Pharmacology:
Therapeutics of Calcium Metabolism

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Outline of Lecture

- **Hypercalcemia**
- **Hypocalcemia**
- **Osteoporosis**

CAUSES OF HYPERCALCEMIA

- Primary Hyperparathyroidism
- Malignancy
- **Other endocrinopathy**
  - **Hyperthyroidism**
  - **Pheochromocytoma**
  - **VIPoma**
  - **Adrenal insufficiency**
- **Medications**
  - **lithium**
  - **thiazide diuretics**
  - **thyroid hormone**
  - **Vitamin A**
  - **Vitamin D**
- **Vitamin D**
  - **Toxicity**
  - **Granulomatous disease**
    - **Tuberculosis**
    - **Sarcoidosis**
    - **Any other**
- **Lymphoma**
- **FHH**
- **Immobilization**
- **Acute or chronic renal disease**

Clinical Features of Hypercalcemia

- Constitutional
- Central nervous system
- Gastrointestinal tract
- Renal
- Cardiovascular

Factors That Influence Symptomatology in Hypercalcemia

- **Serum calcium concentration**
- **Rate of rise**
- **Duration**
- **Individual variability**

Pathophysiologic Features of Acute Hypercalcemia

I. New or Existing Stimulus to Hypercalcemia
- **Osteoclast activation virtually always present**
- **Renal tubular conservation of calcium (PTH, PTHRP)**
- **GI hyperabsorption of calcium (less important)**
- **Reduced mobility**

II. Hypercalcemia Becomes Symptomatic
- **Polyuria**
- **Polydypsia**
- **Anorexia**

Pathophysiologic Features of Acute Hypercalcemia

III. Worsening Hypercalcemia
- **Reduced fluid intake**
- **Continued polyuria**
- **Dehydration**

IV. Reduced Plasma Volume
- **Impaired renal function**
- **Reduced renal calcium clearance**
- **Rapidly worsening hypercalcemia**

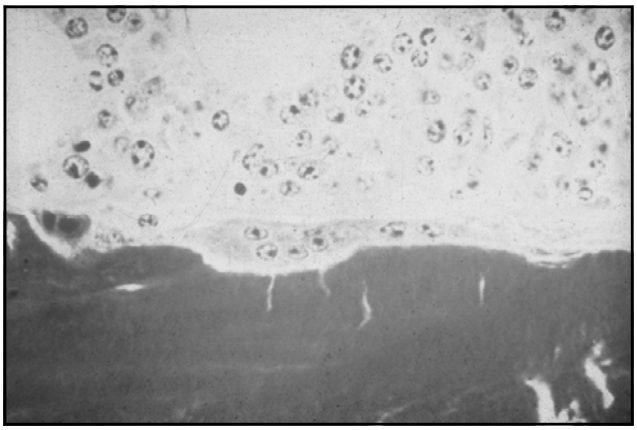
At What Level Should Hypercalcemia Be Treated Emergently?*

- **< 12 mg/dL ?**
- **12-14 mg/dL ?**
- **>14 mg/dL ?**

*Typical nl range 8.4-10.2 mg/dl

General Management of Hypercalcemia

- **Intravenous rehydration**
- **Saline administration**
- **Diuresis with furosemide**
- **Dialysis (if necessary)**
- **Mobilization**

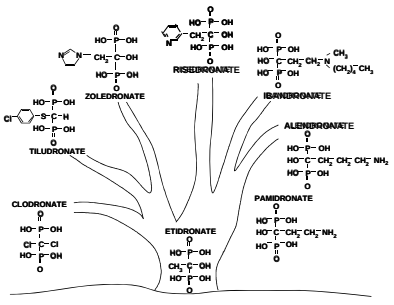


Management of Hypercalcemia

General
- Rehydration
- Saline Administration
- Diuresis with Furosemide
- Dialysis
- Mobilization

Specific
- **Bisphosphonates**
- Plicamycin
- Calcitonin
- Gallium Nitrate
- Phosphate
- Glucocorticoids
- Therapy of Underlying Etiology

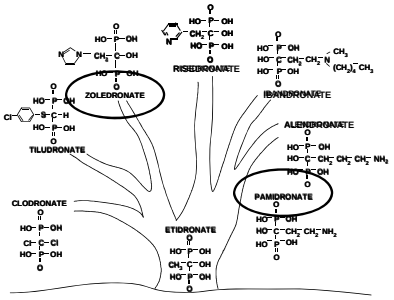
Bisphosphonates

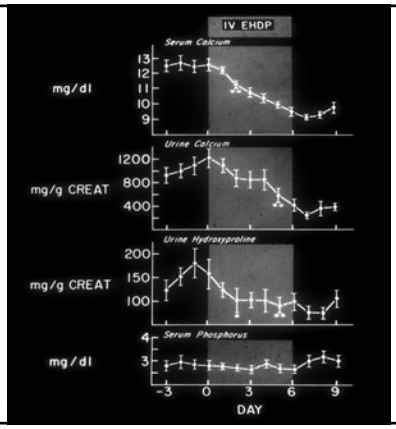


Bisphosphonates For Acute Hypercalcemia

- **Osteoclast inhibitors**
- **Intravenous route necessary**
- **Reduction in serum calcium begins 24-36 hours after first dose**
- **Duration of effect is variable**

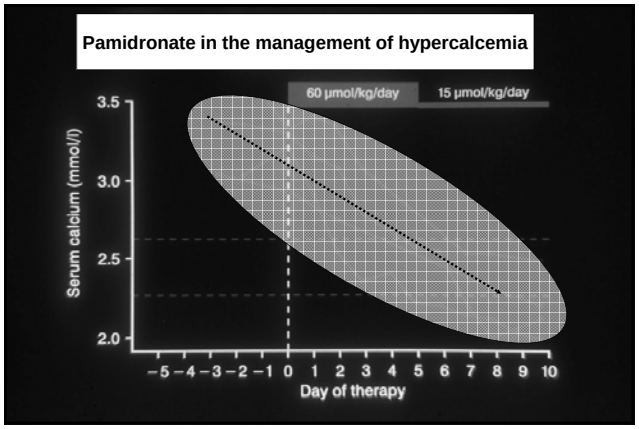
Bisphosphonates for hypercalcemia



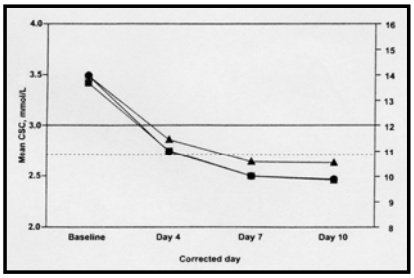


Adverse Effects of Parenteral Etidronate for Hypercalcema

Hypocalcemia (“overshoot”)



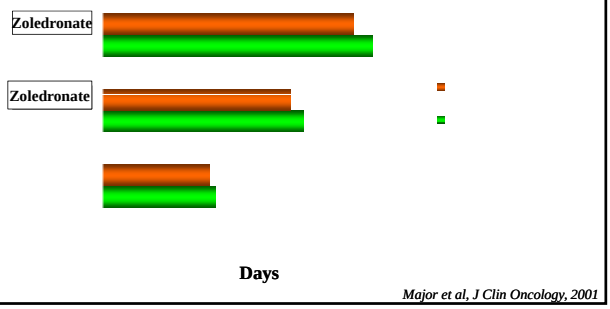
Zoledronate vs. Pamidronate For Hypercalcemia



Mean Corrected Serum Calcium C at baseline and days 4, 7, and 10 after treatment of hypercalcemia with (□) zoledronic acid 4mg, (○) zoledronic acid 8mg, or (△) pamidronate 90mg.

Major et al, J Clin Oncology, 2001

Management of Hypercalcemia Zoledronate vs. Pamidronate



Major et al, J Clin Oncology, 2001

Adverse Effects of Pamidronate and Zoledronate

- **Mild, transient fever (<2°C)**
- **Transient leukopenia**
- **Small reduction in the serum phosphate**
- **Hypocalcemia ("overshoot")**

Management of Hypercalcemia

General
- Rehydration
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- Dialysis
- Mobilization

Specific
- **Bisphosphonates**
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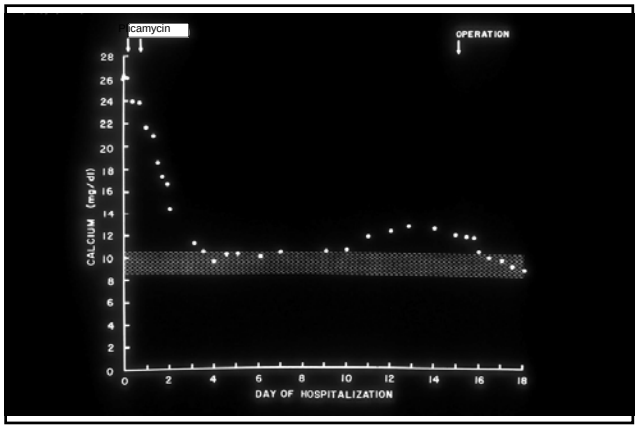
Plicamycin

- **Potent osteoclast inhibitor**
- **Intravenous, daily for up to 5 days**
- **Reduction in serum calcium begins 12-24 hours after first dose**
- **Duration of effect is variable**



Adverse Effects of Plicamycin

- **Hypocalcemia ("overshoot")**
- **Hepatic toxicity**
- **Nephrotoxicity**
- **Bone marrow toxicity (platelets)**

Management of Hypercalcemia

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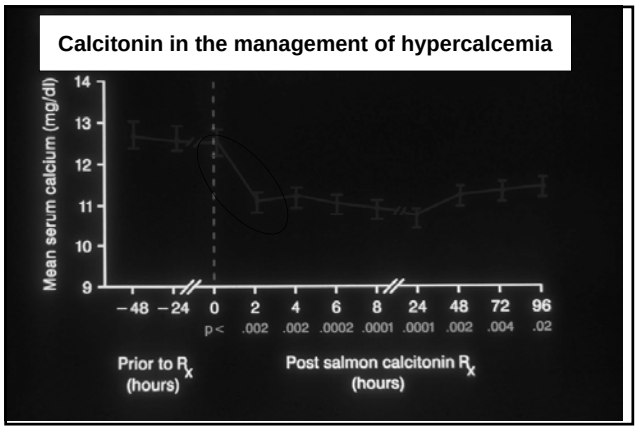
Calcitonin For Hypercalcemia

- **Osteoclast inhibitor**
- **Calciuretic**
- **IV or SC, Q12 hours**
- **Rapid reduction in calcium (within 12 hours)**
- **Weak and short-lived effect**

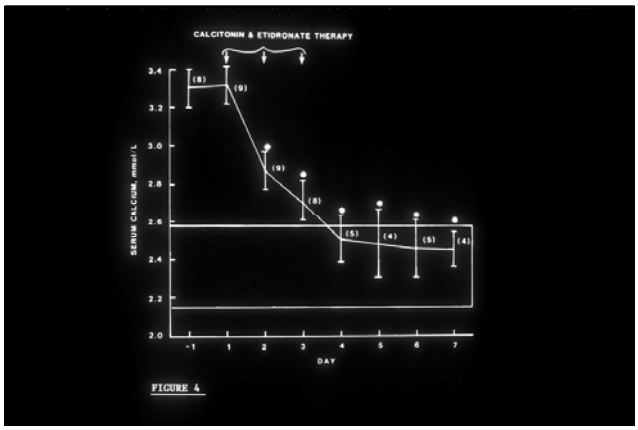


The Most Rapidly Acting Agents For Hypercalcemia

Calcitonin>Plicamycin>Bisphosphonates

Combination Therapy For Hypercalcemia

- **Use of a rapidly acting agent (calcitonin)**
- **Simultaneous with a more potent, but more slowly acting agent (bisphosphonate)**



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- **Glucocorticoids**
- **Therapy of Underlying Etiology**

Outline of Lecture

- **Hypercalcemia**
- **Hypocalcemia**
- **Osteoporosis**

Clinical Features of Hypocalcemia

- **Neuromuscular irritability**
- **Paresthesias (numbness and tingling)**
- **Chvostek's sign**
- **Trousseau's sign**
- **Prolonged Q-T interval**
- **Carpal, pedal, broncho, or laryngeal spasm**
- **Seizures**

Clinical Features of Hypocalcemia

Determinants of signs and symptoms

- **Extent of hypocalcemia**
- **Rapidity of reduction**
- **Duration of hypocalcemia**

Management of Hypocalcemia

Indications for Acute Treatment

- **Symptoms**
- **No symptoms but…**
  - **Serum calcium** (corrected for serum albumin) **<7.5 mg/dL**
  - **History of seizures**
  - **Previous compression fracture**

Emergency Management of Hypocalcemia

Intravenous Preparation of Choice

✓ **Calcium gluconate**

✕ Calcium chloride (do not use)

Emergency Management of Hypocalcemia

FOR **IMMEDIATE** RELIEF OF SYMPTOMS:

1-2 amps of 10% calcium gluconate (93 mg of elemental calcium/amp) intravenously over 10-15 minutes

Emergency Management of Hypocalcemia

To raise the serum calcium by 2-3 mg/dl:

10-15 mg/kg of calcium intravenously (in 1 liter of D_5W) over 6-8 hours

Example:
70 kg individual
15 mg/kg = 1050 mg calcium

Amps of 10% calcium gluconate = 1050 mg/93 mg/10 ml
=
Approximately **11 amps**

Management of Chronic Hypocalcemia

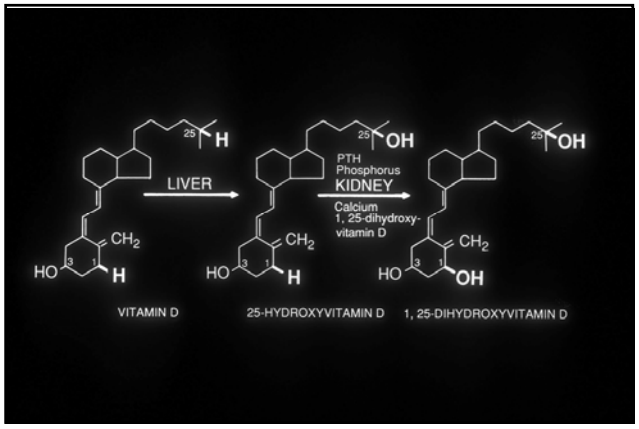
- **Underlying etiology**
- **Oral calcium**
- **Oral Vitamin D**

CALCIUM CONTENT OF MEDICINAL SALTS

Source	Calcium Content (mg/g)	% Calcium
Carbonate	400	40%
Citrate	200	20%
Lactate	128	12.8%
Gluconate	88	8.8%
Glubionate	65	6.5%

Management of Chronic Hypocalcemia

- Underlying etiology
- Oral calcium
- **Oral Vitamin D**
  - **Nutritional**
    (400-800 IU daily)
  - **Pharmacological**
    (>1000 IU day)



Outline of Lecture

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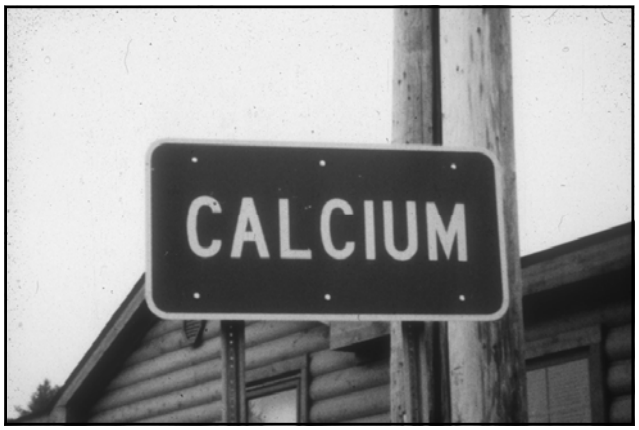
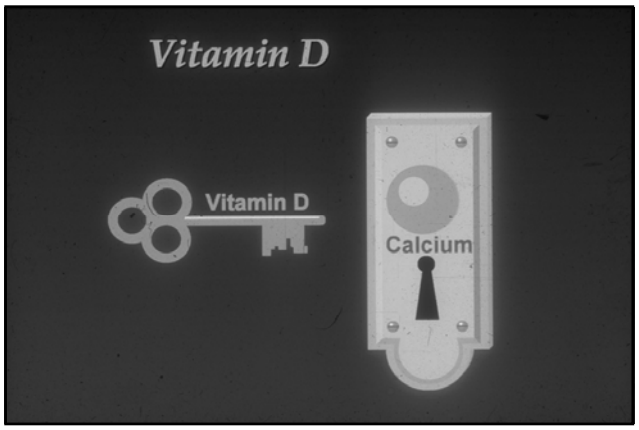


CALCIUM CONTENT OF MEDICINAL SALTS

Source	Calcium Content (mg/g)	% Calcium
Carbonate	400	40%
Citrate	200	20%

- ✓How much?
- ✓How much at a time?
- ✓What form?
- ✓Brand vs generic vs fancy?
- ✓When?
- ✓With food or without food?



Nonpharmacological Approaches to the Management of Osteoporosis*

Calcium
Vitamin D
Exercise
Lifestyle (Smoking, Alcohol, etc)
Fall Prevention

***Recommended for virtually everyone!**

Approved Pharmacologic Therapies in the United States for Osteoporosis

- **Hormone replacement therapy (HT)**
- **Raloxifene**
- **Bisphosphonates**
  - **Alendronate**
  - **Risedronate**
  - **Ibandronate**
  - **Zoledronate**
- **Calcitonin**
- **Teriparatide [humanPTH[1-34)]**

ESTROGEN REDUCES THE RISK OF ALL CLINICAL FRACTURES

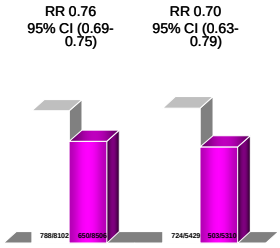
E+P: N=16,608 women ages 45-79
Mean age: 63.2
Placebo or estrogen+progestin

CEE arm: N=10,739 ages 50-79
Mean age: 63.6
Placebo or CEE 0.625 mg daily

Fractures: All clinical fractures (less than 10% were vertebral fractures)

Treatment intervals: E+P 5.2 years; CEE 6.8 years

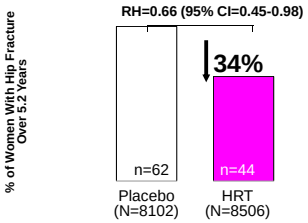
CEE= conjugated equine estrogen.



E+P: Rossouw JE, et al. *JAMA.* 2002;288:321-333.
CEE: Anderson GL, et al. *JAMA*. 2004;291:1701-1712.

WHI HT Study: Combination Arm

Effect of HT and Progestin on Hip Fracture Incidence

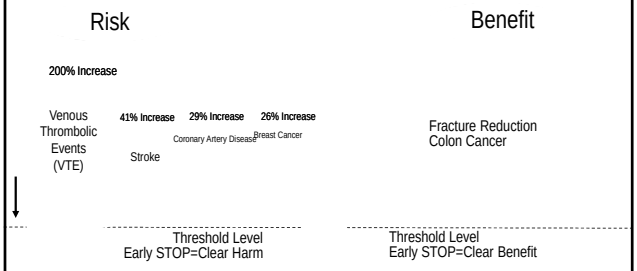


Elements Not Stated in Paper

- Preexisting fractures
- Baseline BMD status
- Calcium or vitamin D intake
- Use of bisphosphonates and/or calcitonin
- Age distribution of fractures

Adapted from: Writing Group for the Women's Health Initiative. *JAMA.* 2002;288:321-333.

WHI HT Study
Findings at Early Interruption of CEE/MPA Arm



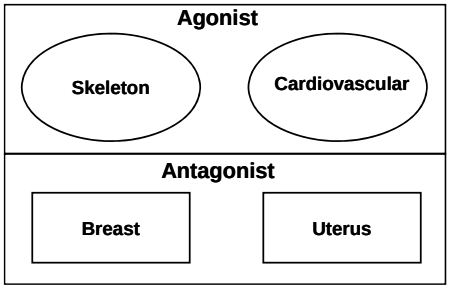
Adapted from: Writing Group for the WHI Investigators. *JAMA*. 2002;288:321-333.

WHI: Conclusions regarding the skeleton*

- Estrogen should not be used as a primary therapy to prevent bone loss
- Estrogen should not be used as a primary approach to the treatment of osteoporosis

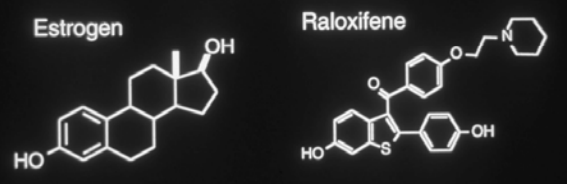
*This is a very controversial issue!

The Concept of an Ideal SERM

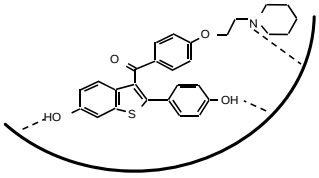


Mitlak BH, et al. *Drugs* 1999;57:653-63.
Lufkin EG, et al. *Rheum Dis Clin North Am* 2001;27:163-85.

Structural Comparisons of Estrogen and Raloxifene



Raloxifene: A Selective Estrogen Receptor Modulator



Basic Side Chain

⇩

Estrogen Antagonist (uterus, breast)

Benzothiophene moiety

⇩

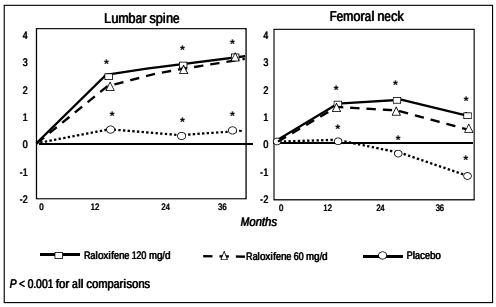
Estrogen Agonist (bone, lipids)

- BMD (bone mineral density) increase
- Decrease in total and LDL cholesterol

RALOXIFENE

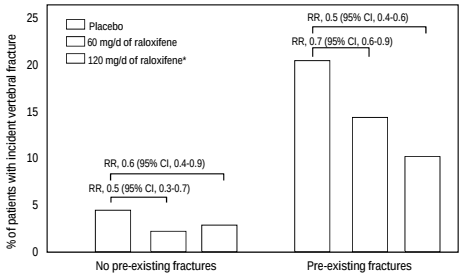
- Well-absorbed from the GI tract
- Can be taken any time
- Once daily medication (60 mg)
- With or without food
- No contraindications in women with upper gastrointestinal symptoms

Effects of Raloxifene on BMD: The MORE Trial–36 Months



Ettinger B, et al. *JAMA* 1999;282:637-45.

Effects of Raloxifene on New Vertebral Fractures: The MORE Trial – 36 Months



***Not FDA-approved dose.**

Ettinger B, et al. *JAMA* 1999;282:634-45.

Raloxifene: Benefits and Risks

Benefits

- **Improved bone mass**
- **Reduced number of vertebral fractures**
- **No breast tenderness**
- **No uterine bleeding or spotting**
- **Reduced risk of breast cancer***
- **No increased cardiovascular risk**

Disadvantages

- **Increased hot flashes**
- **Increased leg cramps**
- **Increased risk of DVT and pulmonary embolism**

*New indication, 2007

Osteoporosis Therapy: Calcitonin

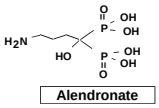
- **Calcitonin** 200 units daily by nasal spray
- **Indication:** treatment of postmenopausal osteoporosis
- **Effects**[1]
  - Very small effect (1-2%) on bone density in spine
  - No effect on bone loss in women within 5 years of menopause
  - Reduced incidence of vertebral fractures (36%) in women with pre-existing vertebral fractures
  - No effect on non-vertebral or hip fractures has been observed
- **Side effects:** nasal stuffiness
- **Contraindications:** hypocalcemia, allergy to calcitonin, pregnancy, recent menopause (<5 years)

[1]Chesnut CH et al. Am J Med. 2000;109:267

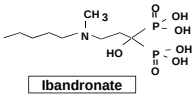
THERAPEUTICS

BISPHOSPHONATES

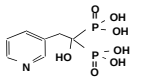
BISPHOSPHONATES APPROVED IN THE US FOR USE IN OSTEOPOROSIS



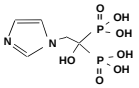
Alendronate



Ibandronate



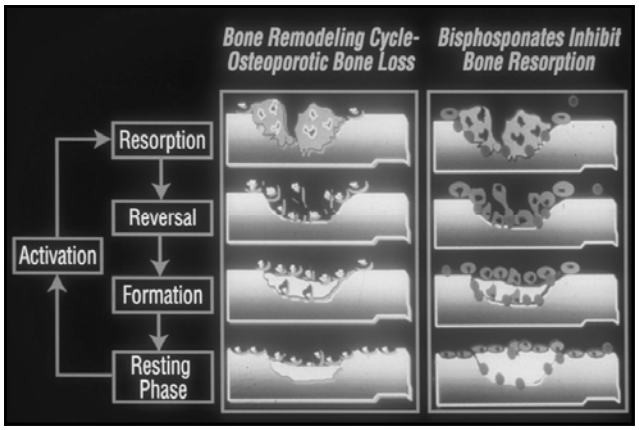
Risedronate

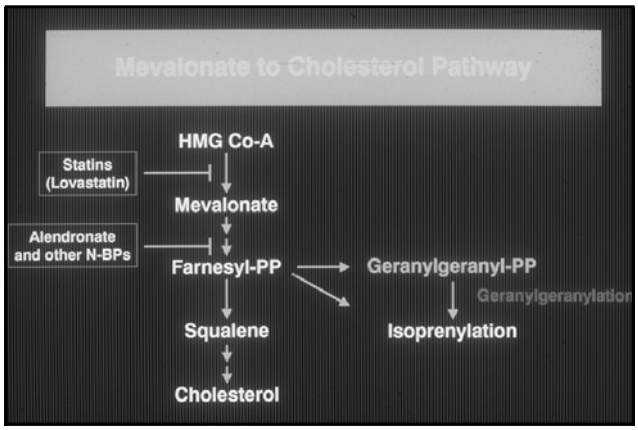


Zoledronate

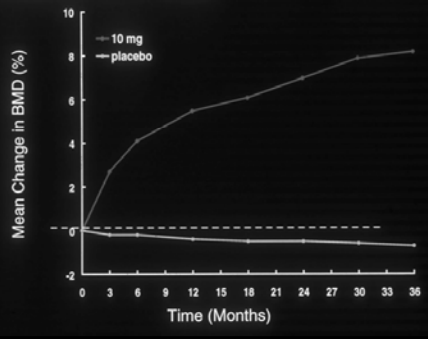
Oral bisphosphonates

- Poorly absorbed (<1.0%)
- Specific requirements for optimal oral absorption
  - Fasting state with plain water only
  - Must be upright
  - No food or drink for at least 30 minutes
    (for Ibandronate, 60 minutes)
- Several half-lives
  - Rapid uptake in bone and clearance by the kidney
  - Prolonged skeletal half-life (years)
- GI intolerance has occurred with orally administered amino-substituted bisphosphonates (alendronate, risedronate, ibandronate)

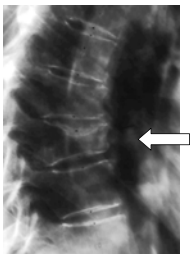




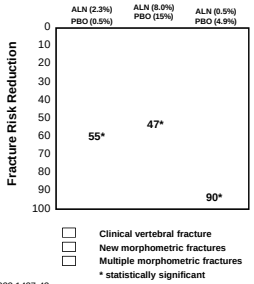
Increase in BMD of the Spine: Alendronate 10mg/day for 3 Years



The Vertebral Fracture

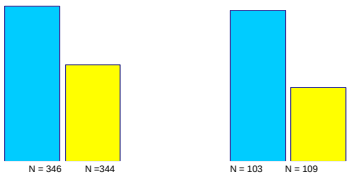


Alendronate: Effect on vertebral fracture



Liberman et al. New Engl J Med, 1995;333:1437-43
Black DM et al. Lancet, 1996;348:1535-41

Risedronate (VERT:Multinational study) Reduction in Relative Risk of New Vertebral Fracture Over Years 0-3 and Years 4-5

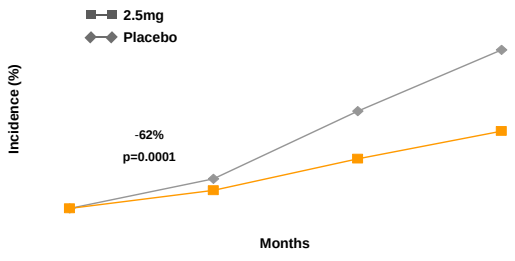


Reginster et al, OI, 2000.

N = subjects with an evaluable baseline and an evaluable post-baseline spinal x-ray.

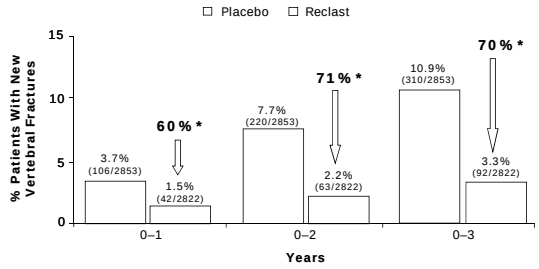
Sorensen et al, Bone 32:220-226 (2003)

Ibandronate: new vertebral fractures – 2.5 mg daily (ITT)



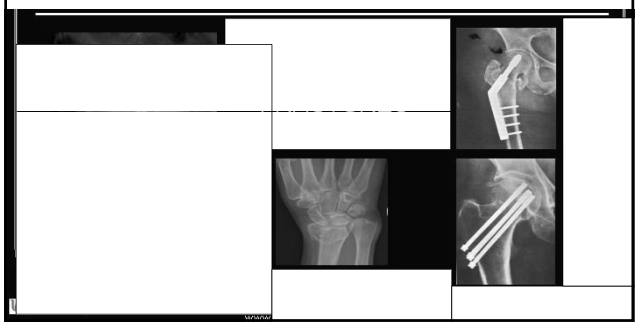
Delmas PD et al. Osteoporosis Int 2004;15:792-798

Reclast Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)

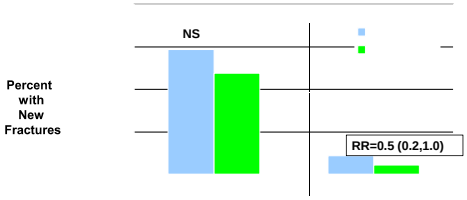


*P < .0001, relative risk reduction vs placebo (95% confidence interval)
Adapted from Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

NON-VERTBRAL FRACTURES



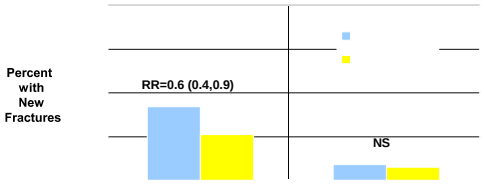
NONVERTEBRAL AND HIP FRACTURES
ALENDRONATE FRACTURE INTERVENTION TRIAL



33 total hip fractures
NVFX = all except pathological, traumatic, face/skull

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

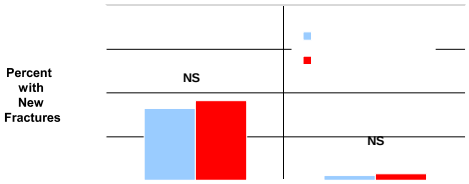
NONVERTEBRAL AND HIP FRACTURES
RISEDRONATE VERT-NA



27 total hip fractures (control + primary treatment group)
NVFx = clavicle, humerus, forearm, pelvis, femur, lower leg; no consideration for trauma

After data from Harris ST et al. *JAMA* 1999;282:1344-1352

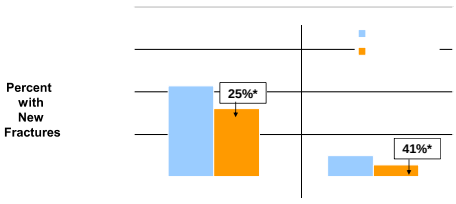
NONVERTEBRAL AND HIP FRACTURES
IBANDRONATE BONE STUDY



10 total hip fractures (control + primary treatment group)
NVFx = all except hands, feet, face, and skull

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

NONVERTEBRAL AND HIP FRACTURES
ZOLEDRONATE HORIZON TRIAL



140 total hip fractures
NVFX = excluding fingers, toes and facial bones

*P<0.05

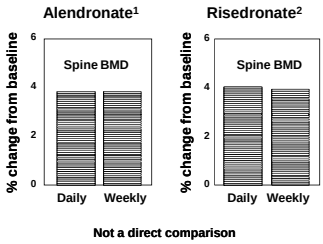
Black DM et al, N Engl J Med 2007;356:1809-1822

ISSUES WITH BISPHOSPHONATES

- INCONVENIENT DOSING REQUIREMENTS (IF USED DAILY)

Bisphosphonates: Weekly Dosing

- Effects of weekly vs daily dosing on BMD and turnover are the same
- Extrapolation of fracture protection from daily studies is reasonable
- Has improved acceptance, but effect on adherence not known



Not a direct comparison

[1]Schnitzer T, et al. Aging Clin Exp Res. 2000;12:1-12
[2]Brown JP, et al. Calcif Tissue Int. 2002;71:103-111

Bisphosphonates
Other administration regimens

- Monthly dosing
  - Ibandronate
  - Risedronate
- Intravenous dosing
  - Ibandronate (every 3 months)
  - Zoledronate (once yearly)

Adverse events with bisphosphonates for osteoporosis

- Upper GI intolerance
- Acute Phase Reaction
- "Oversuppression of bone"[1]
- Osteonecrosis of the jaw[2,3]

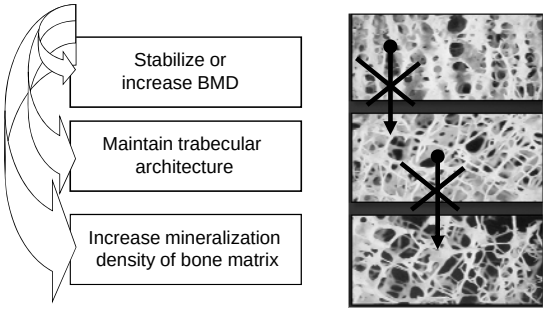
[1]Odvina et al. J Clin Endocrinol Metab, 2005
[2]Bilezikian JP N Eng J Med, 2006
[3]Khosla et al, J Bone Mineral Res, 2007

All Antiresorptive Therapies for Osteoporosis

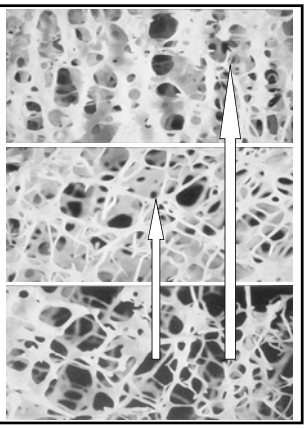
- Hormone replacement therapy (HT)
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin

Inhibit Bone Resorption

Actions of anti-resorptive agents



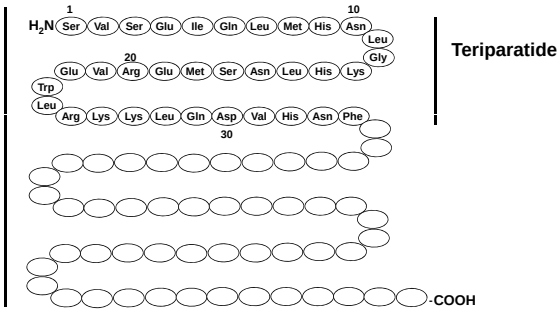
What the antiresorptives don't do…



Approved Therapies in the United States for Osteoporosis

- Hormone therapy (HT)
- Raloxifene
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate
  - Zoledronate
- Calcitonin
- **Teriparatide [human parathyroid hormone (1-34)]**

Human Parathyroid Hormone



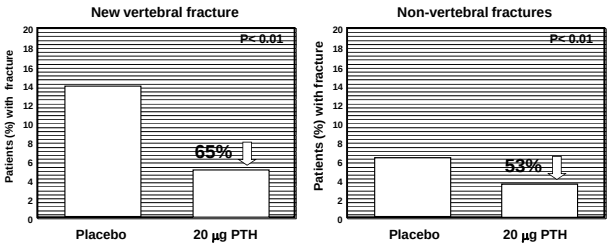
PTH as a Treatment for Osteoporosis: A Paradox

- How can PTH be a potential therapy for osteoporosis when the clinical disorder of chronic PTH excess, primary hyperparathyroidism, is associated with bone loss?

PTH and Dose Determine Effect on Bone

Mode	Effect
Continuous (High Dose)	Catabolic
Daily (Low Dose)	Anabolic

Teriparatide reduces the incidence of Vertebral and Non-Vertebral Fractures in Postmenopausal Women with Osteoporosis



Neer RM, et al. N Engl J Med. 2001;344:1434-41

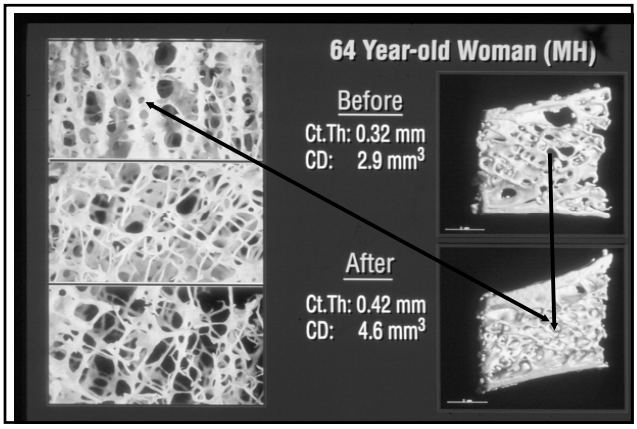
What do the bones actually look like after therapy with PTH?

Improved Trabecular Connectivity After hPTH (1-34) Therapy

Before
CD: 2.9/mm^3

After
CD: 4.6/mm^3

Dempster DW, et al. *J Bone Miner Res*. 2001;16(10):1846-1853.



OSTEOPOROSIS

PREVENTABLE AND TREATABLE