Osteoporosis

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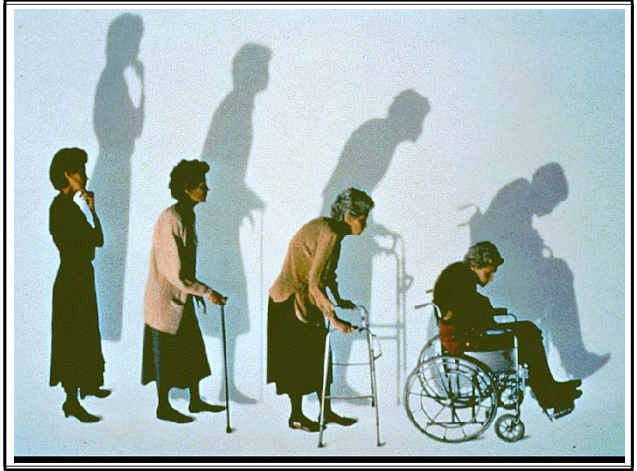


Case

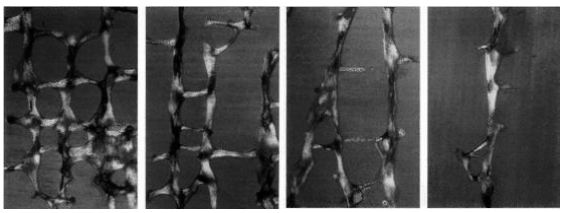
- 55 y.o. caucasian woman
  - Postmenopausal x 3 years
  - No personal history of fragility fracture
  - PMH: COPD
  - Meds: Advair
  - Soc Hx: ½ ppd since teenager
  - Fam Hx: Mother disabled by hip fracture
  - Exam 125 lbs, 5' 5", normal exam
  - Lumbar spine T-score -2.0, Hip -2.1

Osteoporosis

"A skeletal disorder characterized by compromised bone strength predisposed to an increased risk of fracture.

Bone strength reflects an integration of two main features: bone density and bone quality."

NIH Consensus Development Panel JAMA 2001:285:785



Medical Impact of Osteoporosis

- In 2012, ~12 million have osteoporosis 4:1 female:male
- ~ 34 million with osteopenia
- At age 50, ½ women and ¼ men will have osteoporotic fracture in their remaining lifetime
- 2 million fractures annually in men and women age +50 years
  - ~300,000 hip fractures
  - ~550,000 spine fractures
  - ~400,000 wrist fractures
  - ~800,000 fractures at other sites

Burge, R. JBMR 2007;22:465-75

Functional Definition

- Clinical Definition:
  "fragility" fracture in the absence of trauma or in the setting of minimal trauma, such as after a fall from a standing height or less.

- Densitometric:

	T-score:
Osteoporosis	≤ -2.5
Osteopenia	> -2.5 and < -1.0
Normal	≥ -1.0

(Applies to postmenopausal women and men ≥ 50 years)

Medical Impact of Hip Fractures

- 10-20% excess mortality within 1 year
- 2 ½ fold increase in subsequent fracture
- 20% require long-term nursing home care
- Only 40% regain pre-fracture level of independence
- 50% previously ambulatory, unable to walk independently after fracture

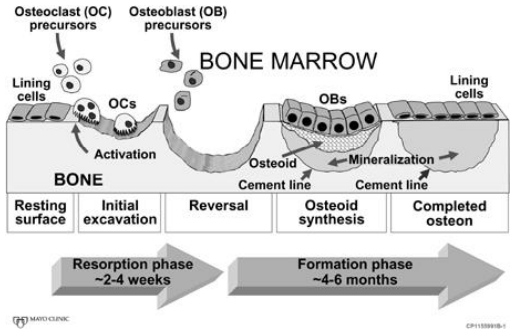
Medical Impact of Spine Fractures

- Back pain, height loss, kyphosis
- Loss of function
  - bending, reaching
  - restrictive lung disease
  - early satiety, decreased appetite, constipation, abdominal pain, distension
- Increased risk of mortality beyond 1 year
  - 86.5% vs. 93.6% (expected) at 1 year
  - 56.5% vs. 69.9% (expected) at 5 year

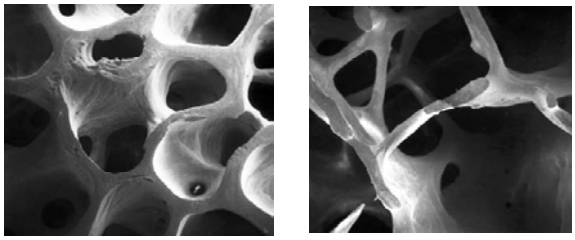
Postmenopausal Osteoporosis

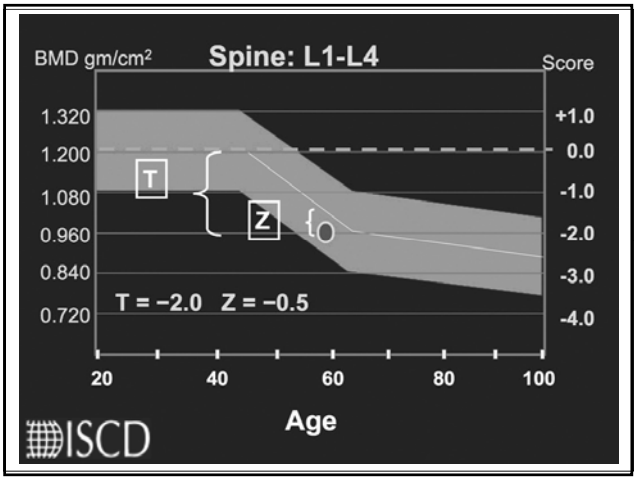
- High bone turnover state
  - Perforation of trabecular plates → rods
  - Loss of connectivity
  - Increase in stress risers in trabecular bone
  - Increase in cortical bone porosity
- Bisphosphonate therapy improves bone strength by preventing deterioration and allows filling in of the remodeling space
- Fracture reduction occurs mainly through ↓ high bone turnover

Bone Turnover



Riggs & Parfitt JBMR 2005;20(2)177-184





Indications for DXA

International Society for Bone Densitometry

- **Women ≥ 65**
- **Postmenopausal women < 65 with risk factors for fracture**
- **Women during the menopausal transition with clinical risk factors for fracture, such as low body weight, prior fracture, or high-risk medication use**
- **Men ≥ 70**
- **Men < 70 with clinical risk factors for fracture.**
- **Fragility fracture**

DXA Scan Indications

- **US Preventive Task Force**
  - **Universal screening in woman ≥ 65 years**
  - **Women ≥ 60 + Risk Factors**

Indications for DXA

International Society for Bone Densitometry

- **Disease/condition associated with low bone mass or bone loss**
- **Medications associated with low bone mass or bone loss**
- **Anyone being considered for pharmacologic therapy**
- **Anyone being treated, to monitor treatment effect**
- **Anyone not receiving therapy in whom evidence of bone loss would lead to treatment**

Factors Contributing to Osteoporosis and Fracture

Endocrine

- Hypogonadism
- Hyperparathyroidism
- Hyperthyroidism
- Hypercortisolism
- Vitamin D deficiency/insufficiency

Medications

- Glucocorticoid
- Anticonvulsant
- Heparin
- Aromatase inhibitor
- GnRH agonist
- Cyclosporin

Common ICD-9 Codes for DXA in Primary Care Setting

733.00	OSTEOPOROSIS UNSPECIFIED
733.01	POSTMENOPAUSAL/SENILE OSTEOPOROSIS
733.90	DISORDER OF BONE AND CARTILAGE UNSPECIFIED (osteopenia)
V49.81	ASYMPTOMATIC POSTMENOPAUSAL STATUS (AGE-RELATED) (NATURAL)
627.2	SYMPTOMATIC MENOPAUSAL OR FEMALE CLIMACTERIC STATES
627.4	SYMPTOMATIC STATES ASSOCIATED WITH ARTIFICIAL MENOPAUSE
V58.65	LONG-TERM (CURRENT) USE OF STEROIDS
V58.69	LONG-TERM (CURRENT) USE OF OTHER MEDICATIONS

Factors Contributing to Osteoporosis and Fracture

Other Disorders

- Gastrointestinal: sprue, IBD, PBC
- Hematologic: myeloma, leukemia, lymphoma
- Rheumatologic: RA, SLE, AS
- Renal: CKD, Hypercalciuria
- Genetic: OI
- Miscellaneous: Transplantation

Lifestyle

- Ethanol
- Cigarettes
- Immobilization
- Dietary calcium (lactose intolerance)
- Hypervitaminosis A

FRAX Limitations

- Does not take into account dose-response
  - Higher GC dose
  - 1 vs. >1 prior fracture
  - cigarettes, alcohol
- Does not apply to patients on osteoporotic drug treatment
- US database does not include age <50
- Future FRAX: add spine BMD

2008 NOF Treatment Intervention

- Hip fracture, clinical or radiographic spine fracture; OR
- Osteoporosis by DXA at femoral neck, total hip, or lumbar spine; OR
- Osteopenia by DXA and any of the following:
  - 10 year estimated risk of hip fracture risk ≥ 3%
  - 10 year major osteoporotic fracture risk ≥ 20%
  - Secondary causes associated with a high risk of fracture (e.g. glucocorticoid therapy)
  - Other prior fragility fractures

Calcium and Vitamin D 2011 IOM Report

1997 Calcium (mg/d)	
1-3 yr	500
4-8 yr	800
9-18 yr	1300
19-50	1000
> 50 yr	1200

2011 Calcium (mg/d)		
	RDA	UL
1-3	700	2500
4-8	1000	2500
9-18	1300	3000
19-30	1000	2500
31-50	1000	2500
51-70 M	1000	2000
51-70 F	1200	2000
>71 M+F	1200	2000

Calcium and Vitamin D 2011 IOM Report

1997 Vitamin D (IU/d)	
0-50 yr	200
51-70	400
>70	600

2011 Vitamin D (IU/d)		
	RDA	UL
1-3	600	2500
4-8	600	3000
9-13	600	4000
14-18	600	4000
19-30	600	4000
31-70	600	4000
>71	800	4000

Treatment of Osteoporosis

- Calcium and vitamin D
- Estrogen and SERMs
- Bisphosphonates
- Anabolic therapy (Forteo)
- RANKL inhibitor – "biologic" therapy

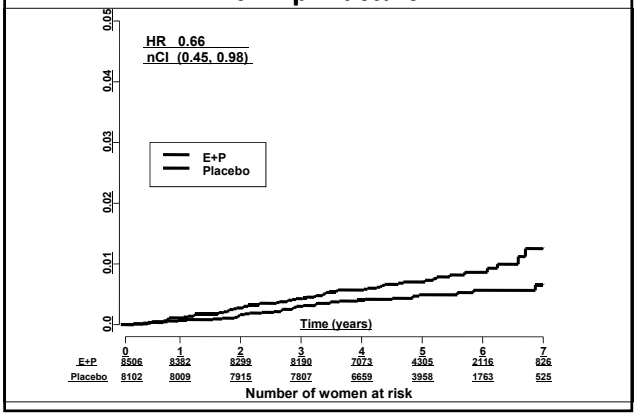
Treatment of Postmenopausal Osteoporosis

Laura Ryan, MD,
Clinical Assistant Professor
Department of Internal Medicine
Division of Endocrinology, Diabetes, & Metabolism
Ohio State University Medical Center

Estrogen/Progesterone

- Effective in both primary prevention of hip and vertebral fractures as well as secondary prevention in those with established osteoporosis
- Dose: Premarin 0.625mg qd (+/- provera)
- Results in increase in both vertebral and spine BMD
- Reduction in hip Fx by 29%; compression fractures by 33%
- Divergence from placebo seen as early as after first year of primary prevention treatment
- Big problem: breast cancer, stroke, dementia, CAD
  - No longer considered first-line therapy

Kaplan-Meier Estimates of Cumulative Hazards for Hip Fracture



Raloxifene

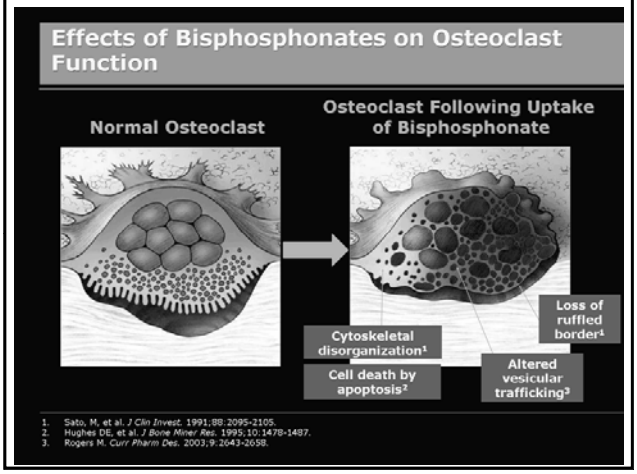
- Found in the MORE trial (Ettinger, JAMA, 1999) to increase BMD in spine and hip by 2.4% (slightly less than estrogen)
- Also prevents vertebral fractures by 38-52%
- Has not been proven to prevent hip fractures
- May make hot flashes worse
- Studies underway looking at Raloxifene for prevention of breast CA and CAD
  - 76% reduction of breast CA and 90% reduction of ER+ breast cancer in MORE trial (5160 pts)

Attributable Risk Summary

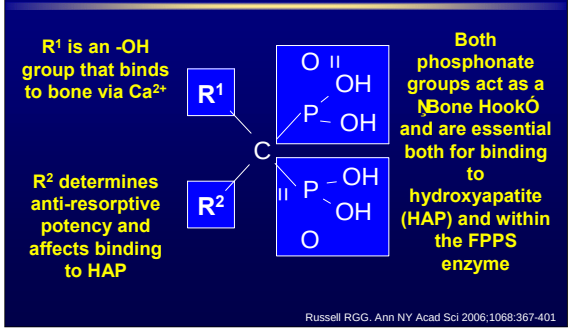
- Excess risk per 10,000 women per year on E+P
  - 8* more women with breast cancer
  - 6* more women with CHD
  - 7* more women with strokes
  - 8 more women with PE
- Risk reduction per 10,000 women per year
  - 6 fewer colorectal cancer
  - 5* fewer hip fractures

Writing Group for WHI Investigators: JAMA 2002; 288: 321-333

*2003 UPDATES: CHD (Manson); Stroke (Wassertheil-Smoller); Breast Cancer (Chlebowski); Hip Fractures (Cauley)



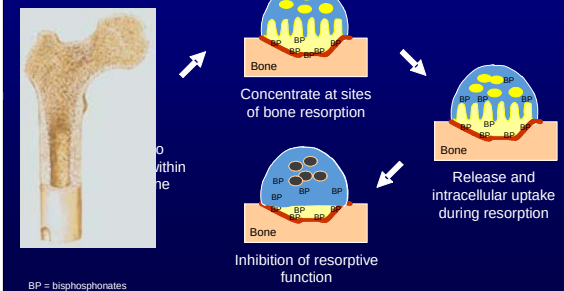
Functional Domains of Bisphosphonate Chemical Structure



Russell RGG. Ann NY Acad Sci 2006;1068:367-401

Bisphosphonate Action at the Cellular Level

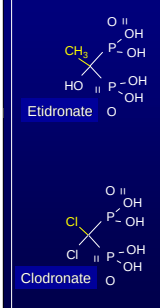
Inhibition of osteoclast resorption activity



Adapted from Russell RGG. Ann NY Acad Sci 2006;1068:367-401

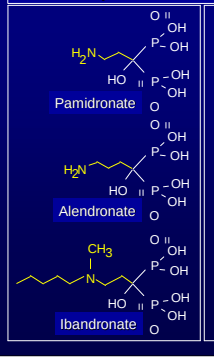
Simple Bisphosphonates

Non-Nitrogen Containing

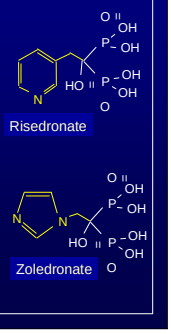


Nitrogen-containing Bisphosphonates

Alkyl



Heterocyclic



Oral Bisphosphonate Dosing

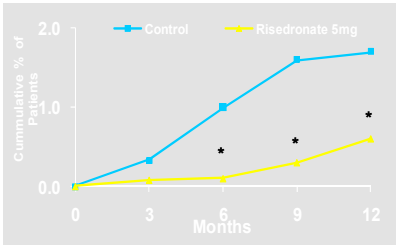
- Once daily, weekly or monthly
- On completely empty stomach
  - No coffee, juice, food – reduces absorption to almost 0%
  - **Cannot be taken with other pills, either!
  - 30min except for monthly Ibandronate: 45min
- Upright x 30 minutes following dosing
  - Do take the pill with 8oz water
- If dose missed, can make it up within 5 days then resume normal day of dosing

Alendronate (Fosamax)

- **Fracture Intervention Trial (FIT)**
  - In all pts with T-score <-1.6, sig reduction in vertebral fractures
  - In pts with T-score <-2.5, or 1 or more previous fragility fractures, sig reduction hip and all clinical fractures

Risedronate Reduces Risk of Clinical Vertebral Fractures Within 6 months

VERT: Pts with 2 or more Fx or T-score <-2.0 and one fracture

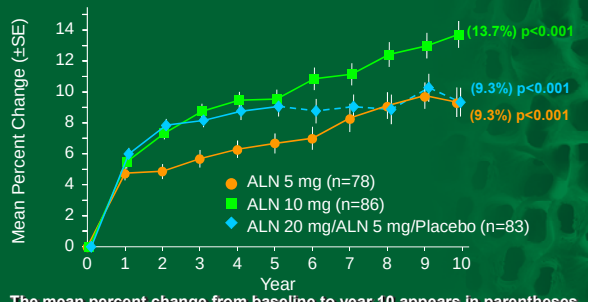


* p <0.05

VERT-NA / VERT-MN (ITT)

Watts et al. JBMR 2001; 16 (S1): SU409

Continuous Increases in Lumbar Spine BMD with Alendronate 10 mg over 10 Years

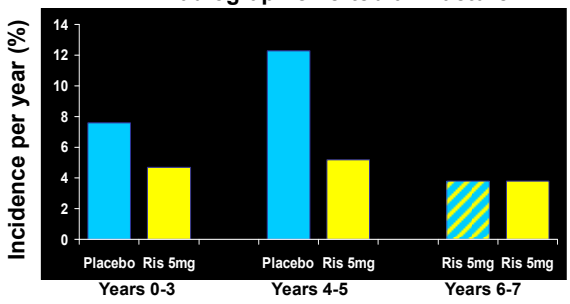


The mean percent change from baseline to year 10 appears in parentheses following each treatment group.

Adapted from Bone HG et al *N Engl J Med* 2004;350:1189–1199.

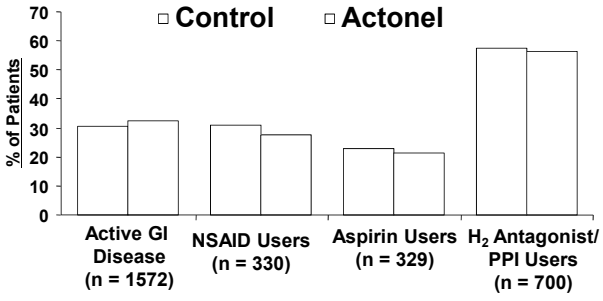
Annualized Incidence of Subjects Experiencing Any New Vertebral Fracture Over Years 0-3, 4-5 or 6-7

VERT-MN: Radiographic Vertebral Fracture*



* Annualized fracture incidence represents the percentage of subjects experiencing any new vertebral fracture divided by the number of years in the observed interval. Sorensen, et al, ISCD abstract, 2/03 annual meeting.

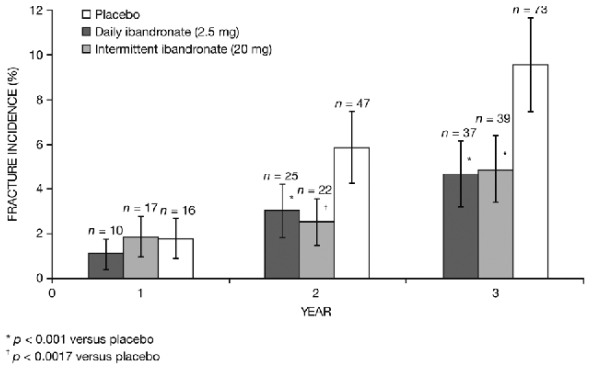
Upper GI Tolerability Comparable to Placebo in Over 5700 "Real World" Patients



PPI = proton pump inhibitor.

Please see Actonel package insert for full prescribing information.

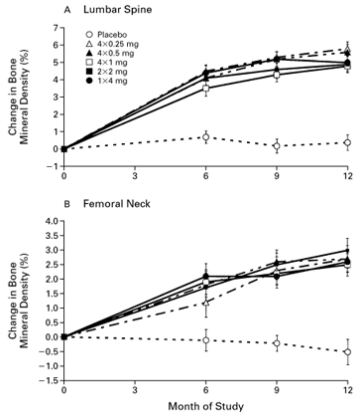
Oral Ibandronate reduces vertebral fractures



Chestnut, et al; J Bone Miner Res 2004;19:1241

Ibandronate (Boniva)

- MOBILE study – 1609 postmenopausal women with osteoporosis
  - Significant increase in BMD at LS and TH
  - Significant reduction in vertebral fracture incidence
  - No sig reduction in hip fracture
- Once monthly dose, 150mg
- IV infusion every three months, 3mg



Zoledronic Acid for treatment of PMO, Reclast

Initial trial evaluating Zoledronic acid in the setting of PMO – One year BMD results

Reid IR et al, *New Engl J Med* 2002;346:653-661.

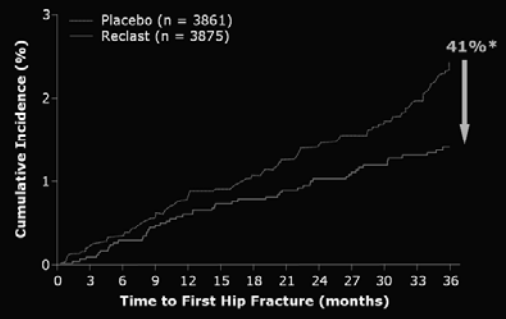
HORIZON Pivotal Fracture Trial: Overview and Study Design

- Objective: To evaluate the potential of once yearly Reclast to decrease fracture risk in postmenopausal women with osteoporosis
- 3-year, randomized, double-blind, placebo-controlled clinical trial
  - 7736 women from 239 clinical centers in 27 countries
- Treatment
  - Annual infusion of either Reclast or placebo
  - Calcium 1000–1500 mg/d; vitamin D 400–1200 IU/d
- Follow-up visits at 6, 12, 24 and 36 months
  - Telephone interviews every 3 months

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

Please see full prescribing information.

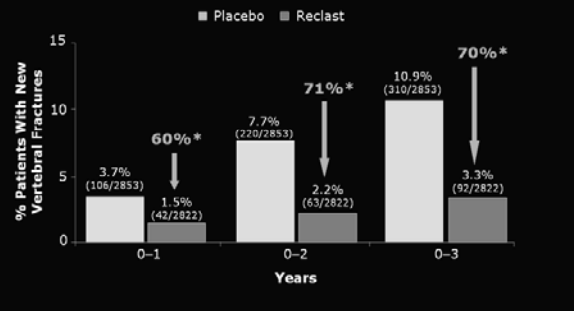
Reclast Reduced Cumulative 3-Year Risk of Hip Fractures (Strata I + II)



*P = .0024, Relative risk reduction vs placebo (95% confidence interval)
Adapted from Black DM, et al. *N Engl J Med.* 2007;356:1809-1822.

Please see full prescribing information.

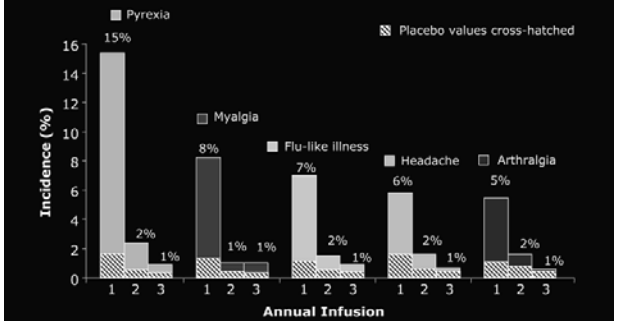
Reclast Reduced 3-Year Risk of Morphometric Vertebral Fractures (Stratum I)



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

Please see full prescribing information.

Most Common Adverse Events Within 3 Days After Infusion



Data on file, Novartis

Adverse Reactions

- Atrial Fibrillation
  - Adjudicated SAEs of atrial fibrillation occurred in 1.3% of patients (50 out of 3862) compared to 0.4% (17 out of 3852) in the placebo group
  - Overall incidence of atrial fibrillation AEs was 2.5% of Reclast patients (96 out of 3862) vs 1.9% (75 out of 3852) in placebo
  - Over 90% of these events in both groups occurred more than a month after the infusion
  - In an ECG sub-study
    - ECG measurements were performed on a subset of 559 patients before and 9 to 11 days after treatment
    - There was no difference in the incidence of atrial fibrillation between treatment groups suggesting these events were not related to the acute infusions

Reclast® (zoledronic acid) Injection [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2007.

Please see full prescribing information.

Important Safety Information about FORTEO

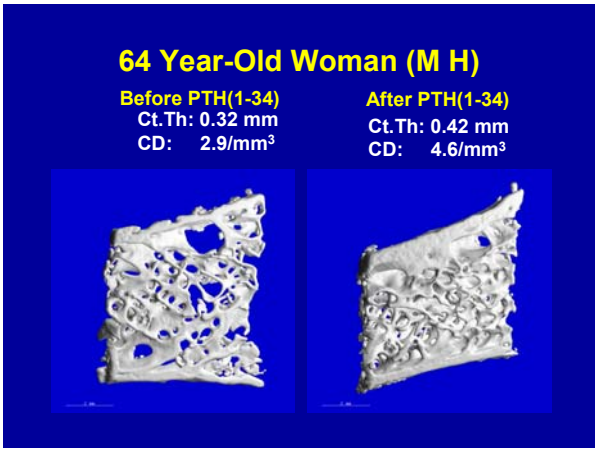
WARNING: POTENTIAL RISK OF OSTEOSARCOMA

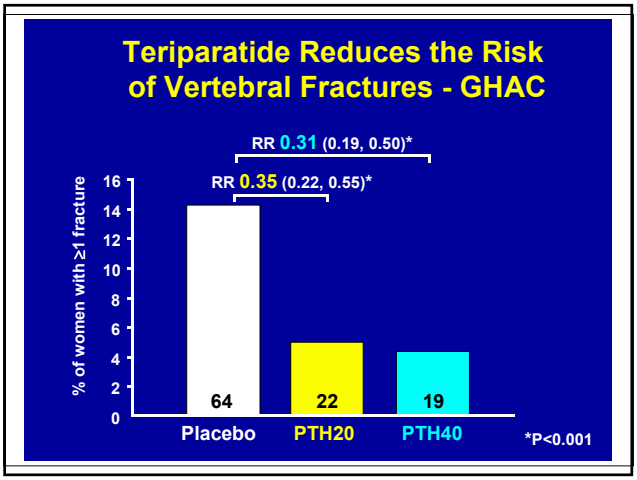
During the drug testing process, the medicine in FORTEO caused some rats to develop a bone cancer called osteosarcoma. In people, osteosarcoma is a serious but rare cancer. Osteosarcoma has been reported rarely in people who took FORTEO. It is not known if people who take FORTEO have a higher chance of getting osteosarcoma. Before you take FORTEO, you should tell your healthcare provider if you have Paget's disease of bone, are a child or young adult whose bones are still growing, or have had radiation therapy.

FDA warning regarding osteosarcoma
Forteo was approved for use in PMO 2002 – since then, no increase in incidence of osteosarcoma over the population in general

Teriparatide (Forteo)

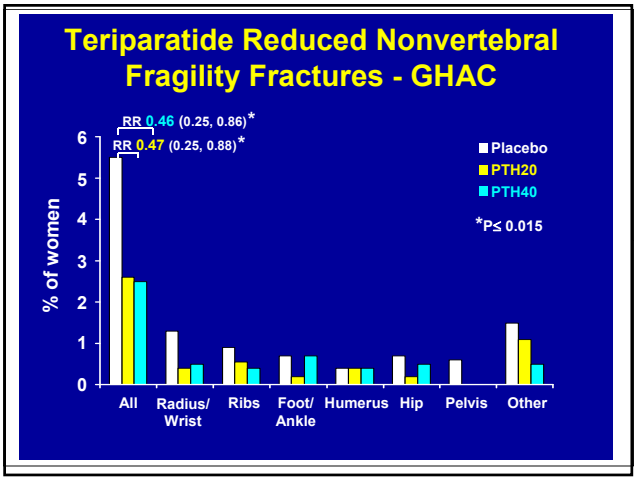
- 1-34 PTH, synthetic
- Anabolic agents – main action is to stimulate osteoblasts
- Daily subcut injection, 20mcg
- Very expensive - $20/d; $6,000/year
- Osteosarcoma warning
- Use for two years, then follow with bisphosphonate
- Currently FDA approved for:
  - Postmenopausal osteoporosis
  - Senile or hypogonadal osteoporosis in men
  - Glucocorticoid-induced osteoporosis





Current therapeutic deficiencies

- Oral bisphosphonates may be difficult to tolerate
- 1/6 of bisphos users "fail" therapy
- <50% of oral bisph users are compliant
- Bisphos cannot be used in renal insufficiency
- Rare incidence of sig bone pain
- What to do with prior jaw non-healing?
- teriparatide is expensive; works best for 18 – 24 months only
- SERMs never proven to prevent non-vert Fx
- Strontium results not yet reproduced



Denosumab – "Prolia"

- Fully human monoclonal antibody to the receptor activator of nuclear factor-kb ligand (RANKL) that blocks its binding to RANK
- Inhibits development and activity of osteoclasts
- Decreases bone resorption, increases bone density
- RANKL expressed on precursors of osteoblasts, marrow stromal cells and activated T cells

FREEDOM Trial

- Multicenter randomized, placebo-controlled trial
- 7868 postmenopausal women aged 60-90
- T-score <-2.5 at LS or total hip eligible
- Excluded if on bisphos within past 5 yrs
- Everyone received daily calcium and vitamin D
- Study group: denosumab 60mg subcut q6mo for 36 months
- Lat spine Xray performed annually
- BMD measured annually
- BTM only measured on 160 subjects

Cummings S et al, NEJM, August 2009, 756 - 765

Table 1. Baseline Characteristics of the Subjects.*

Variable	Denosumab (N=3902)	Placebo (N=3906)
Age		
Mean — yr	72.3±5.2	72.3±5.2
Group — no. (%)		
<70 yr	1030 (26.4)	1028 (26.3)
70–74 yr	1637 (42.0)	1642 (42.0)
≥75 yr	1235 (31.7)	1236 (31.6)
Body-mass index†	26.0±4.1	26.0±4.2
Region — no. (%)‡		
Western Europe	1761 (44.8)	1773 (45.1)
Eastern Europe	1374 (34.9)	1355 (34.4)
Latin America	472 (12.0)	462 (11.7)
North America	282 (7.2)	297 (7.5)
Australia and New Zealand	44 (1.1)	48 (1.2)
T score		
Lumbar spine	−2.82±0.70	−2.84±0.69
Total hip	−1.89±0.81	−1.91±0.81
Femoral neck	−2.15±0.72	−2.17±0.71
Prevalent vertebral fracture — no. (%)		
Yes	929 (23.8)	915 (23.4)
No	2864 (73.4)	2854 (73.1)
Unreadable or missing data	109 (2.8)	137 (3.5)
Serum 25-hydroxyvitamin D — ng/ml§	23.1±11.7	22.9±11.3

FREEDOM Trial
Baseline characteristics

Cummings S et al, NEJM, August 2009, 756 - 765

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<70 yr	1030 (26.4)	1028 (26.3)
70–74 yr	1637 (42.0)	1642 (42.0)
≥75 yr	1235 (31.7)	1236 (31.6)
Body-mass index†	26.0±4.1	26.0±4.2
Region — no. (%)‡		
Western Europe	1761 (44.8)	1773 (45.1)
Eastern Europe	1374 (34.9)	1355 (34.4)
Latin America	472 (12.0)	462 (11.7)
North America	282 (7.2)	297 (7.5)
Australia and New Zealand	44 (1.1)	48 (1.2)
T score		
Lumbar spine	−2.82±0.70	−2.84±0.69
Total hip	−1.89±0.81	−1.91±0.81
Femoral neck	−2.15±0.72	−2.17±0.71
Prevalent vertebral fracture — no. (%)		
Yes	929 (23.8)	915 (23.4)
No	2864 (73.4)	2854 (73.1)
Unreadable or missing data	109 (2.8)	137 (3.5)
Serum 25-hydroxyvitamin D — ng/ml§	23.1±11.7	22.9±11.3

FREEDOM Trial
Baseline characteristics

Cummings S et al, NEJM, August 2009, 756 - 765

Table 1. Baseline Characteristics of the Subjects.*

Variable	Denosumab (N=3902)	Placebo (N=3906)
Age		
Mean — yr	72.3±5.2	72.3±5.2
Group — no. (%)		
<70 yr	1030 (26.4)	1028 (26.3)
70–74 yr	1637 (42.0)	1642 (42.0)
≥75 yr	1235 (31.7)	1236 (31.6)
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FREEDOM Trial
Baseline characteristics

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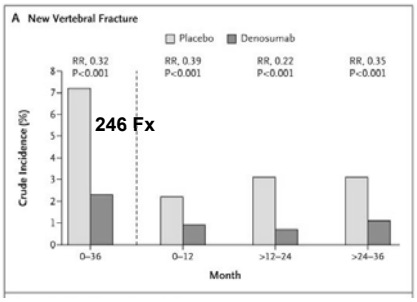
FREEDOM Trial: Incidence of new Vertebral Fracture



Cummings S et al, NEJM, August 2009, 756 - 765

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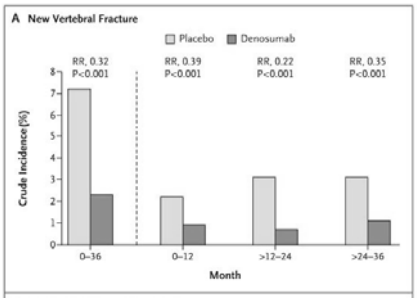

Cummings S et al, NEJM, August 2009, 756 - 765

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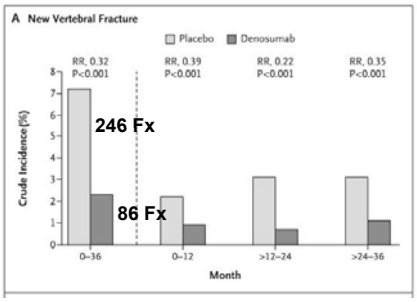

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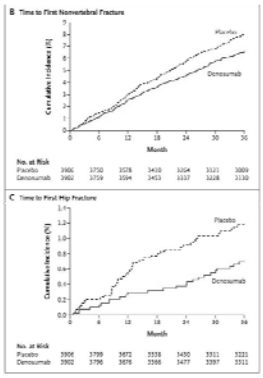

FREEDOM Trial: Time to first Non-Vert and Hip fractures

Cummings S et al, NEJM, August 2009, 756 - 765

Table 3. Adverse Events.*

Event	Denosumab (N = 3886)	Placebo (N = 3876)	P Value†
	no. (%)		
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of a study drug	192 (4.9)	202 (5.2)	0.55
Adverse events			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	NA
Serious adverse events			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary heart disease	47 (1.2)	39 (1.0)	0.41
Peripheral vascular disease	31 (0.8)	30 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in at least 2% of subjects‡			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling§	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in at least 0.1% of subjects¶			
Cellulitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

* NA denotes not applicable.

FREEDOM Trial Adverse Events

Cummings S et al, NEJM, August 2009, 756 - 765

Predefined adverse events:

- Osteonecrosis of the jaw
- Non-healing non-vertebral fractures
- Femoral shaft fractures
- Hypocalcemia
- Opportunistic infections
- Atrial fibrillation

Table 3. Adverse Events.*

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FREEDOM Trial Adverse Events

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Table 3. Adverse Events.*

Event	Denosumab (N=3886)	Placebo (N=3876)	P Value†
	no. (%)		
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
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FREEDOM Trial Adverse Events

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Serial Monitoring

- Spine – significant gains from treatment can usually be seen in one year
  - Hip often takes 24 months
- See changes (↑ or ↓) in six months with patients on glucocorticoids
- ISCD recommends yearly BMD until bone mass stable or improving, then every two years

Adverse Events

- Delayed Fracture healing
  - 2 cases in denosumab group
  - 4 cases in placebo group
- Femoral shaft fracture
  - 0 cases in denosumab group
  - 3 cases in placebo group**
- Cellulitis
  - Serious AE: 12 in denosumab, 1 in placebo
  - All AE: 47 denosumab, 36 in placebo (no diff)