for women over age 70

2008 Guideline
- Vitamin D 400-800 IU/d for all women under age 50
- Vitamin D 800-1,000 IU/d for all women over age 50

Recommendations for Calcium and Vitamin D
- Calcium
  - 1200-1500 mg/day
- Vitamin D
  - 800-1000 IU/day
  - May safely use up to 2000 IU/day
    - Aim for 25(OH) vitamin D level ≥ 30 ng/mL
    - Toxicity rare unless chronic doses > 10,000 IU daily
- For deficient vitamin D levels
  - 50,000 IU once/twice weekly for 8-12 doses
  - After correction, use 1000 IU/day or 50,000 IU 1-2x/mo

Which calcium product contains the most elemental calcium?
1. 1000 mg of calcium carbonate
2. 1000 mg of calcium citrate
3. 1000 mg of calcium phosphate
4. 1000 mg of calcium gluconate

Vitamin D Supplementation Decreases Fall and Fracture Risk

Which calcium product contains the most elemental calcium?

Recommendations for Calcium and Vitamin D

Pharmacologic Options for Osteoporosis Treatment in Women
- Antiresorptive Agents
  - Lower bone turnover, maintain/improve bone mass, stabilize bone architecture
    - Hormone (salmon calcitonin)
    - SERM (raloxifene)
    - Bisphosphonates
      - alendronate with/without vitamin D
      - risedronate
      - ibandronate
      - zoledronic acid
- Anabolic Agent
  - Increase bone turnover with bone formation, > bone resorption, increase bone mass, and improve bone architecture
    - Teriparatide
**FDA-Approved Osteoporosis Indications**

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<th>Reduce Hip Fractures</th>
<th>Reduce Nonvertebral Fractures</th>
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<td>Teriparatide</td>
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**Raloxifene Update**

- Osteoporosis indication: vertebral fracture reduction in women
- Adverse events: hot flashes, venous thromboembolic events, leg cramps
- 9/13/07: FDA-approved raloxifene “...for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and postmenopausal women at high risk for developing breast cancer.”

**Bisphosphonates**

- Most commonly prescribed therapy for osteoporosis
- Oral bisphosphonates indicated for prevention and treatment of postmenopausal osteoporosis, IV formulation indicated for treatment only
- Adverse events: esophageal irritation or erosion (oral only), hypocalcemia, bone pain
- Contraindications: esophageal dysmotility (oral only), significant renal dysfunction, hypocalcemia
- Warnings: rare cases of osteonecrosis of the jaw (ONJ)

**Bisphosphonate Indications for Osteoporosis**

<table>
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<tr>
<th>Top Menopausal Prevention</th>
<th>Oral Menopausal Treatment</th>
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<th>Treatment Steroid-induced</th>
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**Risedronate Update**

- FDA approves risedronate 150 mg once-monthly dosing on April 24, 2008
  - Study shows similar improvement in BMD compared to 5 mg daily
- Additional indications
  - Reduction of spine and nonvertebral fractures
  - Prevention and treatment of steroid-induced osteoporosis
  - Treatment of male osteoporosis

**Ibandronate Update: Results from Meta-analysis**

- Annual cumulative exposure 210.8 mg
- Placebo


**Ettinger B et al. JAMA. 1999;282:637-645.**


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Zoledronic Acid Update

- FDA approves use of zoledronic acid for the treatment of postmenopausal osteoporosis on September 17, 2007
- Additional indications
  - Reduction of spine, nonvertebral, and hip fractures
- Available as 5 mg IV infusion given ≥ 15 minutes once yearly


Zoledronic Acid Cumulative Reduction in 3-Year Risk of Clinical Fractures

Teriparatide (Parathyroid Hormone) Update

- Current indications: treatment of postmenopausal women and men with osteoporosis at high-risk of fracture
- Daily 20 mcg injection for a maximum of 2 years
- Recent studies in glucocorticoid-induced osteoporosis (GIOP): Among patients with osteoporosis at high risk for fracture, BMD increased more in patients receiving teriparatide than in those receiving alendronate
- Indication in EU label 04/2008, request to FDA for supplemental indication filed 2007


Assessing Therapeutic Response

Follow-up BMD in the Treated Patient

- Repeat labs and BMD testing after two years in patients taking pharmacotherapy for osteoporosis
- BMD maintained or increased = satisfactory response
- BMD decline
  - Assess technical issues (e.g. validity of DXA comparison)
  - Assess compliance and dosing
  - Consider and re-evaluate for secondary causes
  - Patient may be a true “non-responder”


Long-Term Therapy

- Mrs. Smith has been treated for osteoporosis with an oral bisphosphonate for the past 7 years because of the following T-scores:
  - Lumbar Spine: -2.6
  - Femoral Neck: -2.5
- Her T-scores have improved to their current values:
  - Lumbar Spine: -1.6
  - Femoral Neck: -1.5
- Her previous doctor is suggesting she stop her medication in favor of a drug holiday; she has never had a fracture; she seeks a second opinion from you

What do you tell her?

1. “I am opposed to a drug holiday. I recommend you continue your bisphosphonate as usual.”
2. “Let’s determine your absolute fracture risk using the FRAX™ tool – if your 10-yr all major osteoporosis-related fracture probability is ≤ 20%, we will stop treatment.”
3. “I recommend you stop your medicine for a year, then we will recheck your BMD.”
4. “Because these medicines are incorporated into bone, I am concerned about the potential for you developing ‘frozen bone.’ I believe 7 years is enough. I suggest you stop this medicine and remain off it indefinitely.”

Mrs. Brown returns 8 years later, following a hip fracture

• She is now 78
• She was initially prescribed a weekly bisphosphonate, but was lost to follow-up until now
• Evaluation in the hospital showed normal chemistries, TSH, and vitamin D level
• Further questioning reveals she has been taking her bisphosphonate 1-3 times a month, often with coffee; Recent refills were provided by another physician.

Absorption and Tolerability of Oral Bisphosphonates

affected when dosing instructions are not followed

• Coffee or juice can reduce absorption by as much as 60%.
• Calcium supplements can interfere with absorption and should not be taken at the same time as oral bisphosphonate therapy.
• GI side effects are more likely when dosing instructions are not followed.
• Even when complete instructions are given, between 25% and 50% of patients disregard at least one requirement.

Persistence increases with weekly bisphosphonates but remains suboptimal

Poor Compliance and Persistence Lead to Compromised Fracture Risk Reduction

![Bar chart showing the impact of compliance on fracture risk reduction.]

Bisphosphonate Treatments
Dosing Frequency

<table>
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<th>Agent</th>
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<th>Monthly</th>
<th>Quarterly</th>
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</tr>
<tr>
<td>Zoledronic acid</td>
<td></td>
<td></td>
<td></td>
<td>5 mg IV infusion</td>
</tr>
</tbody>
</table>

Postfracture Management
- By definition, patient has osteoporosis
  - Can get DXA to determine severity
- Evaluate for contributing factors
- Initiate calcium and vitamin D supplementation
- Consider physical therapy
- Begin pharmacologic therapy (can be started in hospital or on discharge)
  - Decision to treat does not require BMD

Individualizing Therapy
Each Modality has its Clinical Place

- Calcium and Vitamin D
- Exercise
- Fall Risk Evaluation
- Alendronate
- Risedronate
- Calcitonin
- Teriparatide
- Zoledronic Acid
- Raloxifene

Take Home Messages
Treatment of Osteoporosis
- Osteoporosis is an important public health concern
- Fracture risk incorporates both BMD and other important risk factors and should be calculated to help determine need for therapy
- Consider secondary causes of bone loss
- Recommend lifestyle modifications in all patients with or at risk for osteoporosis
- Pharmacotherapy should be individualized to the patient
- Patients who have had fractures are at high risk for future fractures and should be targeted for pharmacologic intervention

The Prevention and Treatment of Postmenopausal Osteoporosis
Appendix

WHI Trial: Vitamin D and Colon
Risk of Colon Cancer Increases as Vitamin D Levels Fall


Vitamin D and Tuberculosis
- 67 patients with pulmonary TB
- All patients received standard medical treatment
- In addition, patients were randomly assigned to high dose vitamin D or placebo

25-OH Vitamin D Levels
After 50,000 IU Bolus of D2 and D3

25-OH Vitamin D Level
Days

Manifestations of Vitamin D Deficiency
- Osteoporosis
- Muscular weakness, falls, myalgias
- Cancers
- Cardiovascular benefits
- Neurologic: Multiple Sclerosis
- Endocrinology: Type 1 Diabetes
- Rheumatologic: Rheumatoid Arthritis
- Dermatologic: Psoriasis
- Immunologic: Infections

Death & Vitamin D Supplementation
- Meta-analysis of 18 randomized controlled clinical trials
- Vitamin D vs placebo
- 57,311 patients
- Death from all causes was higher in placebo group
How to Interpret Osteoporosis Clinical Trials

- Nomenclature
  - Morphometric vertebral fractures
  - Clinical vertebral fractures
  - Nonvertebral fractures
  - Hip fractures
- History of previous fractures?

**EXAMPLE OF AN OSTEOPOROSIS CLINICAL TRIAL**

**Alendronate: The Fracture Intervention Trial**

**Vertebral Fractures in Postmenopausal Women (FIT)**

**WITHOUT PRIOR VFx**

- Hip T-score ≤ -2.5; Age range=54-81 yrs
- PBO: n=812
  - 50% Reduction at year 4, p=0.006
- ALN: n=819
  - 50% of patients with fracture

**WITH PRIOR VFx**

- Hip T-score ≤ -1.6; Age range=55-81 yrs
- PBO: n=965
  - 47% Reduction at year 3, p<0.001
- ALN: n=981
  - 51% Reduction at year 3, p=0.047
  - 56% Reduction at year 4, p=0.044

**Patients with Fracture (%)**

**Effect of Nasal Calcitonin on Hip and Vertebral Fractures**

**PROOF 5-Year Analysis**

- 5-year randomized, double-blind, placebo-controlled
- Most patients had 1-5 vertebral Fx at baseline (n = 910 of 1255)

**Raloxifene**

**Effect on Radiographic Vertebral Fractures (MORE)**

- 50% Reduction at year 3, RR, 0.5 (95% CI, 0.4-0.8)
- Age range up to 80
- Placebo Raloxifene 60 mg/d
  - n=770
  - n=769
  - n=1522
  - n=1490

- No reduction in nonvertebral or hip fractures

**Ibandronate**

**Effect on New Morphometric Fractures (BONE)**

- 9.6% vs 4.7% Reduction at year 3, p=0.0001
- With 1-4 prior VFx
- LS BMD ≥ 2
- Age range = 55-80 yrs

**More = Multiple Outcomes of Raloxifene Evaluation; RR = Relative Risk**

**Ettinger B et al. JAMA. 1999;282:637-645.**

**Chesnut CH III et al. J Bone Miner Res. 2004;19:1241-1249.**


**Cummings SR et al. JAMA. 1998;280:2077-2082.**

**Black DM et al. J Clin Endocrinol Metab. 2000;85;4118-4124.**

**Black DM et al. Lancet. 1996;348:1535-1541.**

**Cummings SR et al. Lancet. 1996;348:1535-1541.**
Risedronate Clinical Trial Data

**Vertebral Fracture Reduction**

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent of Patients</th>
<th>p- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>5 mg Risedronate</td>
<td>41%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Nonvertebral Fracture Reduction**

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent of Patients</th>
<th>p- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>5 mg Risedronate</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Teriparatide Effect on Fractures

**Incidence of New Vertebral Fractures**

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage of Women with ≥1 Fracture</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>49%</td>
<td>448</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>41%</td>
<td>444</td>
</tr>
</tbody>
</table>

**Effect on Nonvertebral Fractures**

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk of Developing 1 or More New Fragility Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>RR 0.35 (95% CI=0.22-0.55)</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>RR 0.35 (95% CI=0.22-0.55)</td>
</tr>
</tbody>
</table>

Total Hip BMD Change in FLEX Population From Beginning of FIT to Completion of FLEX

<table>
<thead>
<tr>
<th>Year</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>0</td>
</tr>
<tr>
<td>F1</td>
<td>1</td>
</tr>
<tr>
<td>F2</td>
<td>2</td>
</tr>
<tr>
<td>F3</td>
<td>3</td>
</tr>
<tr>
<td>F4</td>
<td>4</td>
</tr>
<tr>
<td>F5</td>
<td>5</td>
</tr>
</tbody>
</table>

**Total Hip BMD Change in FLEX Population**

- FIT: 3 - 4.5 years
- FLEX: 3 years

- FL 0 FL 1 FL 2 FL 3 FL 4 FL 5
- F 0 F 1 F 2 F 3 F 4 F 5

- Time between FIT and FLEX: 1 - 2 years
- Mean Percent Change: 2.4% (p=0.01)

**Notes:**