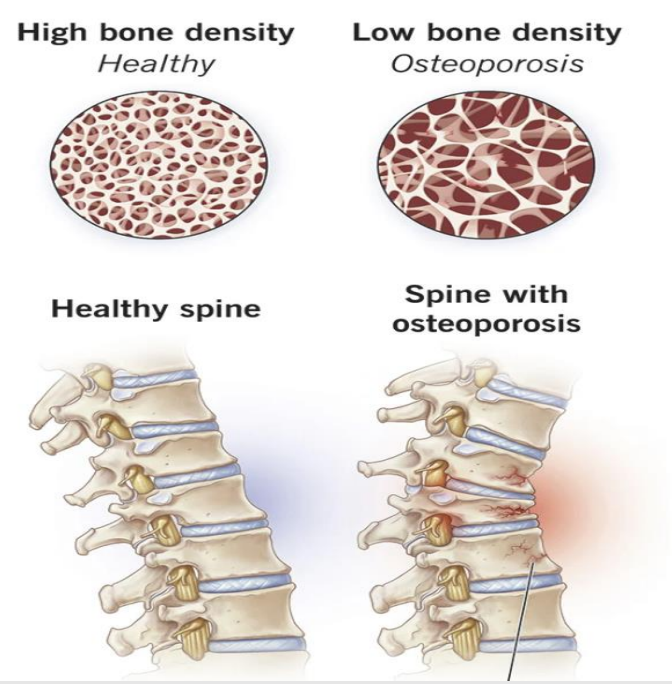
骨質疏鬆症的治療策略及挑戰



臺北榮民總醫院 內分泌新陳代謝科
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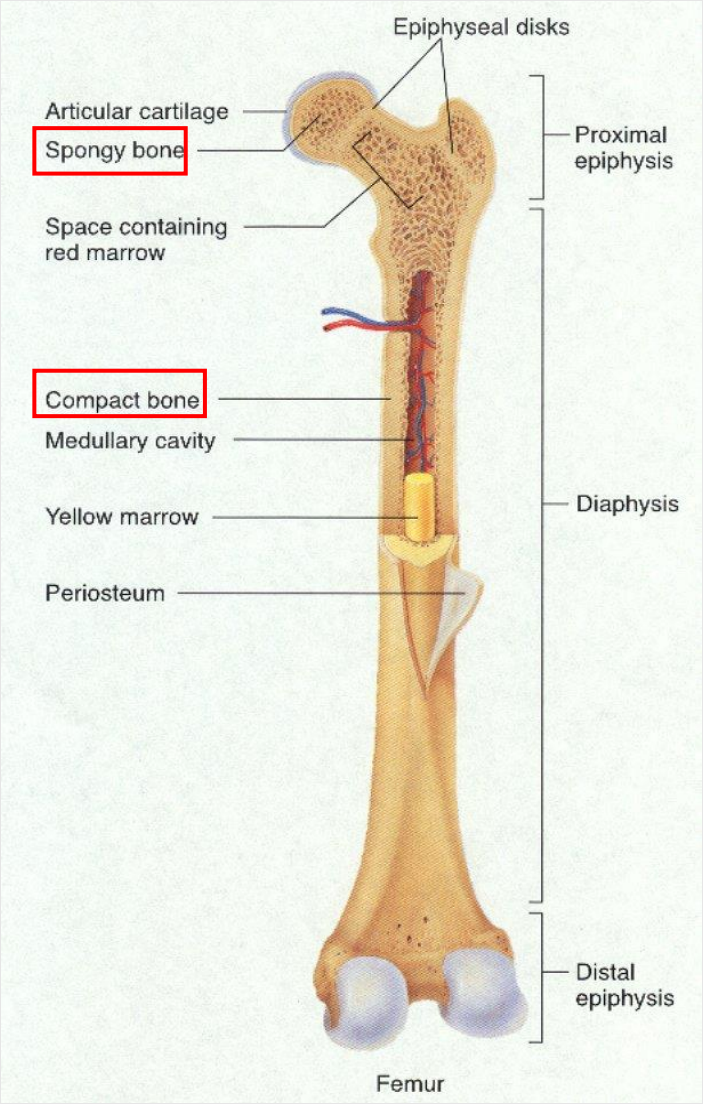
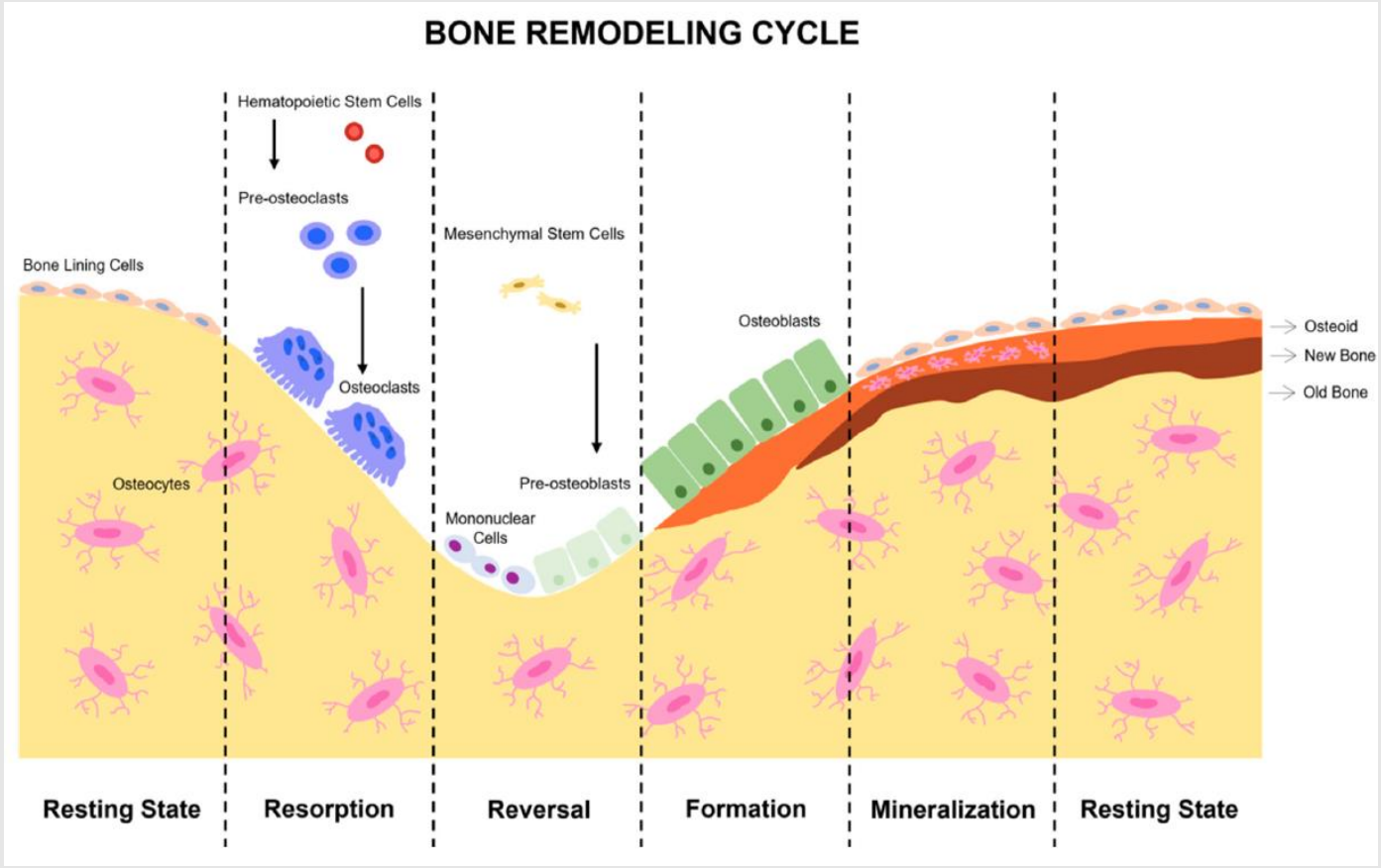
Human skeleton

- **Cortical bone** 80% (compact)
  - 85% calcified
  - Rigidity
  - Long bone fracture
- **Cancellous bone** 20% (Trabecular; spongy)
  - 20% calcified
  - Strength and elasticity
  - Axial skeleton
  - Vertebral fracture



(Adapted from SM Ott, in JP Bilezikian et al [eds]: Principles of Bone Biology, vol. 18, 1996, pp 231–241.)

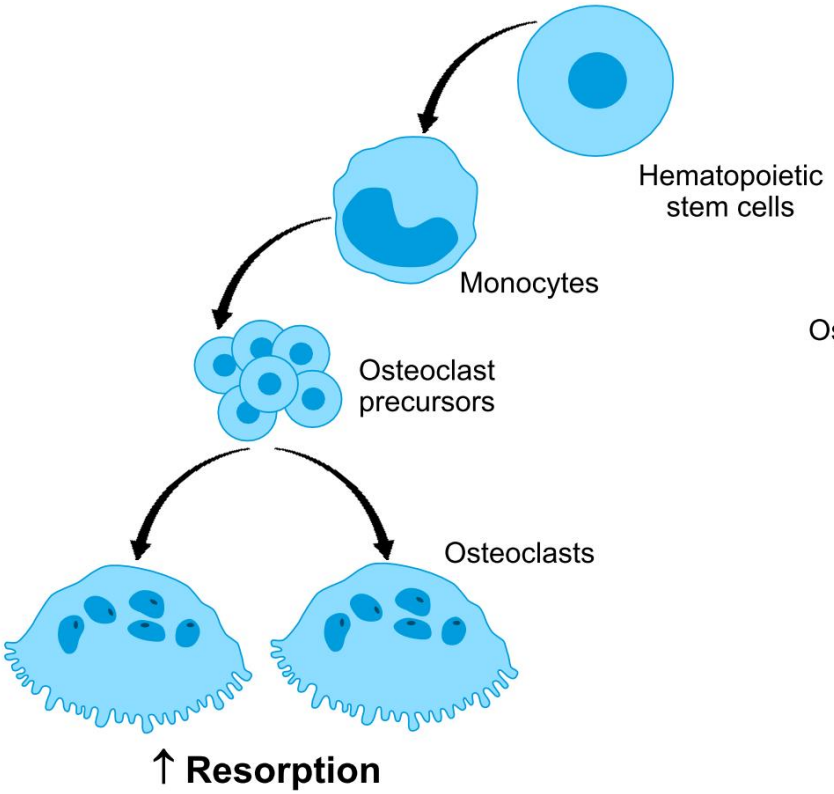
Bone remodeling cycle
~120 days



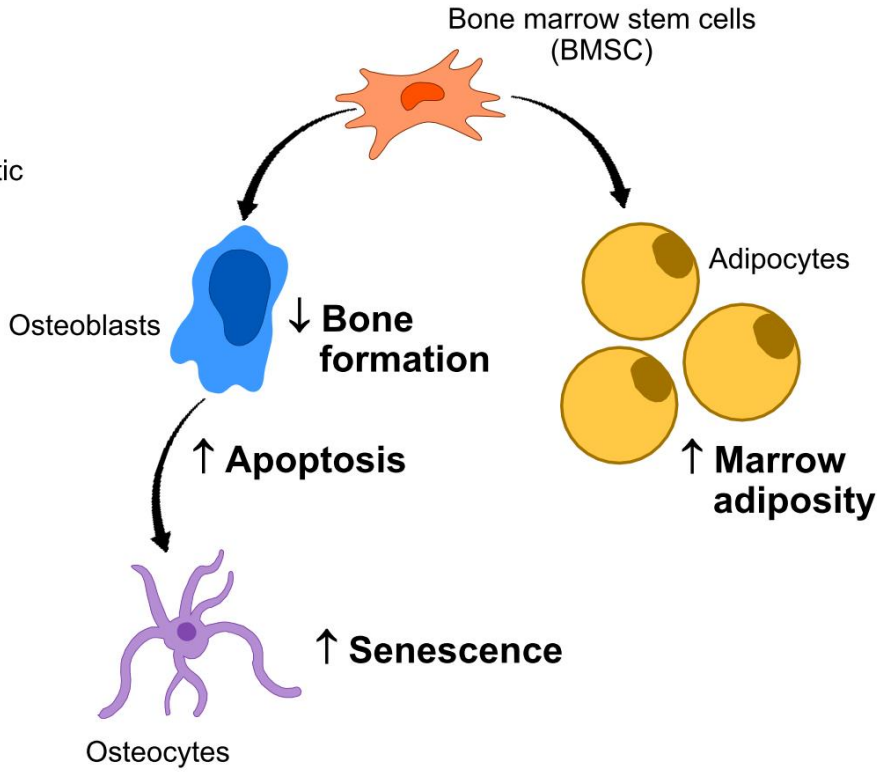
--Int. J. Mol. Sci. **2022**, 23, 9465.

SKELETAL AGING

HALLMARKS

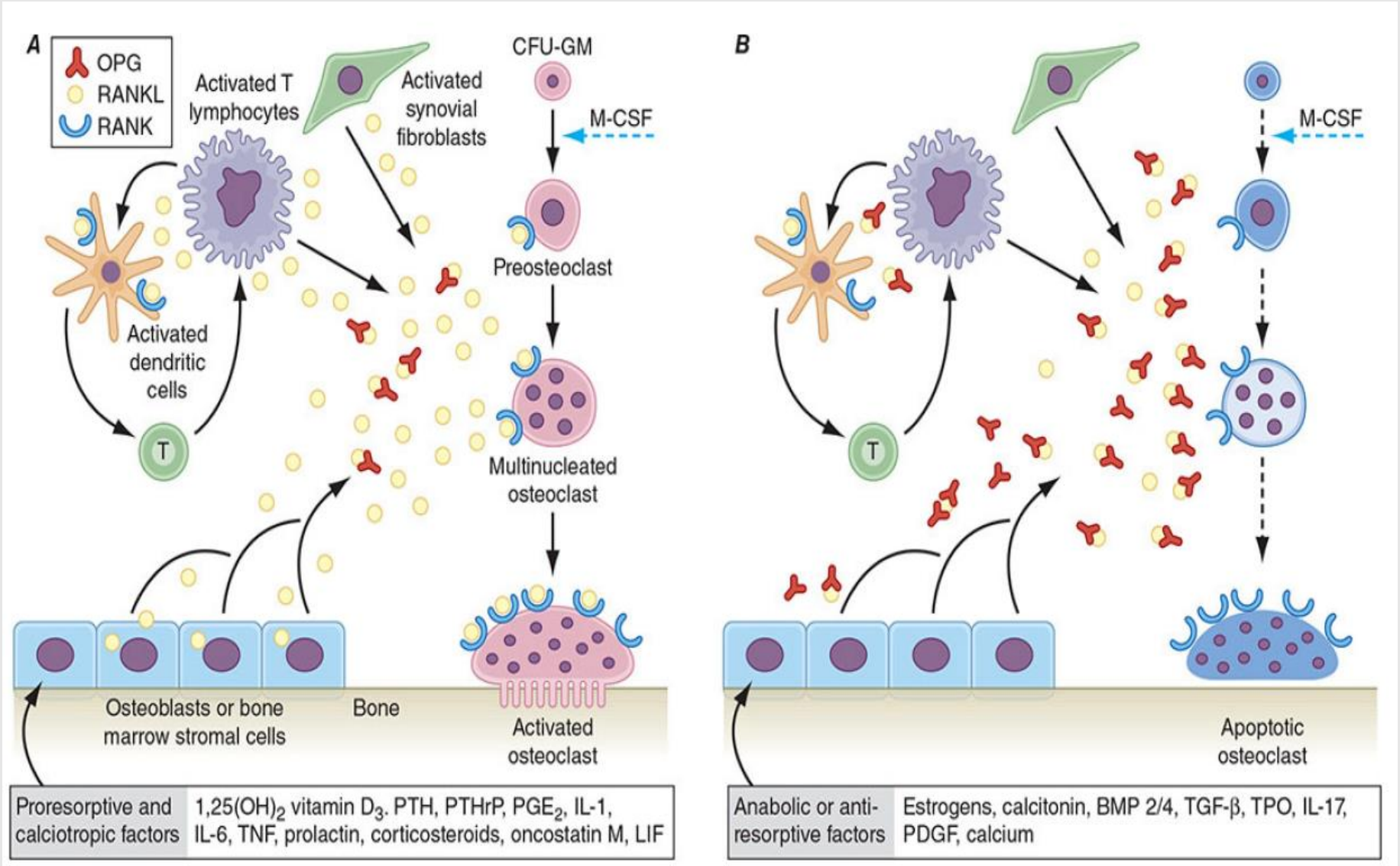


Mesenchymal stem cells



Redrawn from: Sfeir JG, et al. *Mayo Clin Proc* 2022

Hormonal control of bone resorption



OPG: Osteoprotegerin

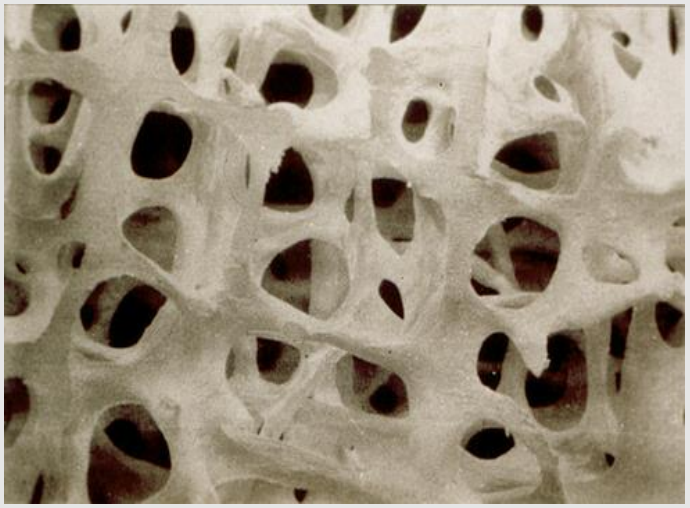
---Harrison's Internal Medicine 21st ed.

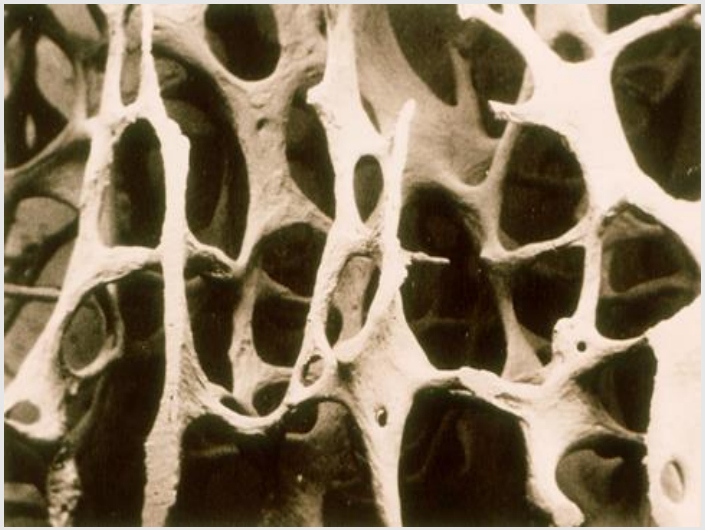
Osteoporosis--definition

"**Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. *Bone strength* primarily reflects the integration of *bone density* and *bone quality*.**

--NIH Consensus Development Conference

---*JAMA 2001;*285: 785-95





Osteoporosis (Greek)
osteon: bone poros: small hole

Osteoporosis

Compromises Bone Strength
Increases Risk of Fracture

Bone Strength = **Bone Quality** + **Bone Density**

1. **Architecture**
2. **Turnover**
3. **Damage Accumulation**
4. **Mineralization**
5. **Collagen quality**

aBMD = g/cm^2
vBMD = g/cm^3

Adapted from NIH Consensus Development Panel on Osteoporosis. JAMA 2001

Osteoporosis

- Systemic skeletal disease (any where)
  -- common in vertebral & hip fractures
- pathogenesis
  - inadequate peak bone mass
  - Resorption > formation (uncoupling)
- increased incidence with age

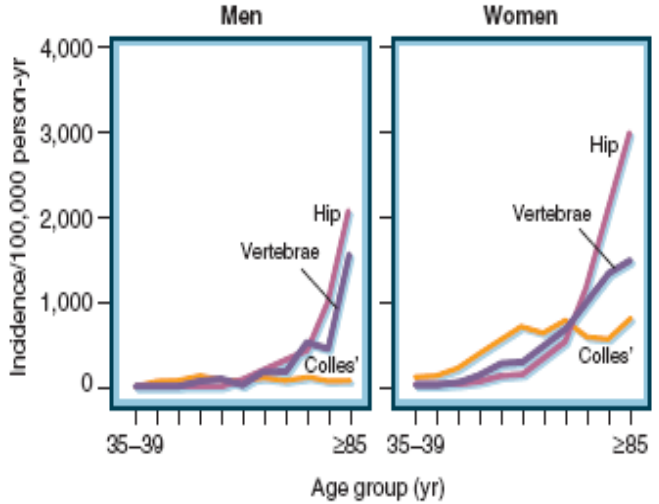
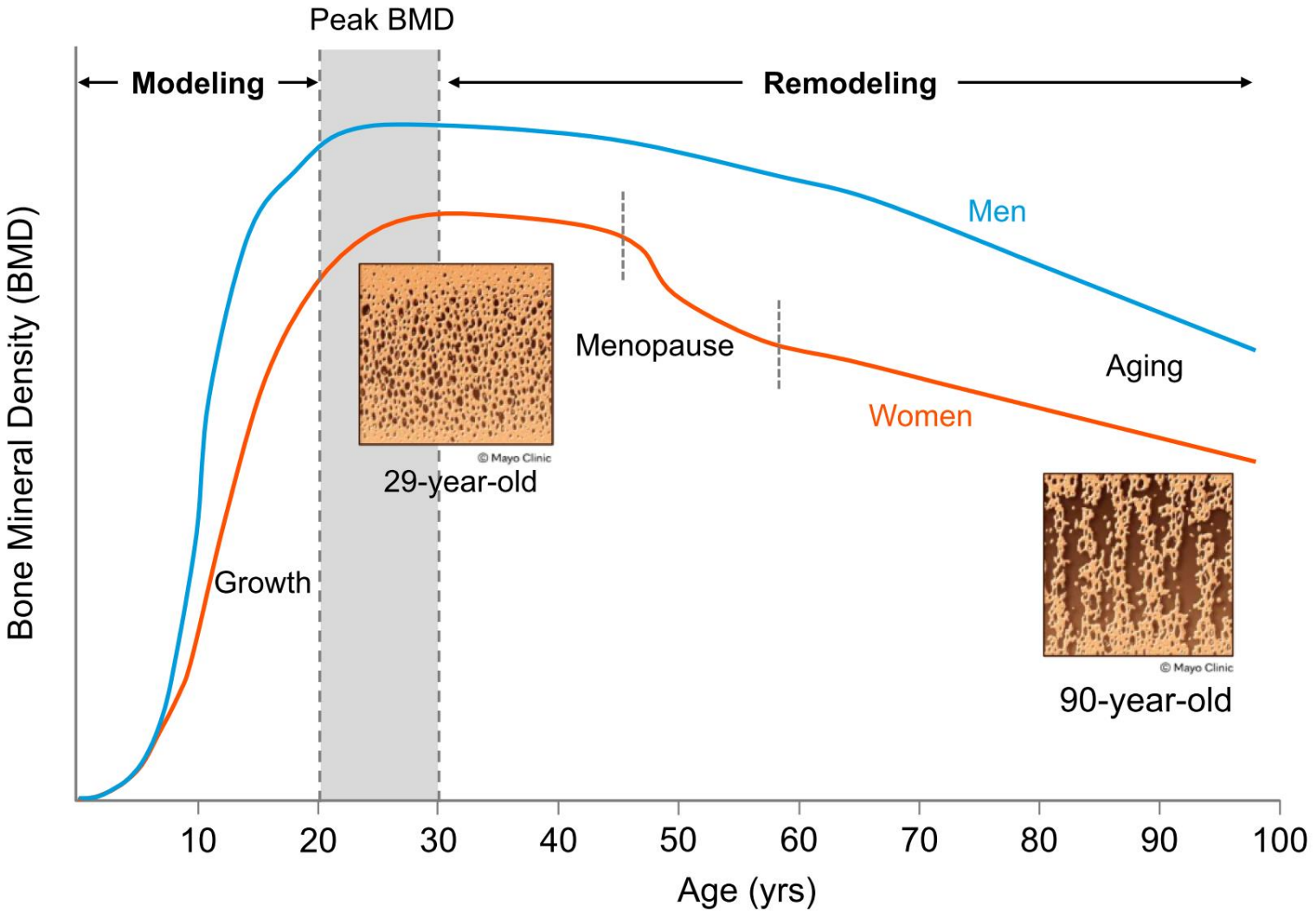


Figure 29-14 Age-specific incidence rates for hip, vertebral, and Colles' fractures in Rochester, Minnesota. (From Cooper C, Melton LJ. Epidemiology of osteoporosis. *Trends Endocrinol Metab.* 1992;3:224. Copyright 1992 by Elsevier Science Inc.)

- **Age>50 Y/O**, any fracture should be considered as potentially related to osteoporosis
- Most women meet the diagnostic criterion for osteoporosis by age 70-80 (typically around age 50 for menopause)



Redrawn from: Sfeir JG, et al. *Mayo Clin Proc* 2022

Osteoporosis-related fractures

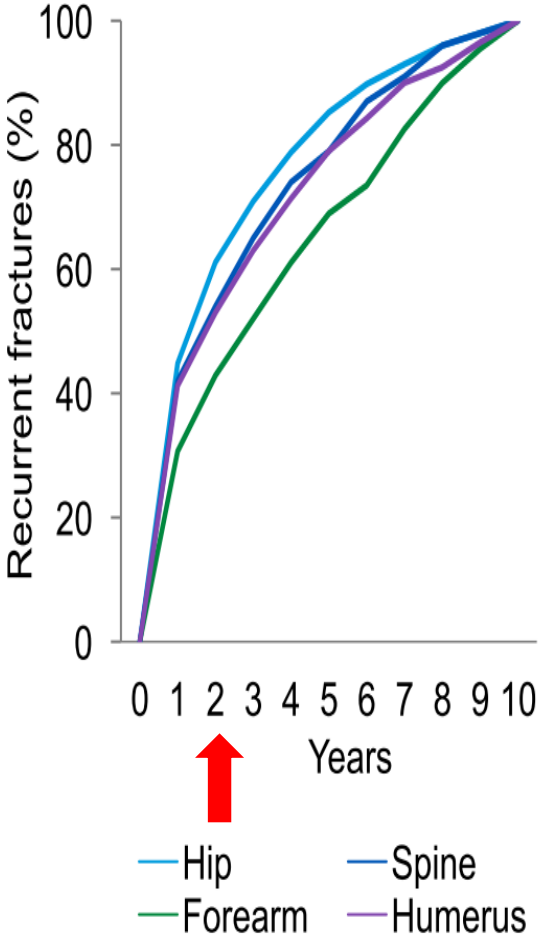
- Adulthood fractures of any bone that occur in the setting of trauma less than or equal to **a fall from standing height**, with the exception of fingers, toes, face and skull

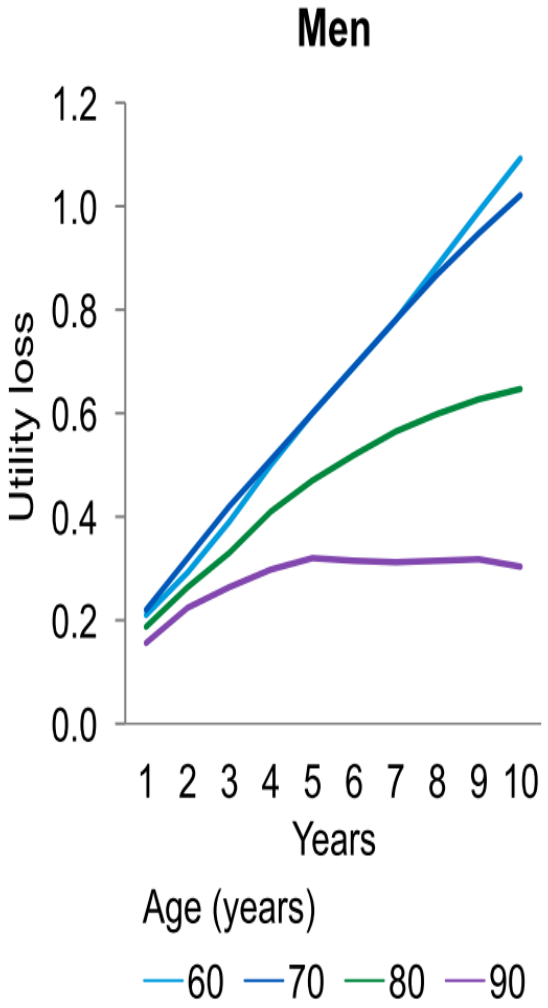
- ***Hip fracture***
  - Lifetime probability that a 50-year-old white individual will have a hip fracture is 14% for women and 5% for men
  - **Risk:** Caucasians ≈ Hispanics ≈ Asians >> American Africans
  - 20-25% mortality during the year after surgery
  - 30% of survivors requiring long-term home care
  - Incidence of hip fracture double every 5 years after age 70

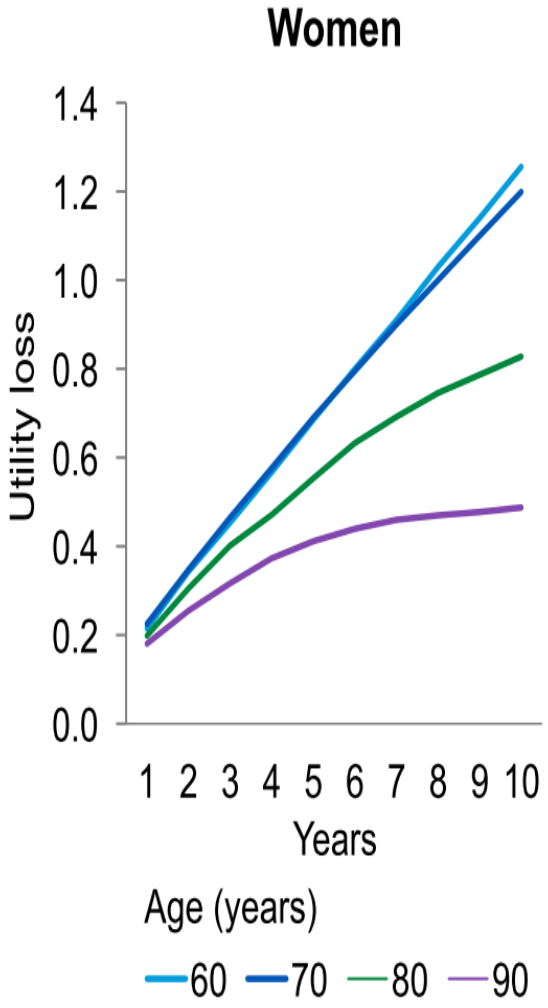
Epidemiology

- **Hip fracture**
  - Most devastating result of osteoporosis (risk is greatest in the first 6 months; decreased over time)
  - Most after a fall; 80% in women
  - 90% p't >50y/o; incidence increased exponentially with age
  - Age-related decrease in bone mass at proximal femur and age-related increase in falls
- **Vertebral fracture**
  - Only ¼ results from falls; most due to routine activities such as bending or lifting light objects
  - prevalence (♂=♀); occupation-associated trauma in men
  - relative asymptomatic & multiple fractures induced height loss
- **Wrist fracture**
  - Most in women, 50% of them are > 50y/o

MORBIDITY AFTER A FRACTURE







Redrawn from: Kanis, JA, et al. *Osteoporos Int* 2018

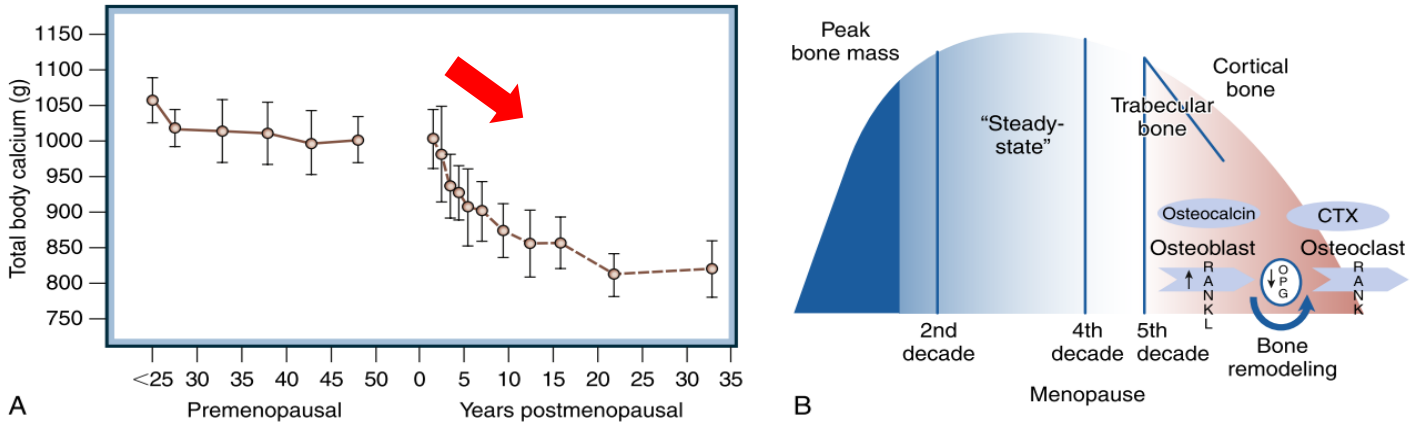
Prevalence of osteoporosis in Taiwan (>50 Y/O)

表 1 、50 歲以上民眾罹患骨質疏鬆症比率

年齡分層	男	女	全體
50-64 歲	8.9%	20.2%	14.6%
65-74 歲	10.5%	33.3%	22.6%
75 歲以上	14.3%	33.5%	23.8%
總計	10.2%	25.2%	17.9%

1. 資料來源：98 年國民健康訪問暨藥物濫用調查　2013.10.20. 國民健康署
2. 百分比經加權處理，具全國代表性
3. 骨質疏鬆定義：最近一年內，以自述且經醫師診斷有骨質疏鬆者才算

1. Female>>Male 2.Elderly



• **Fig. 30.15** (A) Bone mass development, maintenance, and loss: trabecular bone loss starts earlier and is more intense than in cortical bone. (B) The decline of total body calcium with years since menopause. *CTX,* cross-linked telopeptide of type I collagen; *OPG,* osteoprotegerin; *RANK,* receptor activator of nuclear transcription factor κB. (Redrawn from Tella SH, Gallagher JC. Prevention and treatment of postmenopausal osteoporosis. *J Steroid Biochem Mol Biol.* 2014;142:155–170.)

---William's textbook of Endocrinology, 2020 14th ed, p.1277

TABLE 411-1 Risk Factors for Osteoporosis Fracture

NONMODIFIABLE	POTENTIALLY MODIFIABLE
Personal history of fracture as an adult	Current cigarette smoking
History of fracture in first-degree relative	Estrogen deficiency
Female gender	Early menopause (<45 years) or bilateral ovariectomy
Advanced age	Prolonged premenstrual amenorrhea (>1 year)
White race	Poor nutrition especially low calcium and vitamin D intake
Dementia	Alcoholism
	Impaired eyesight despite adequate correction
	Recurrent falls
	Inadequate physical activity
	Poor health/frailty

---Harrison's Internal Medicine 21st ed.

TABLE 404-2 Diseases Associated with an Increased Risk of Generalized Osteoporosis in Adults

Hypogonadal states	**Hematologic disorders/malignancy**
Turner's syndrome	Multiple myeloma
Klinefelter's syndrome	Lymphoma and leukemia
Anorexia nervosa	Malignancy-associated parathyroid hormone (PTHrP) production
Hypothalamic amenorrhea	Mastocytosis
Hyperprolactinemia	Hemophilia
Other primary or secondary hypogonadal states	Thalassemia
Endocrine disorders	**Selected inherited disorders**
Cushing's syndrome	Osteogenesis imperfecta
Hyperparathyroidism	Marfan's syndrome
Thyrotoxicosis	Hemochromatosis
Diabetes mellitus (both type 1 and 2	Hypophosphatasia
Acromegaly	Glycogen storage diseases
Adrenal insufficiency	Homocystinuria
Nutritional and gastrointestinal disorders	Ehlers-Danlos syndrome
Malnutrition	Porphyria
Parenteral nutrition	Menkes' syndrome
Malabsorption syndromes	Epidermolysis bullosa
Gastrectomy	**Other disorders**
Severe liver disease, especially biliary cirrhosis	Immobilization
Pernicious anemia	Chronic obstructive pulmonary disease
Rheumatologic disorders	Pregnancy and lactation
Rheumatoid arthritis	Scoliosis
Ankylosing spondylitis	Multiple sclerosis
	Sarcoidosis
	Amyloidosis

---Harrison's Internal Medicine 21st ed. Table 411-2

Common Secondary Causes

Table 1. Common Secondary Causes of Osteoporosis and Laboratory Evaluations.*

Possible Cause of Osteoporosis	Laboratory Test
Vitamin D deficiency	Measurement of serum 25-hydroxyvitamin D level
Primary hyperparathyroidism	Measurement of fasting serum calcium and parathyroid hormone levels
Celiac disease	Measurement of serum tissue transglutaminase, total IgA, and gliadin levels
Idiopathic hypercalciuria	Measurement of 24-hour urine calcium excretion after discontinuation of calcium supplements
Hyperthyroidism	Measurement of serum thyrotropin and total thyroxine levels
Myeloma	Serum and urine immunoelectrophoresis

* Additional information regarding secondary causes of osteoporosis can be found in Tannenbaum et al.[2] and Jamal et al.[3]

---N Engl J Med. 2010 Nov 18;363(21):2027-35.

Factors leading to osteoporotic fractures

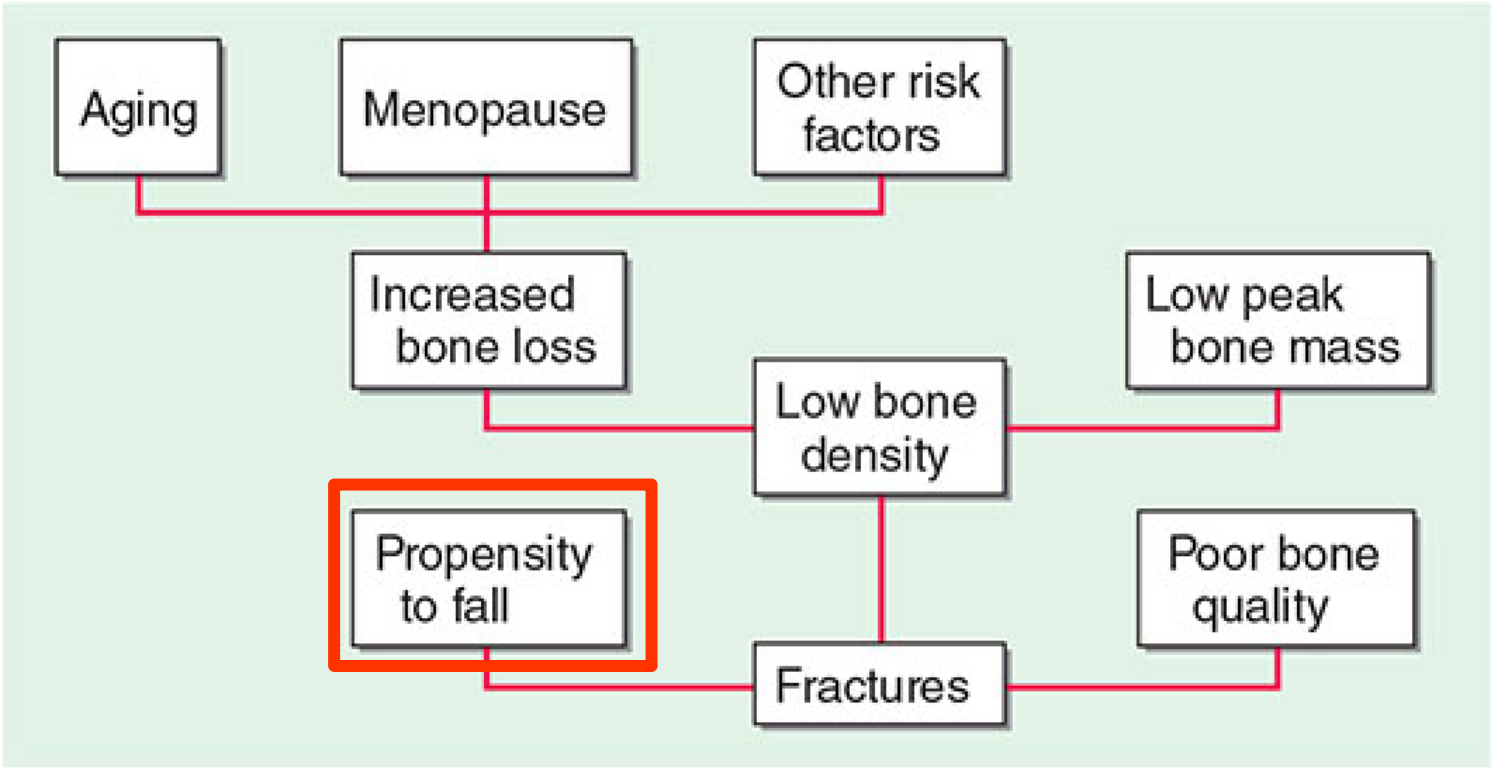


FIGURE 411-3 Factors leading to osteoporotic fractures.

---Harrison's Internal Medicine 21st ed.

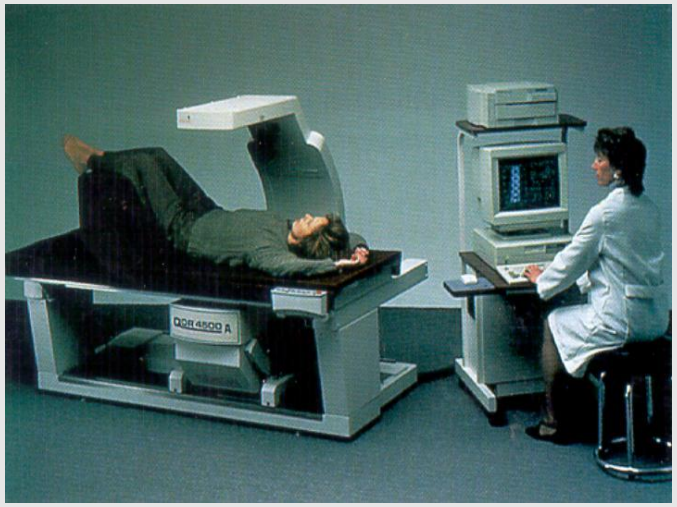
Drugs associated with risk of Osteoporosis

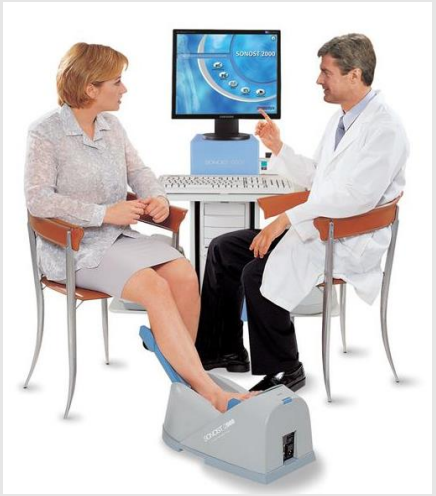
TABLE 411-3 Drugs Associated with an Increased Risk of Generalized Osteoporosis in Adults	
Glucocorticoids	Excessive thyroxine
Cyclosporine	Aluminum
Cytotoxic drugs	Gonadotropin-releasing hormone agonists
Anticonvulsants	Heparin
Aromatase inhibitors	Lithium
Selective serotonin reuptake inhibitors	Protein pump inhibitors
	Thiazolidinediones
	Androgen deprivation therapies

---Harrison's Internal Medicine 21st ed.

Investigations--imaging

- **Radiography** (clinical diagnosis; low-trauma)
  - deformed vertebra, compression fracture
- **Bone mass density**
  - **Dual-energy X-ray absorptiometry (DXA)**
  - Single-energy X-ray absorptiometry
  - Quantitative CT (QCT)
  - Quantitative ultrasound (screening)





Indications for BMD Testing

TABLE 411-4 Indications for Bone Mineral Density Testing

- Women aged ≥65 and men aged ≥70; regardless of clinical risk factors
- Younger postmenopausal women, women in the menopausal transition, and men aged from 50 to 69 with clinical risk factors for fracture
- Adults who have a fracture at or after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids at a daily dose >5 mg prednisone or equivalent for >3 months associated with low bone mass or bone loss

---Harrison's Internal Medicine 21st ed.

Diagnosis

TABLE 30.1 Diagnostic Categories for Osteoporosis Based on Measurements of BMD and Bone Mineral Content

Category	Definition
Normal	BMD ±1 SD of the young adult reference mean
Low bone mass (osteopenia) **Low bone density**	BMD >1 SD and <2.5 SD lower than the young adult mean
Osteoporosis	BMD >2.5 SD lower than the young adult mean
Severe osteoporosis (established osteoporosis)	BMD >2.5 SD lower than the young adult mean in the presence of one or more fragility fractures

BMD, Bone mineral density; *SD*, standard deviation.

---William's textbook of Endocrinology, 2020 14th ed, p.1276

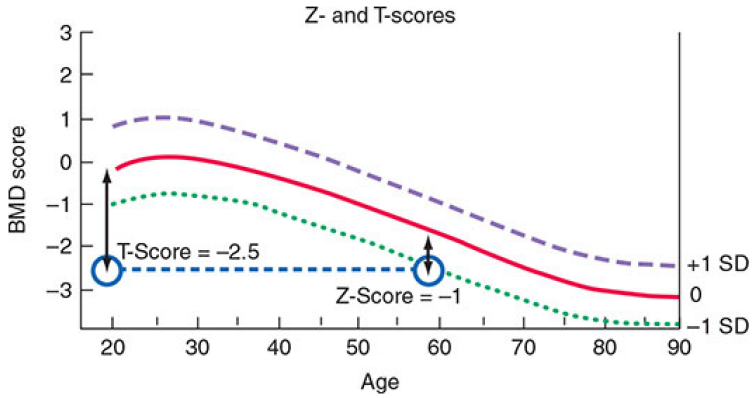


FIGURE 411-6 Relationship between Z-scores and T-scores in a 60-year-old woman. BMD, bone mineral density; SD, standard deviation.

---Harrison's Internal Medicine 21st ed.

- Use the **lowest** central DXA T score of PA L-spine, femoral neck, or total hip
- **T-score:**
  - The number of SDs from the mean bone density values in normal sex-matched young adults (20-29 Y/O)
  - Postmenopausal women, men ≧50y/o
- Z-score:
  - The number of SDs from the normal mean value for age- and sex-matched control subjects
  - Premenopausal females and men ≦50y/o
  - ≦-2.0: below the expected range of age;
    ＞-2.0: within the expected range of age

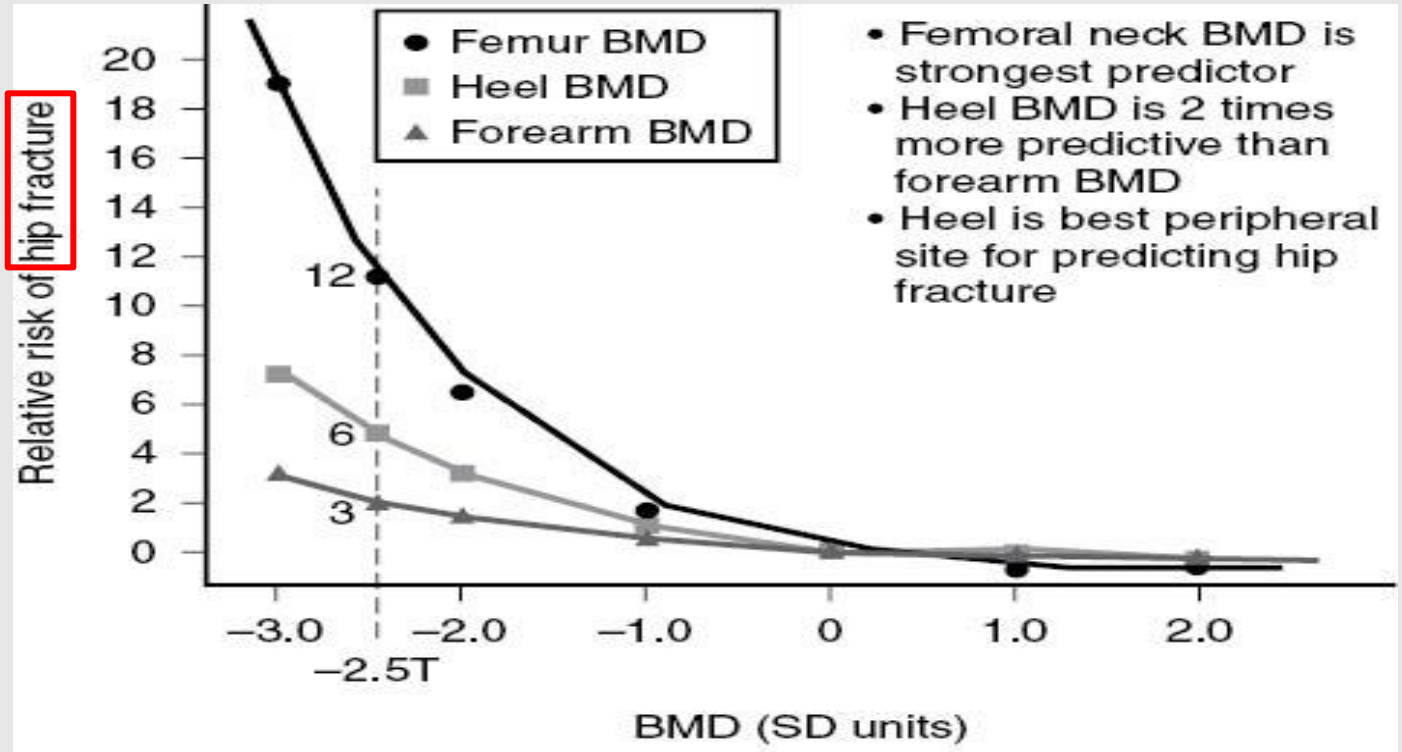


FIGURE 68-1. Hip fracture incidence as a function of BMD measured at the hip, spine, and forearm in postmenopausal women.

(Data from Cummings SR, Black DM, Nevitt MC, et al: Bone density at various sites for prediction of hip fractures, Lancet 341:72–75, 1993.)

- Highest risk occurs future fracture **within the first 2 years** after the first fracture.

Endocrinology - Adult and Pediatric, 6th Edition

By J. Larry Jameson, MD, PhD and Leslie J. De Groot, MD

>50% of fractures among postmenopausal women occur in those with low bone density

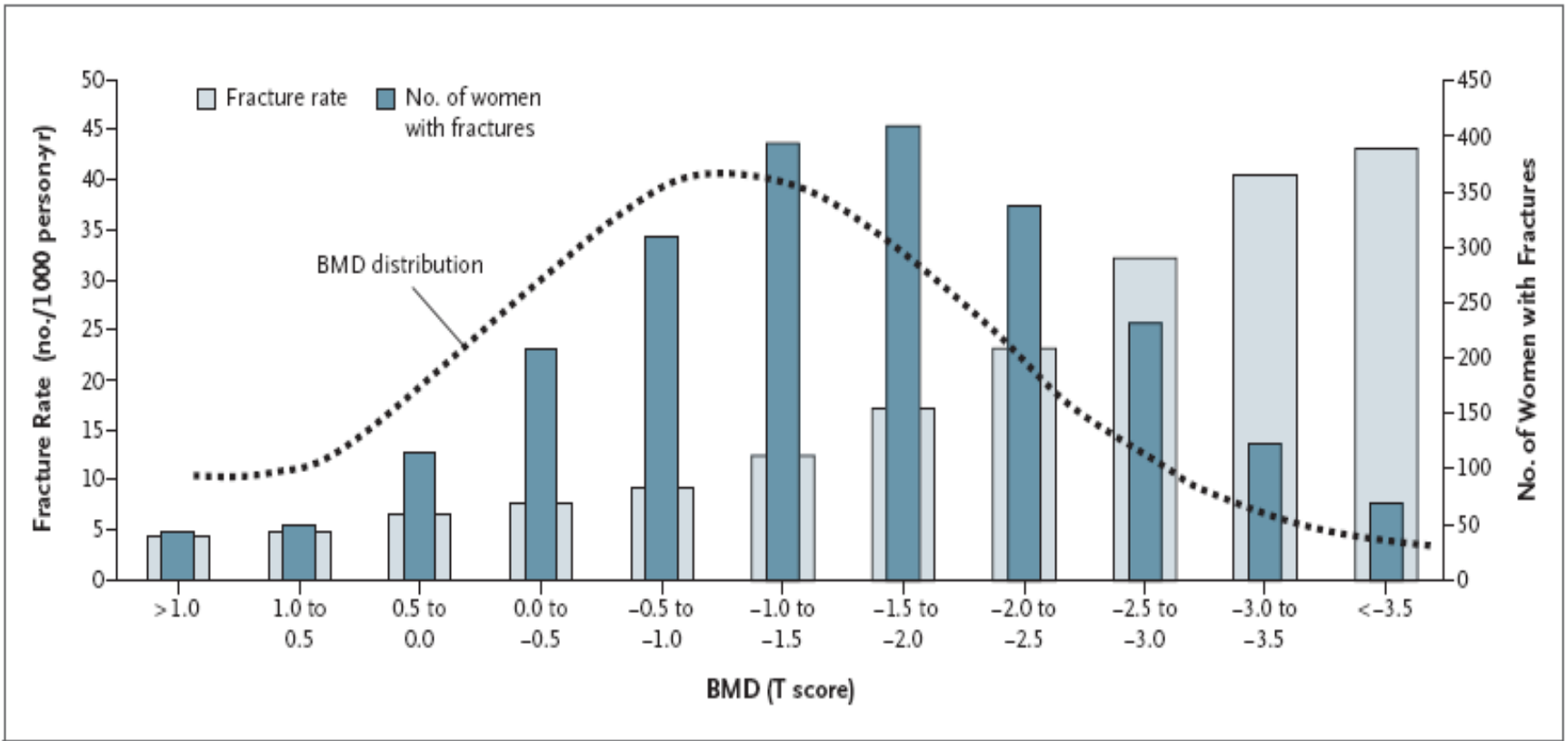
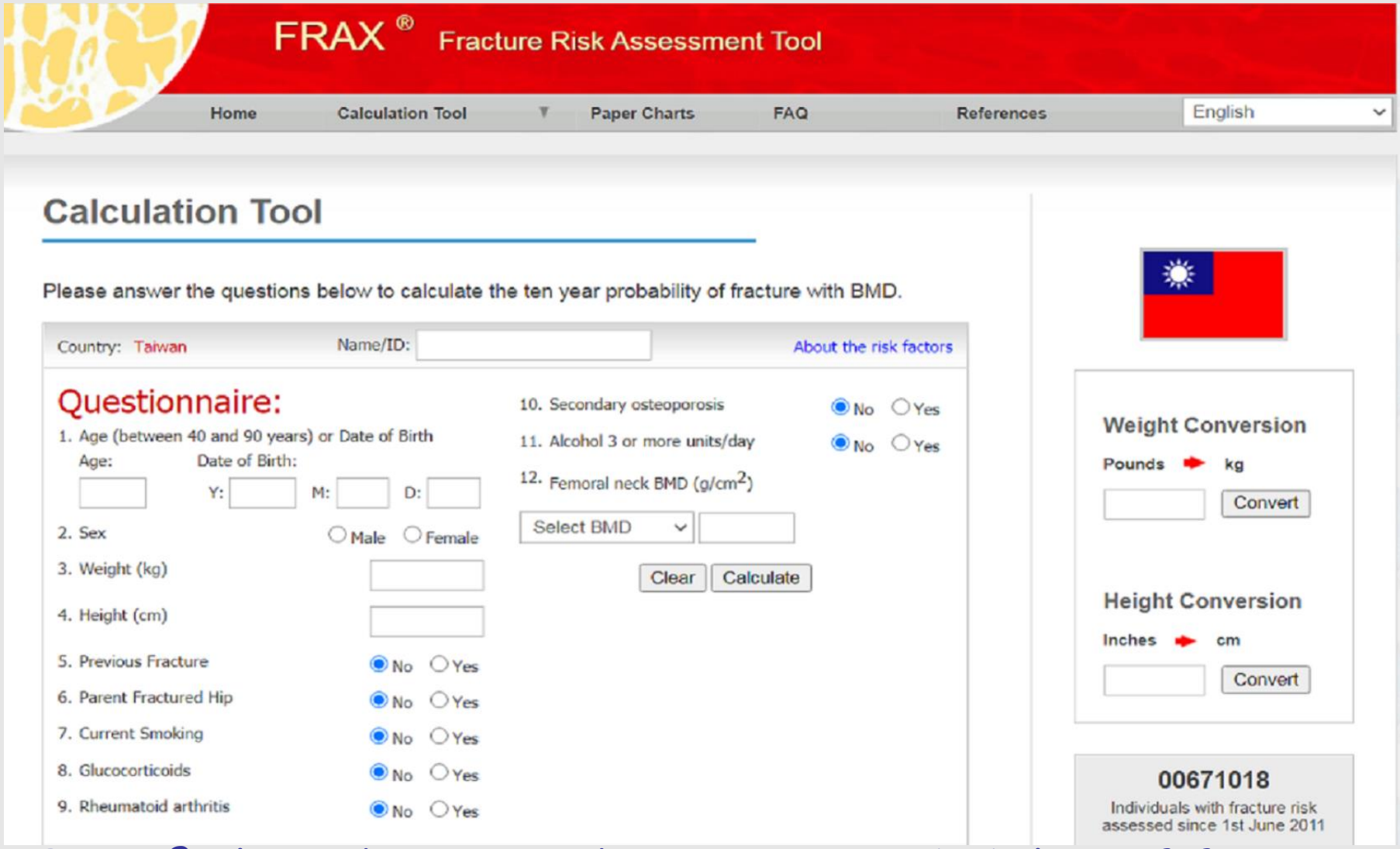


Figure 1. Fracture Rate and the Number of Women with Fractures According to Peripheral Bone Mineral Density (BMD).
Data are from Siris et al.[10]

---N Engl J Med. 2007 May 31;356(22):2293-300.

FRAX® Score

Website under University of Sheffield, UK



FRAX® algorithms give the 10-year probability of fracture

High risk--- Hip ≧ 3% or Major fracture ≧ 20%

---Harrison's Internal Medicine 20th edition, p. 2952

Panel: Procedures proposed in the investigation of osteoporosis

Routine

- History and clinical examination
- Blood count, sedimentation rate, or C-reactive protein
- Serum calcium, phosphate, alkaline phosphatase, liver transaminases, creatinine
- Serum 25-hydroxyvitamin D (recommendations vary according to resources, but routine measurement in patients with osteoporosis is recommended in some guidelines)
- Thyroid function tests
- Bone densitometry (dual energy x-ray absorptiometry)

Other procedures (if indicated)

- Lateral x-rays of thoracic and lumbar spine or dual energy x-ray absorptiometry-based vertebral fracture assessment
- Serum immunoelectrophoresis and urinary Bence-Jones proteins
- Parathyroid hormone, urinary calcium
- Serum testosterone, sex hormone binding protein, follicle-stimulating hormone, luteinising hormone
- Markers of bone turnover
- 24 h urinary free cortisol, overnight dexamethasone suppression test
- Endomysial and tissue transglutaminase antibodies
- Isotope bone scan

---*Lancet* 2019; 393: 364–76

Biochemical markers

Biochemical markers of bone turnover may:

- Predict risk of fracture independently of bone density.
- Predict extent of fracture risk reduction when repeated after 3–6 months of treatment with FDA-approved therapies.
- Predict magnitude of BMD increases with FDA-approved therapies.
- Predict rapidity of bone loss.
- Help determine adequacy of patient compliance and persistence with osteoporosis therapy.
- Help determine duration of "drug holiday" (data are quite limited to support this use, but studies are under way).

Abbreviations: BMD, bone mineral density; FDA, U.S. Food and Drug Administration.

Source: Adapted from the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and Treatment of Osteoporosis. © National Osteoporosis Foundation.

Biochemical markers

TABLE 411-6 Biochemical Markers of Bone Metabolism in Clinical Use
Bone formation
Serum bone-specific alkaline phosphatase
Serum osteocalcin
Serum propeptide of type I procollagen
Bone resorption
Urine and serum cross-linked N-telopeptide
Urine and serum cross-linked C-telopeptide

---Harrison's Internal Medicine 21st ed.

Prevention and therapy
---prevent fractures---

- Nutrition and calcium supplementation
  - Calcium >1.2 g/d (slow bone loss)
  - Vit. D 800-2000 U/d (serum 25(OH)D above 30 ng/mL)
  - Weight-bearing physical exercise and prevention of falls

- Management of fractures
  - Hip→ require operation if indication
  - Vertebral → bed-rest
  - Rehabilitation
  - Pain relief (mild analgesics & local physical therapy)
    (Calcitonin→ analgesic effect)

National Osteoporosis Foundation (NOF)
--Initiation of pharmacologic intervention--

Guidelines for pharmacologic intervention in postmenopausal women and men ≥50 years of age

History of hip or vertebral fracture.
T-score ≤-2.5 (DXA) at the femoral neck or spine, after appropriate evaluation to exclude secondary causes.
T-score between -1 and -2.5 at the femoral neck or spine, and a 10-year probability of hip fracture ≥3 percent or a 10-year probability of any major osteoporosis-related fracture ≥20 percent based upon the United States-adapted WHO algorithm.

DXA: dual-energy x-ray absorptiometry; WHO: World Health Organization.

References:

1. *Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int 2014; 25:2359.*
2. *Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; 97:1802.*

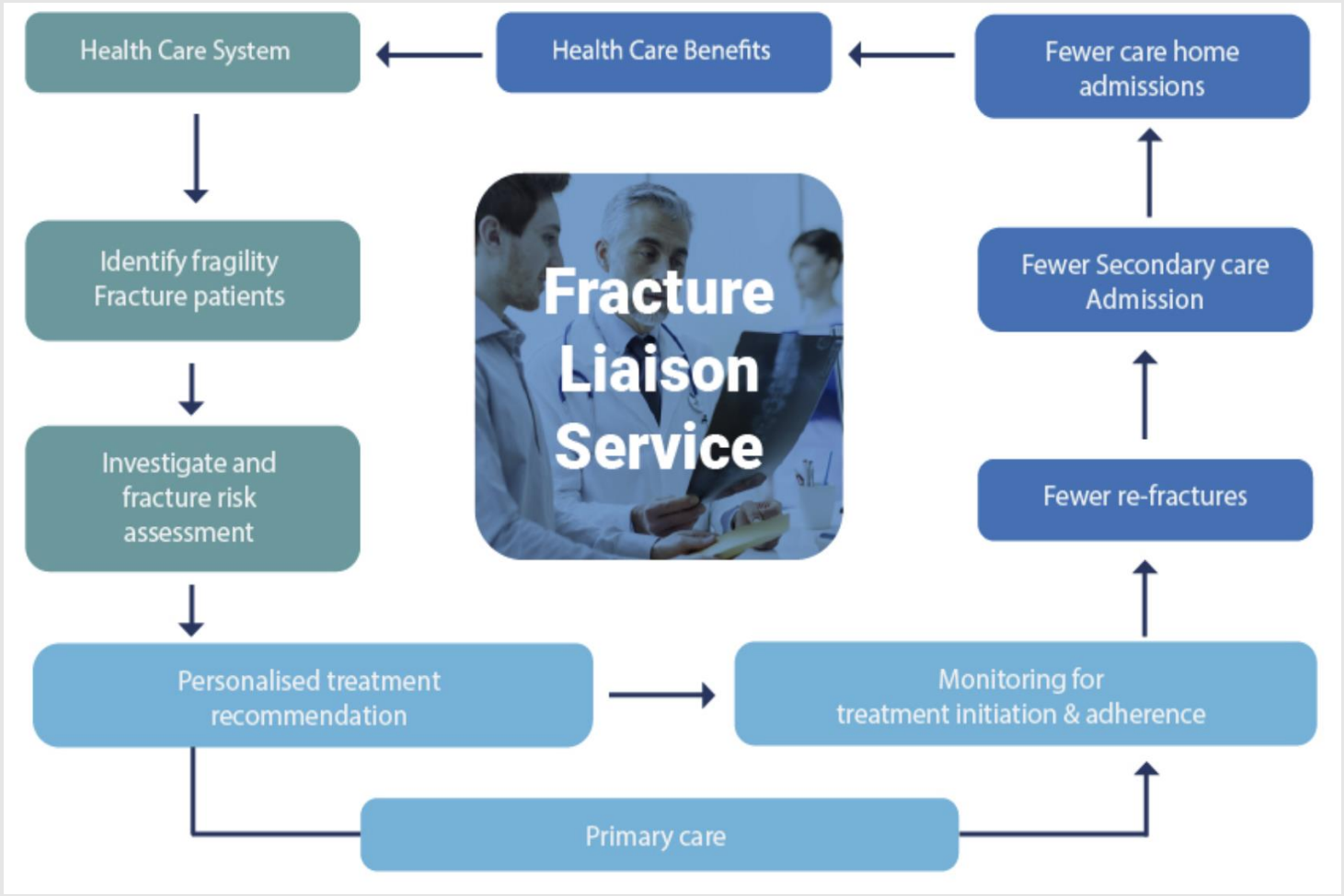
---Harrison's Internal Medicine 20th edition, p. 2952

Fracture liaison service

- Patients (>50Y/O) with fractures are largely not screened or treated for osteoporosis
- <25% of fracture patients receive follow-up care
- In the Kaiser system (USA), a 20% decline in hip fracture occurrence with the introduction of a fracture liaison service
- Health care professional (usually a nurse or physician's assistant) educate patients and coordinate evaluation and osteoporosis treatment as patients move through the ER, inpatient care in an acute care hospital, rehabilitation hospital care, and/or orthopedic practice to outpatient management

---Harrison's Internal Medicine 21st ed.

Fracture liaison service



Pharmacologic Tx of Osteoporosis

- Anti-resorptive agents
  - HRT (Hormone replacement therapy)
  - SERMs (selective estrogen receptor modulators)
  - Bisphosphonates
  - Calcitonin
  - Denosumab (RANKL inhibitor)

- Anabolic agents (increase bone formation)
  - Intermittent PTH (teriparatide, *abaloparatide*)
  - Romosozumab

- *健保不給付或台灣尚無此類藥物*

---Harrison's Internal Medicine 21th edition

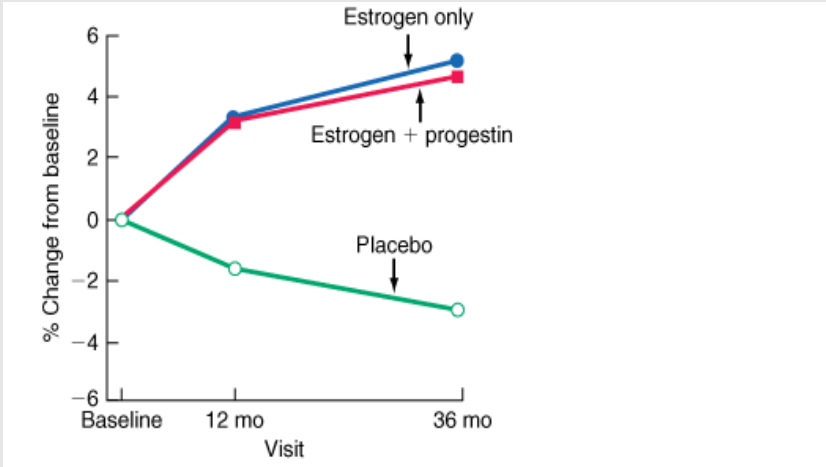
Hormone Replacement Therapy (HRT)

- Various types of Estrogen
  -- reduced bone turnover, prevent bone loss, small increase bone mass
- Estrogen replacement ↓50% osteoporosis-related Fx
- Rapid bone loss after discontinued HRT (no residual protective effect by 10 years after stop HRT)
- WHI (Women's Health Initiative) trial: HRT↑CVD & breast ca.

→↓24% all clinical fractures

→ Estrogen-only did not increase heart attack or breast ca.

→decrease use of HRT (E+P)



A Spine

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Women's Health Initiative (WHI)

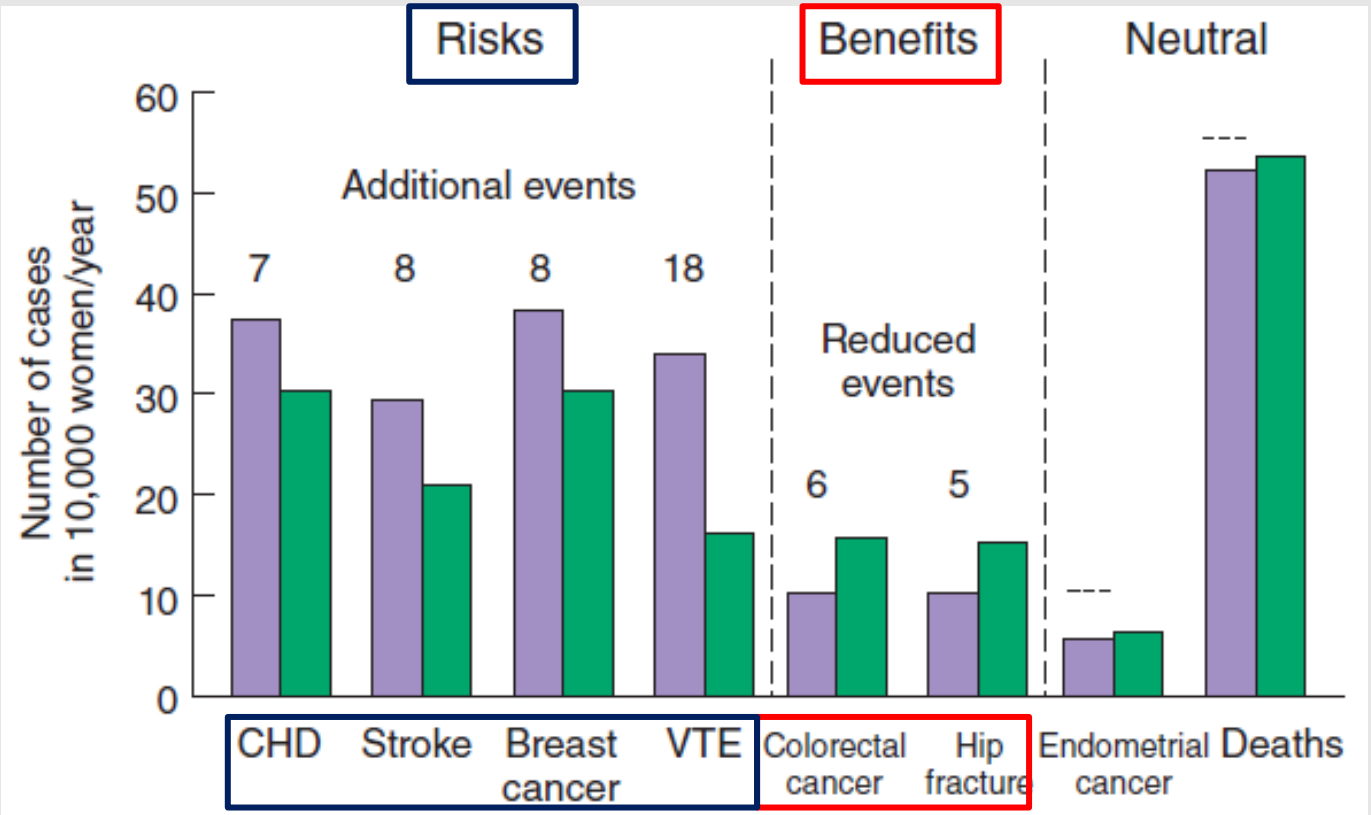


FIGURE 425-8 **Effects of hormone therapy on event rates:** green, placebo; purple, estrogen and progestin. CHD, coronary heart disease; VTE, venous thromboembolic events. *(Adapted from Women's Health Initiative. WHI HRT Update. Available at http://www.nhlbi.nih.gov/health/women/upd2002.htm.)*

---Harrison's Internal Medicine 20th edition, p. 2953

Selective Estrogen Receptor Modulators (SERMs)

- Have effects similar to those estrogen on bone, but they act as antagonists in the breast
- May reduce risk of breast cancer (Tamoxifen)
- Raloxifene is approved for prevention & treatment of osteoporosis; produces modest effects on bone density

  → as well as prevention of breast cancer
- Raloxifene reduce the risk of vertebral fracture in osteoporotic patients; increase risk of thromboembolism and hot flashes

- Raloxifene (60 mg/day) increases 1.4-2.8% bone density & reduces vertebral fracture by 30-50%.

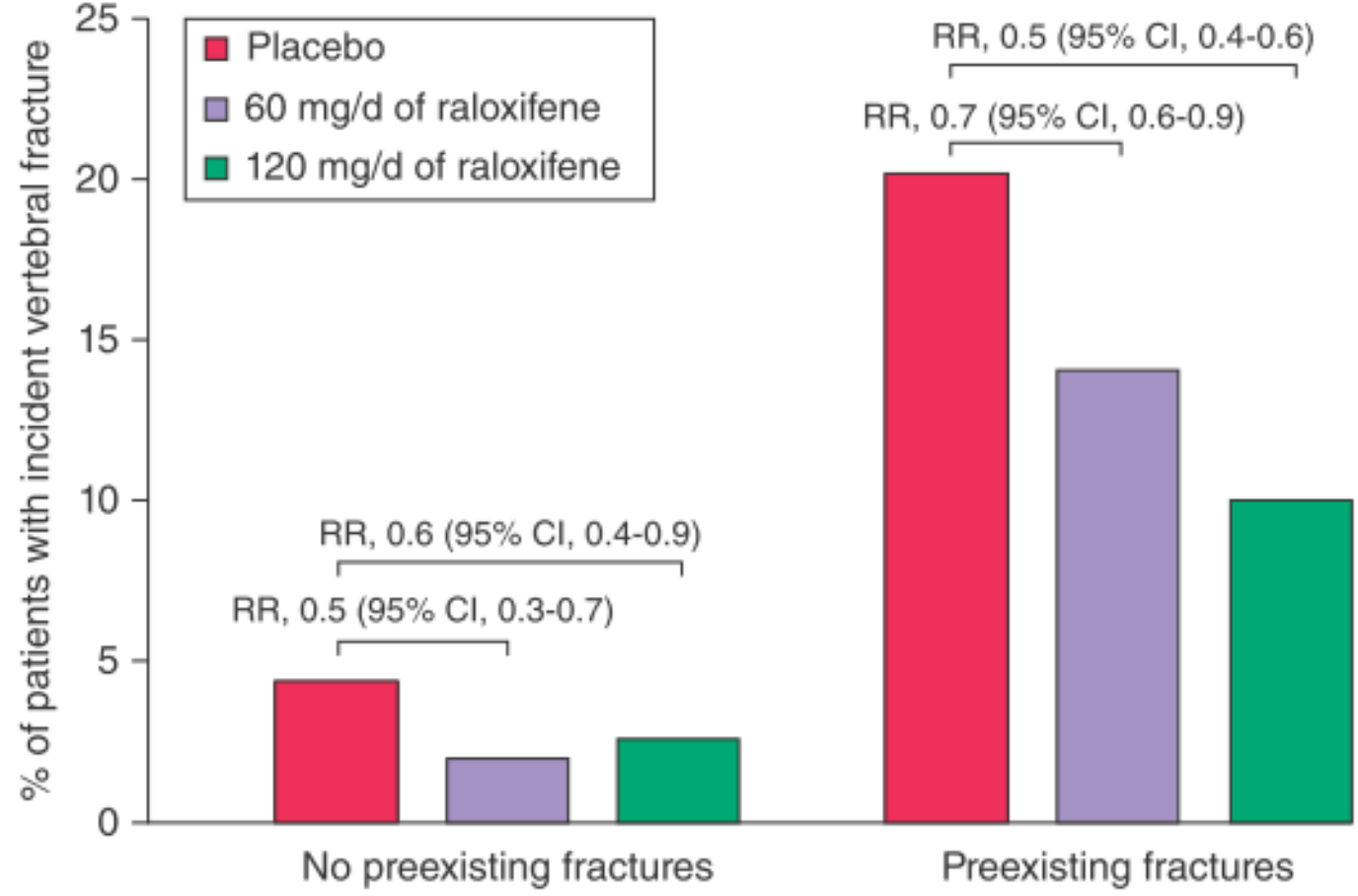


FIGURE 404-10 Effects of two doses of raloxifene on incident vertebral fractures in the MORE trial. *(After B Ettinger et al: JAMA:282:637, 1999.)*

---Harrison's Internal Medicine 20th edition, p. 2955

Bisphosphonates

- 2nd generation: alendronate, risedronate,
  (N-containing) ibandronate, zolendronate
- Decrease bone resorption, increase bone mass in spine and hip
- Alendronate 5mg/day for prevention of osteoporosis
- Poorly GI absorption (empty stomach use) and esophageal irritation in orally; Atrial fibrillation
- Severe Adverse Effects: Osteonecrosis of jaw and atypical femoral fractures

Serious Adverse Effect of Bisphosphonates

Osteonecrosis of Jaw (ONJ)
通常在dental procedure
(拔牙及implant)後bone exposure

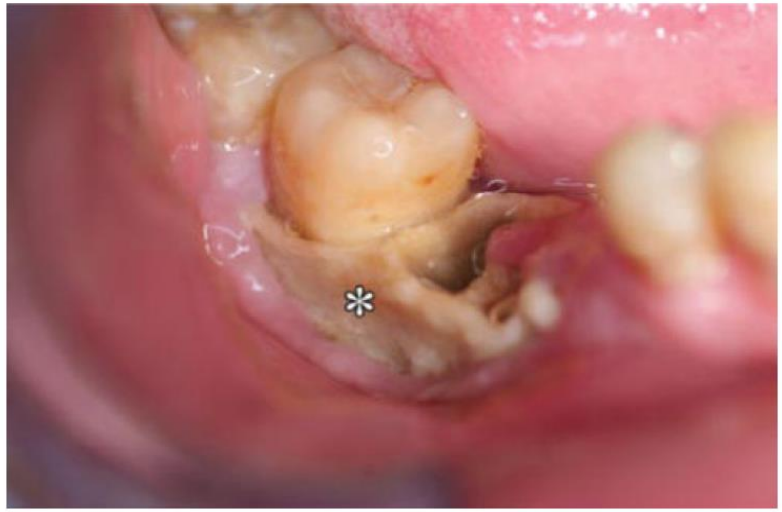
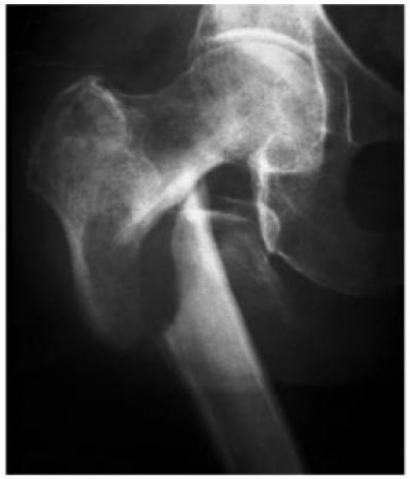
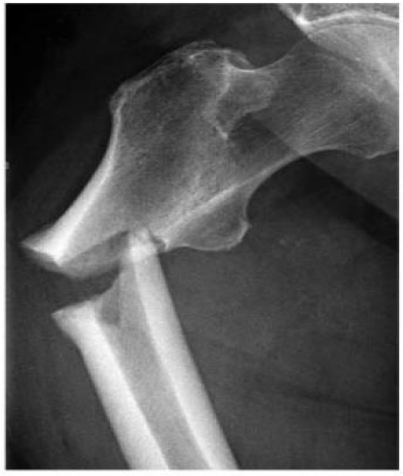


FIG. 4. Photograph showing an area of bone exposure (*asterisk*) in a patient with bisphosphonate-associated ONJ. [Reproduced from Y. Morag *et al.*, Bisphosphonate-related osteonecrosis of the jaw: a pictorial review. RadioGraphics 29:1971–1984, 2009 (47), with permission. © Radiological Society of North America.]

Atypical Femoral Fracture



TYPICAL Subtrochanteric Fracture
- Spiral pattern
- Substantial comminution
- Thin cortices



ATYPICAL Subtrochanteric Fracture
- Transverse or short oblique orientation
- No comminution
- Thick cortices – focal or generalized

FIG. 5. Radiographic appearance and characteristics of a typical *vs.* atypical subtrochanteric fracture (courtesy of Dr. Melvin Rosenwasser, Columbia University, New York, NY).

- **ONJ** is more prevalent in cancer victims receiving high-dose bisphosphonate for skeletal metastasis
- **Oral antibiotic rinses and oral systemic antibiotics** may be useful to prevent ONJ

Effects of various bisphosphonates on clinical fractures

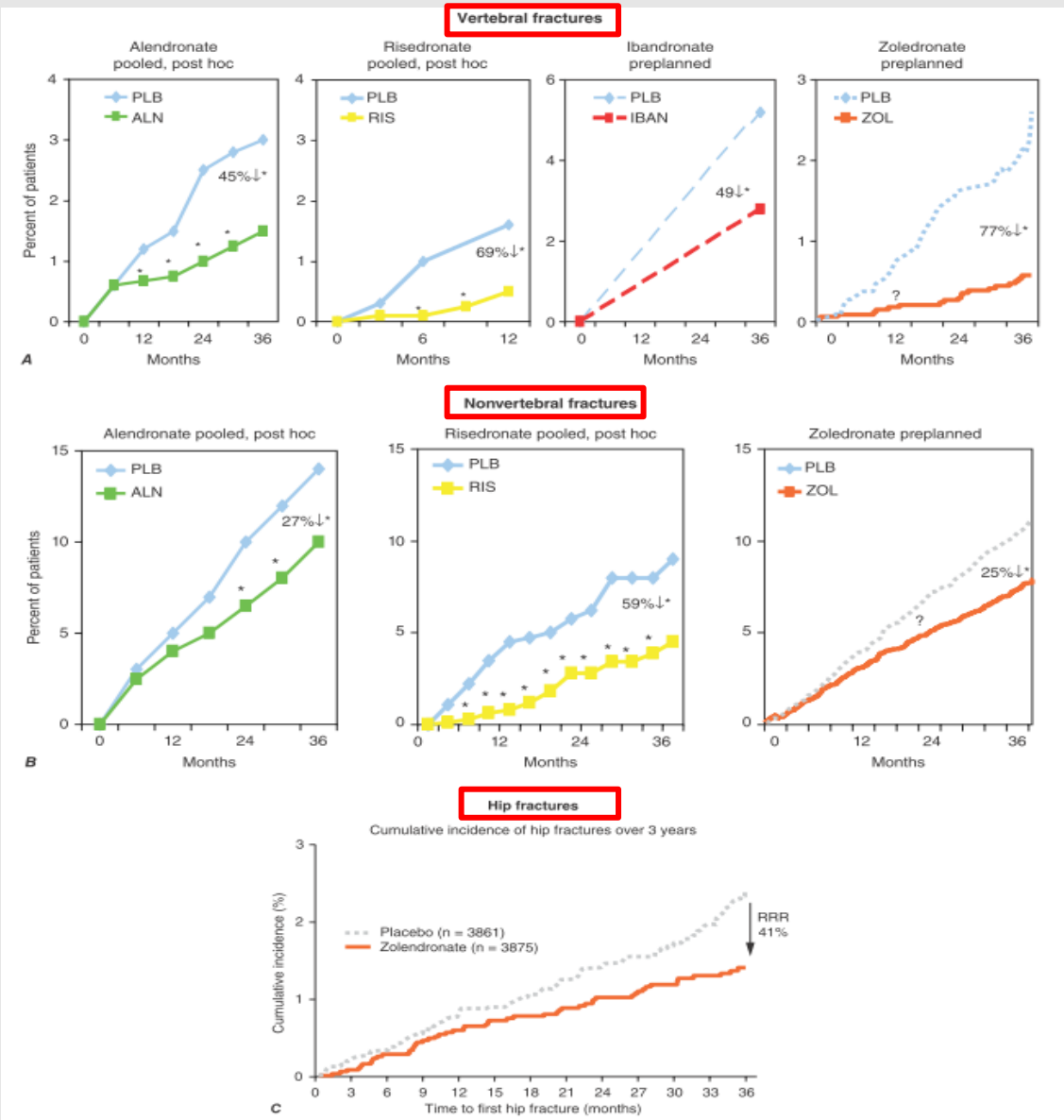


FIGURE 404-9 **Effects of various bisphosphonates on clinical vertebral fractures A.** nonvertebral fractures **B.**, and hip fractures **C.** Plb, placebo; RRR, relative risk reduction. (*After DM Black et al: J Clin Endocrinol Metab 85:4118, 2000; C Roux et al: Curr Med Res Opin 4:433, 2004; CH Chesnut et al: J Bone Miner Res 19: 1241, 2004; DM Black et al: N Engl J Med 356:1809, 2007; JT Harrington et al: Calcif Tissue Int 74:129, 2003.*)

Contraindicated
when eGFR<30-35 ml/min

---Harrison's Internal Medicine 20th edition, p. 2954

Duration of Bisphosphonate therapy

- Re-evaluate BMD & treatment strategy every 3-5 years for long-term bisphosphonate use

Table 5
Duration of therapy

AACE/ACE 2020	Endocrine Society 2020	ESCEO/IOF 2019/2020
Oral bisphosphonates for 5 y for high risk/up to 10 y for very high risk Zoledronate 3 y for high risk/up to 6 y for very high risk Assess fracture risk annually	Reassess fracture risk at 3–5 y	Reassess bisphosphonate use after 3–5 y Reassess after a new fracture

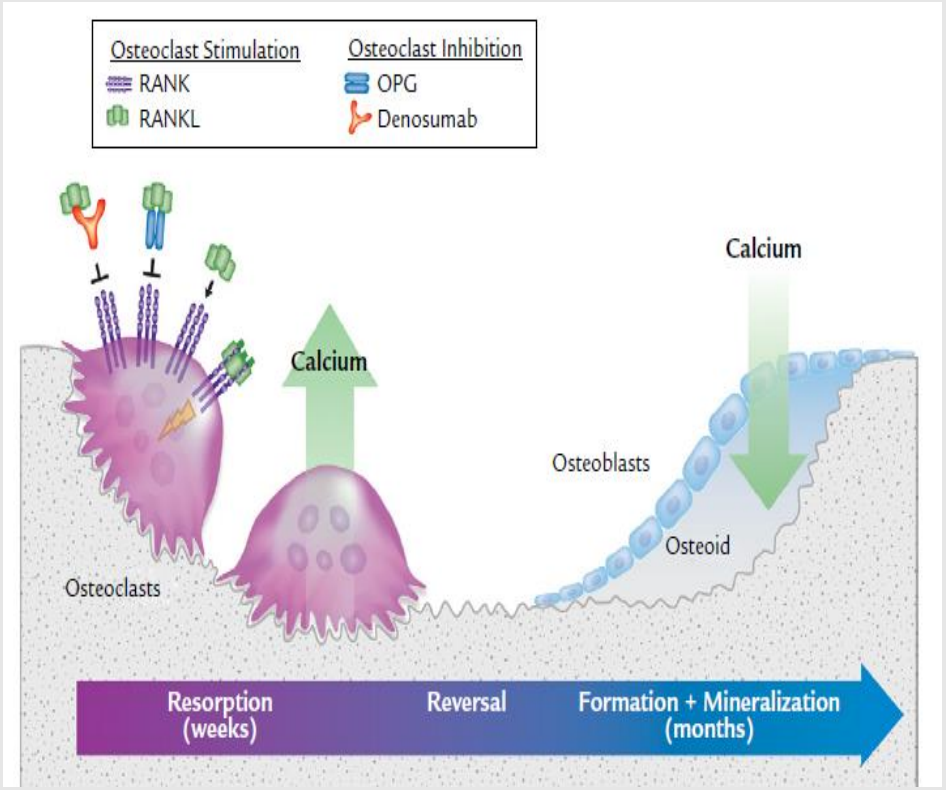
Abbreviations: AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; ESCEO/IOF, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis/International Osteoporosis Foundation.

---Endocrinol Metab Clin N Am 2021;50:167–178

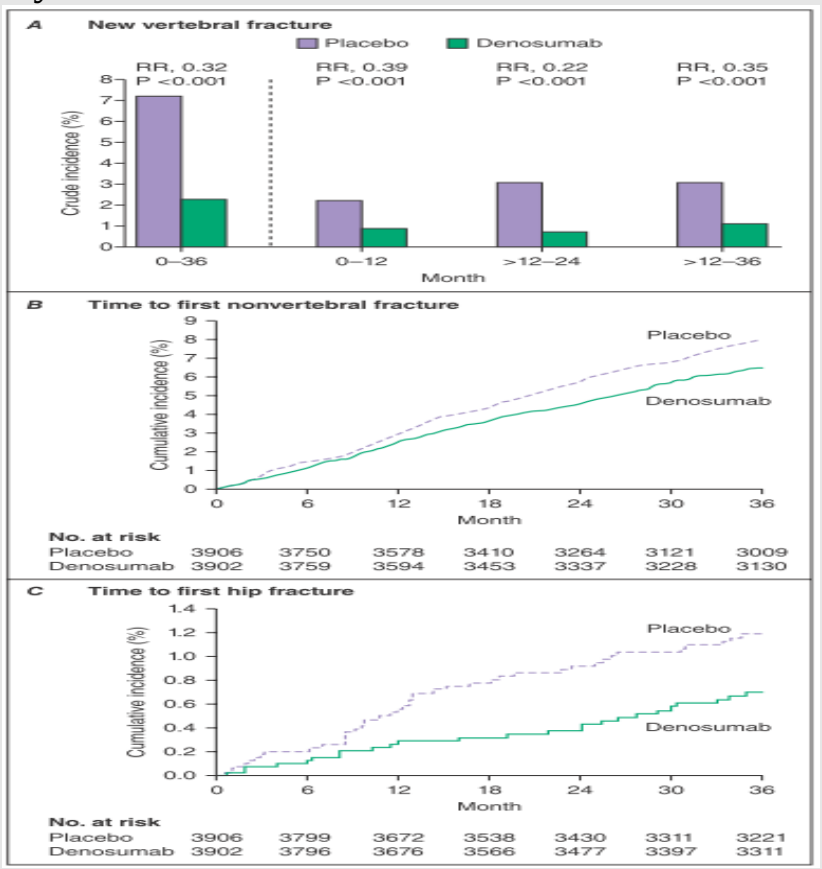
Calcitonin

- **inhibitor of osteoclast and bone resorption**
- **Nasal spray or SC injection→ IV form (榮總)**
- **Weaker effect on bone mass than other available agents**
- **Analgesic effect**
  (useful in p't with recent painful vertebral fractures)
- **EMA and FDA removed the indication of treatment for osteoporosis in 2012**
- **Current use in patients with hypercalcemia**

Denosumab (RANKL inhibitor)



After 3 years of denosumab,



---Harrison's Internal Medicine 21th edition

- Approved by US FDA in 2010 for **postmenopausal woman & man**
- Side effect: **ONJ, atypical femur fractures**, hypocalcemia
- Denosumab may increase the risk of ONJ and atypical femur fractures similarly to bisphosphonates

Follow-up of BMD after 6 years of Denosumab

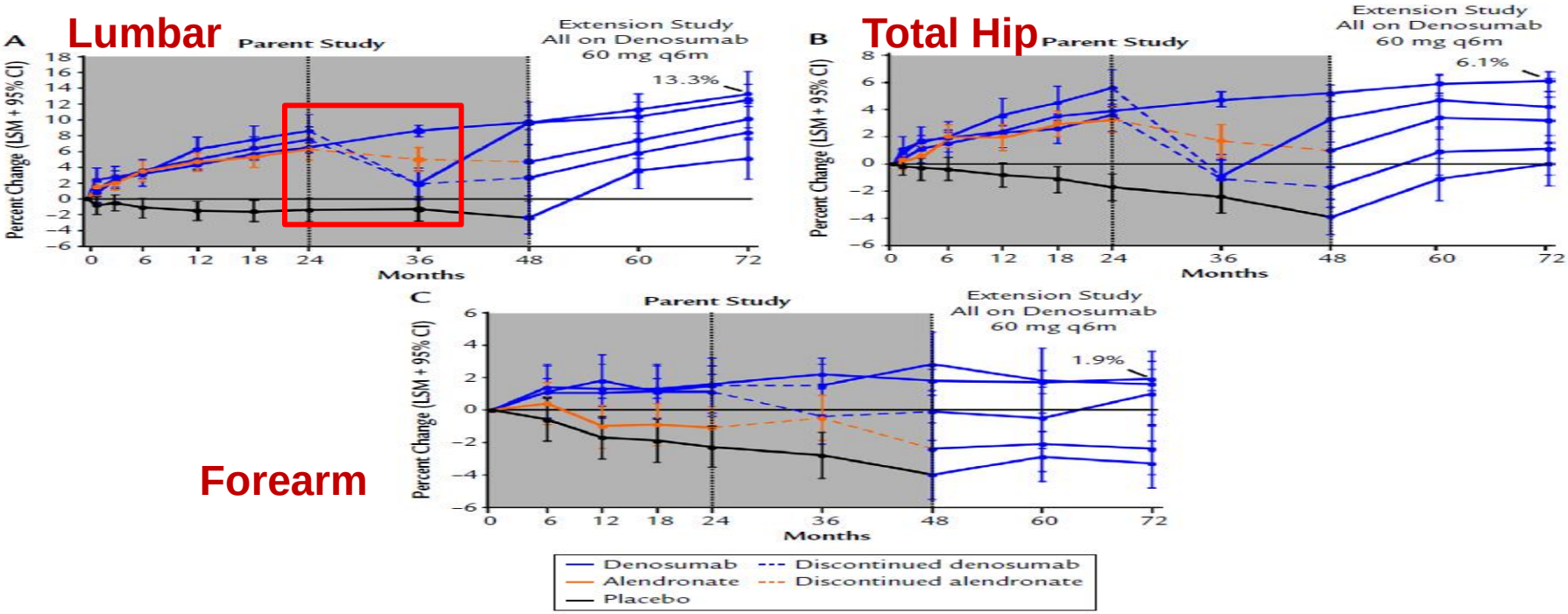


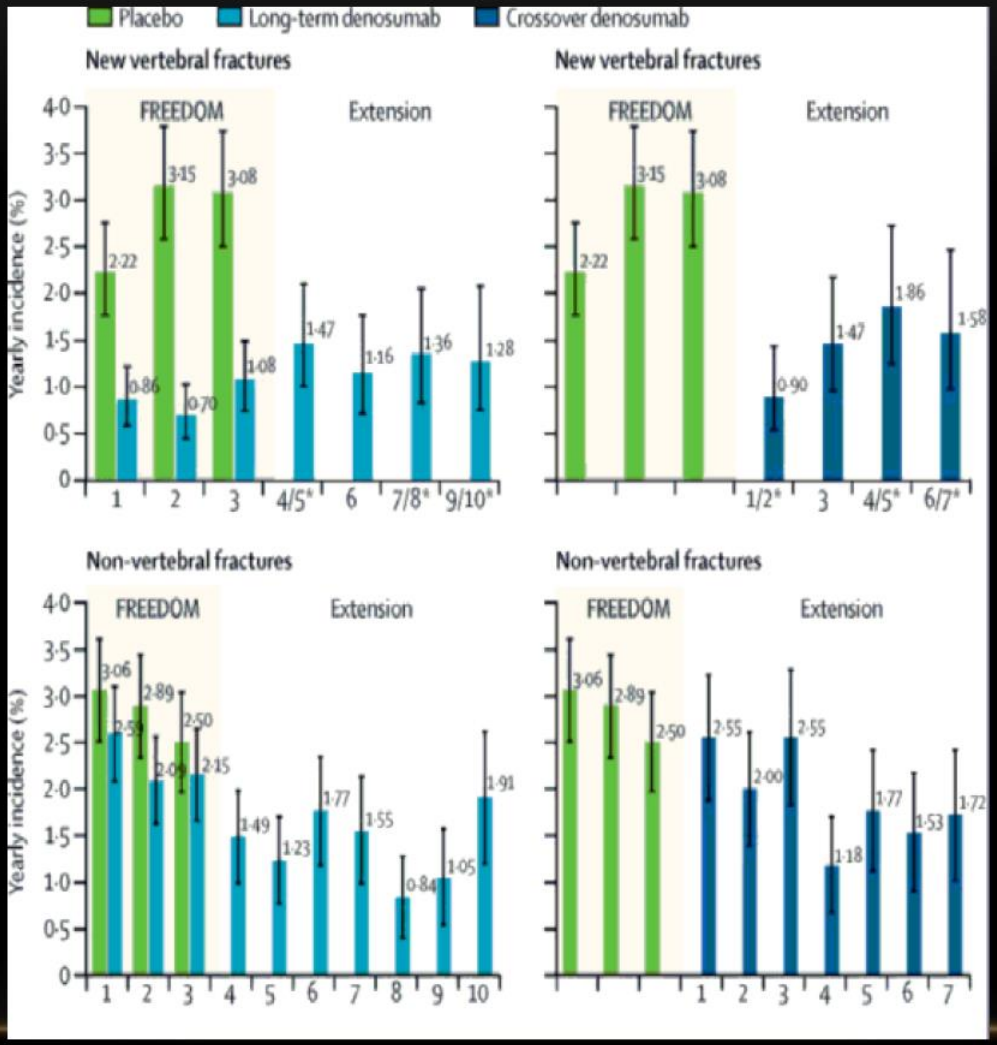
Figure 2. Effect of 6 years of treatment with denosumab on bone mineral density (BMD) at the (A) lumbar spine, (B) total hip, and (C) one-third radius in postmenopausal women with low bone mass. BMD values are shown as percentage change from parent study baseline (least squares mean [LSM] + 95% CI). q6m = every 6 months. Reproduced with permission from Miller PD, Wagman RB, Peacock M, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a phase 2 clinical trial. *J Clin Endocrinol Metab.* 2011;96:394 – 402. *Copyright 2011, The Endocrine Society.*

- Effects of denosumab on bone remodeling **reverse** after 6 months if the drug is not taken on schedule.
- IOF guidelines: Use of bisphosphonate after denosumab therapy to prevent an increase in vertebral fracture rate
- A single infusion of zoledronic acid seems to maintain BMD for 1–2 years but may need to be repeated. Oral bisphosphonates can also be prescribed.

---Harrison's Internal Medicine 21st ed.

---Endocrinol Metab Clin N Am 2021;50:167–178

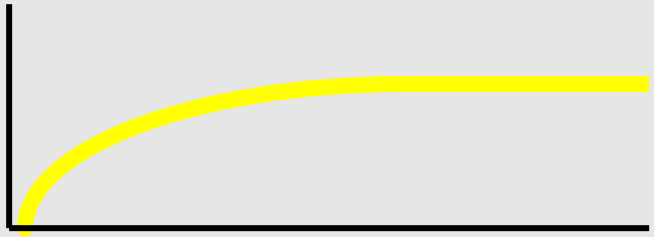
EFFECT OF 10 YEARS OF DENOSUMAB ON FRACTURES



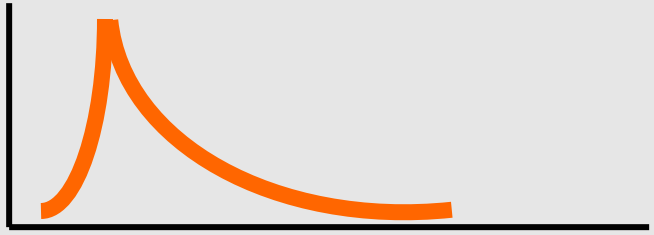
Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol 2017; 5: 513–523.

Parathyroid hormone (PTH)
Mode of Delivery Determines Bone Activity

Continuous exposure results in increased osteoclastic bone resorption



Intermittent exposure results in increased osteoblast number and bone formation.



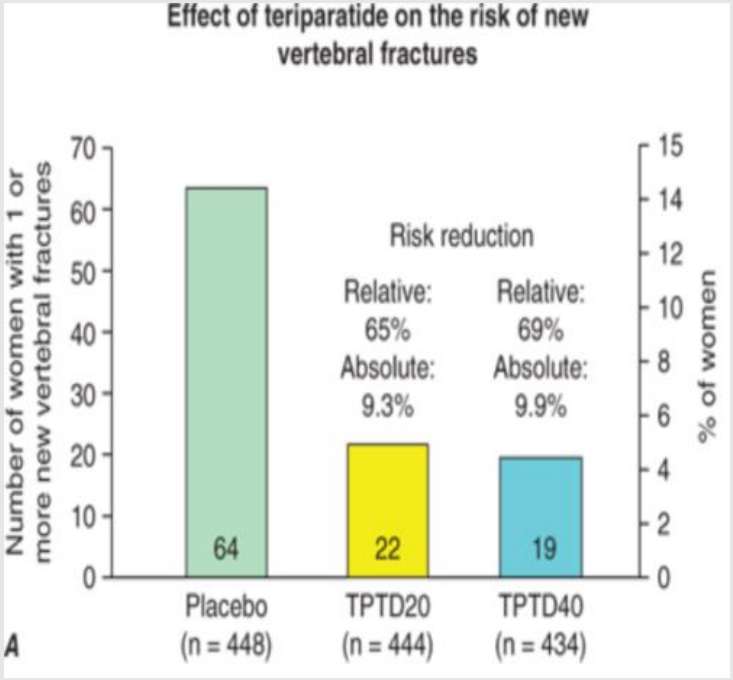
Dobnig & Turner. Endocrinology 1997;138:4607-4612

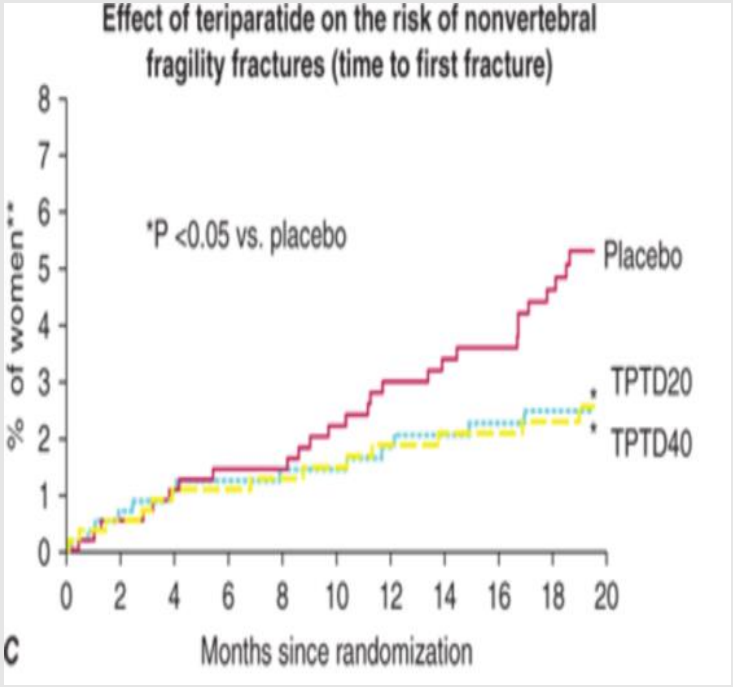
Parathyroid hormone (PTH)

- Low-dose synthetic PTH(1-34) (teriparatide) QD

--- increase in trabecular bone mass with little loss or even a gain of cortical bone in femur and reduced the incidence of fractures

--- careful for hypercalcemia and hypercalciuria





---Harrison's Internal Medicine 20th edition, p. 2957

Romosozumab

(Monoclonal anti-sclerostin antibody)

---increase in bone formation and decline in bone resorption

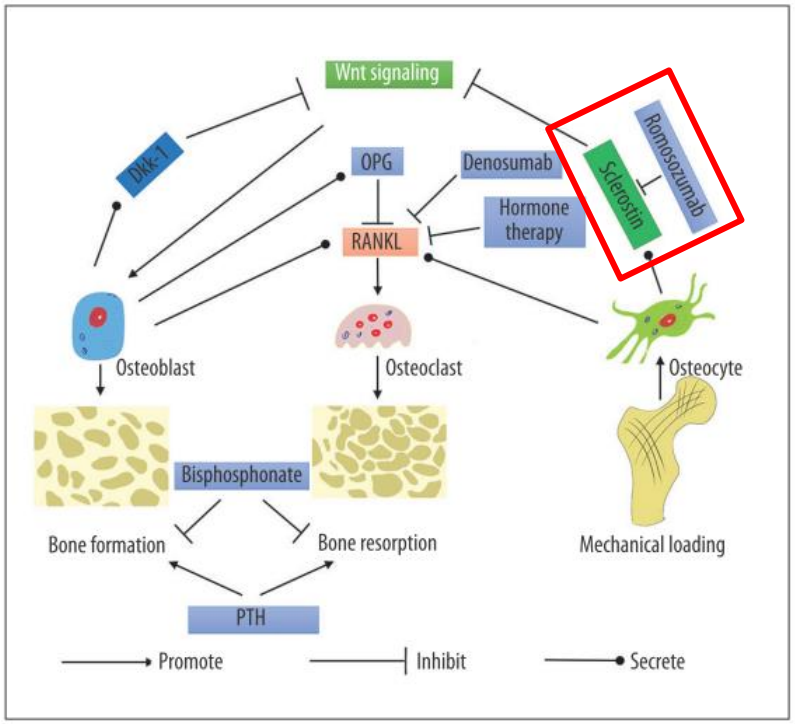


Figure 1. The signaling pathways involved in bone remodeling. Dkk-1 – Dickkopf-related protein 1; OPG – osteoprotegerin; PTH – parathyroid hormone; RANK – receptor activator of NF-κB; RANKL – receptor activator of NF-κB ligand.

--- Med Sci Monit 2018;24:8758-8766.

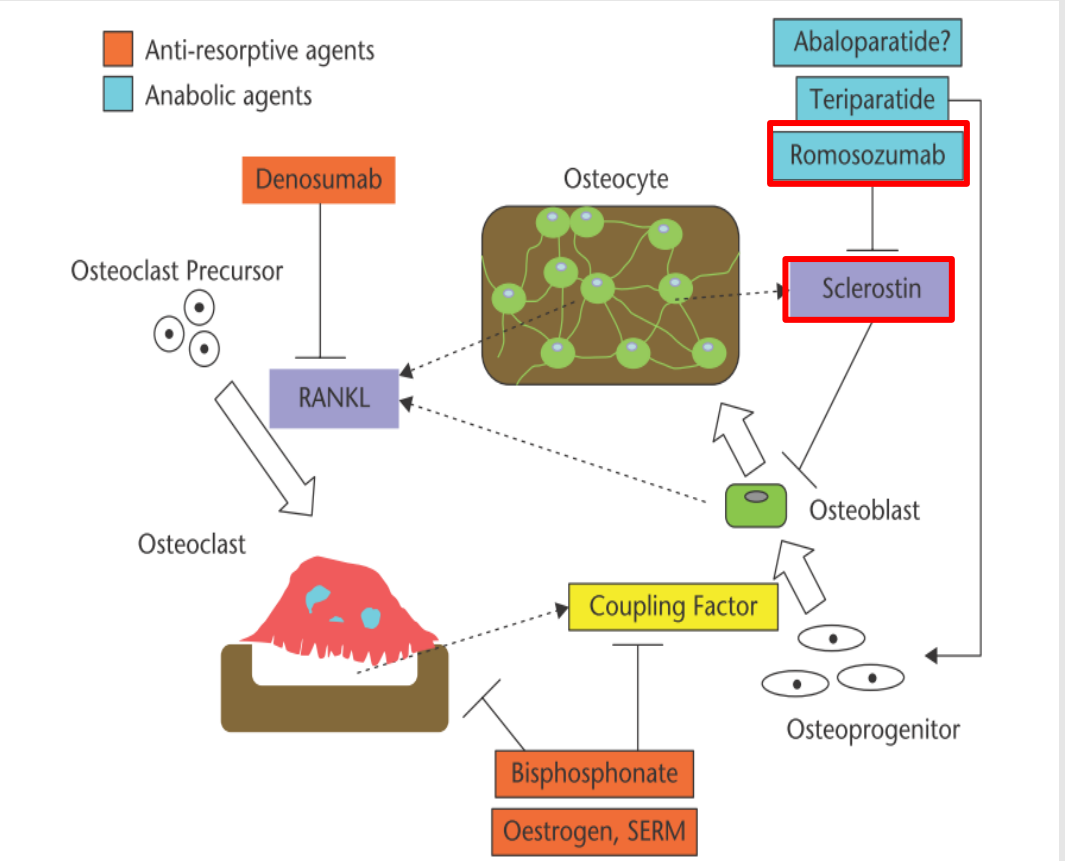


Fig. 1 Regulation of bone metabolism and mechanisms of action of anti-osteoporotic drugs.

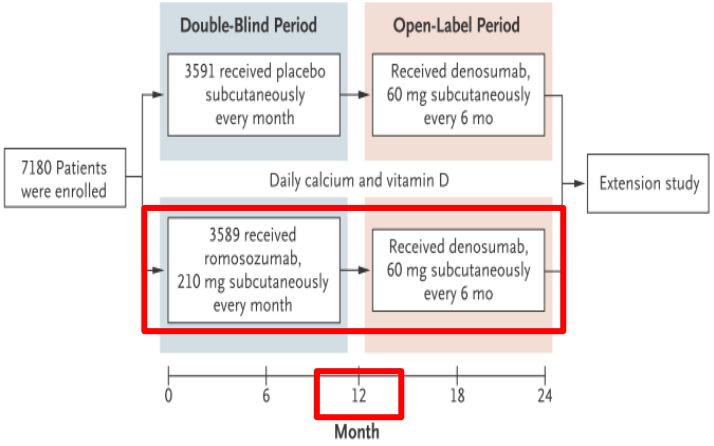
--- EFORT Open Rev 2019;4:158-164.

The NEW ENGLAND JOURNAL of MEDICINE

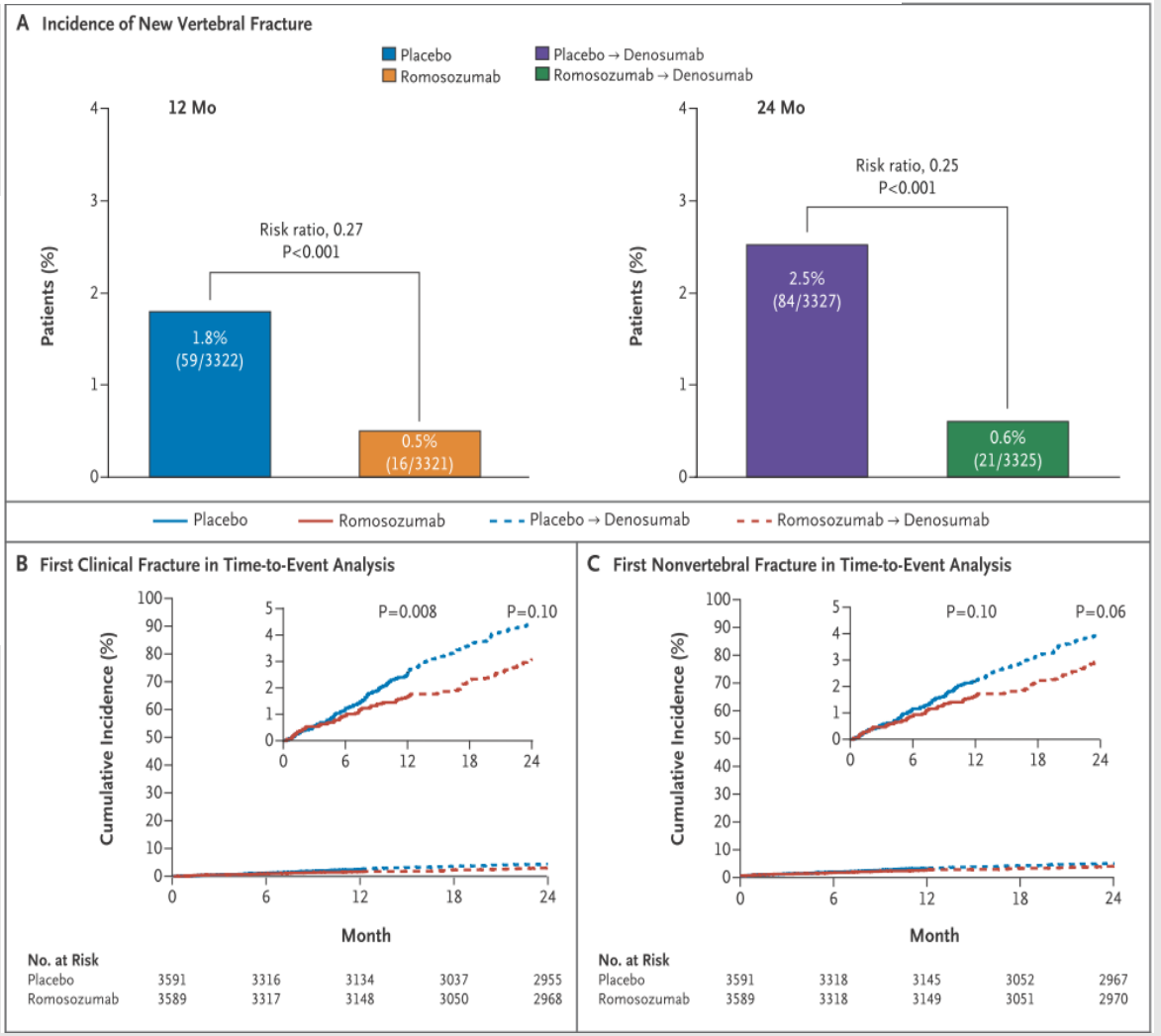
ORIGINAL ARTICLE

Romosozumab Treatment in Postmenopausal Women with Osteoporosis

FRAME study



- **BMD** ↑13% in the spine & almost ↑ 7% in the hip in 1 year with romosozumab



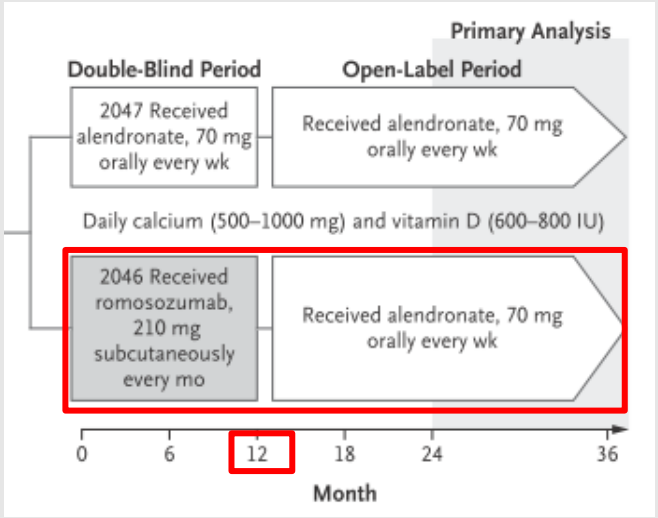
---New Engl J Med 2016;375:1532-43.

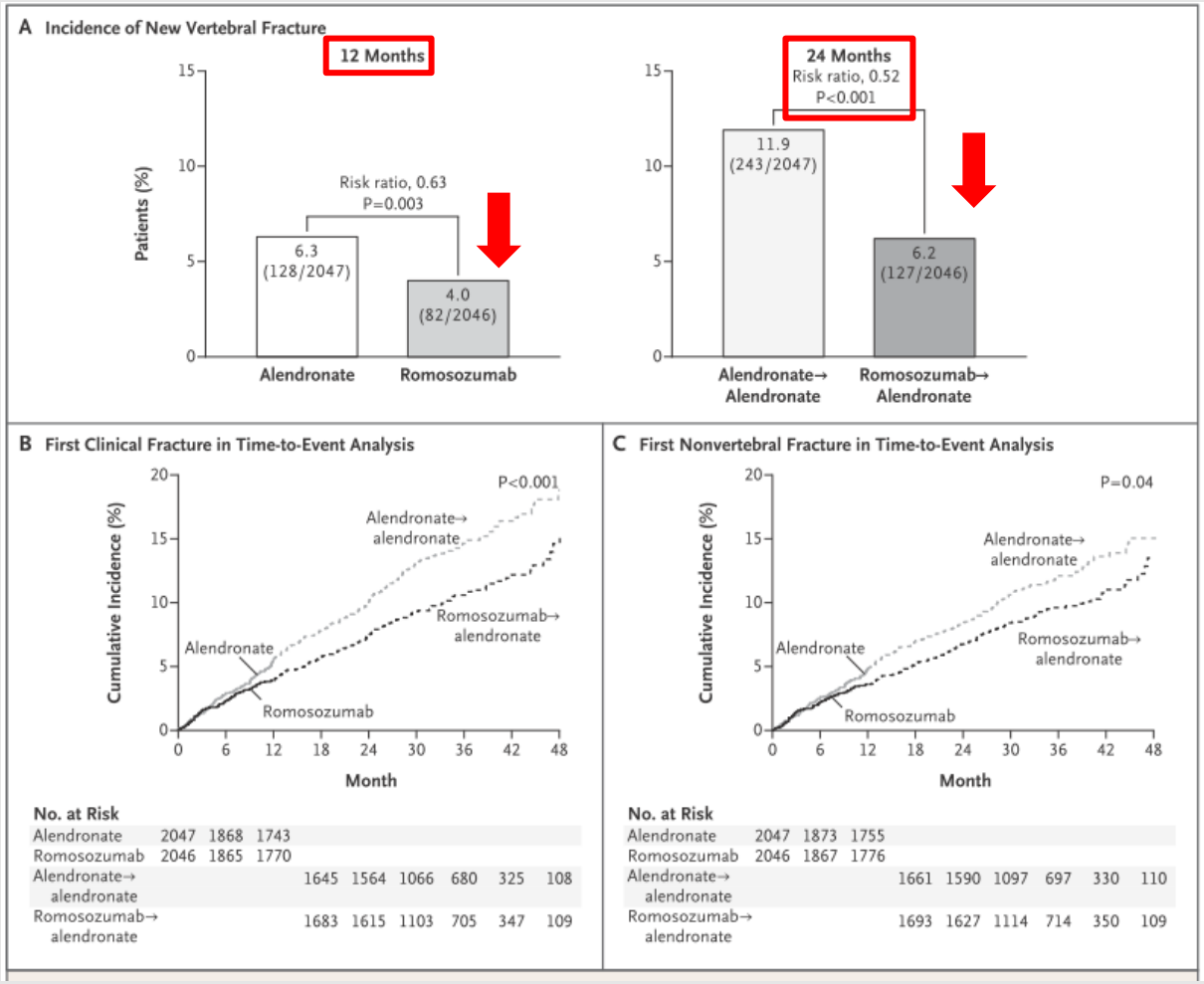
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 12, 2017 VOL. 377 NO. 15

Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

ARCH study





---New Engl J Med 2017;377:1417-27.

Cardiovascular Safety of Romosozumab vs PTH Analogues for Osteoporosis Treatment: A Propensity-Score-Matched Cohort Study

Joshua Stokar[1] and **Auryan Szalat**[1]

[1]Department of Internal Medicine, Faculty of Medicine, Osteoporosis Center, Hadassah Medical Center, The Hebrew University of Jerusalem, 9124001 Jerusalem, Israel

In a diverse real-world setting, prescription of romosozumab for osteoporosis is associated with less adverse CV events when compared to PTH analog therapy

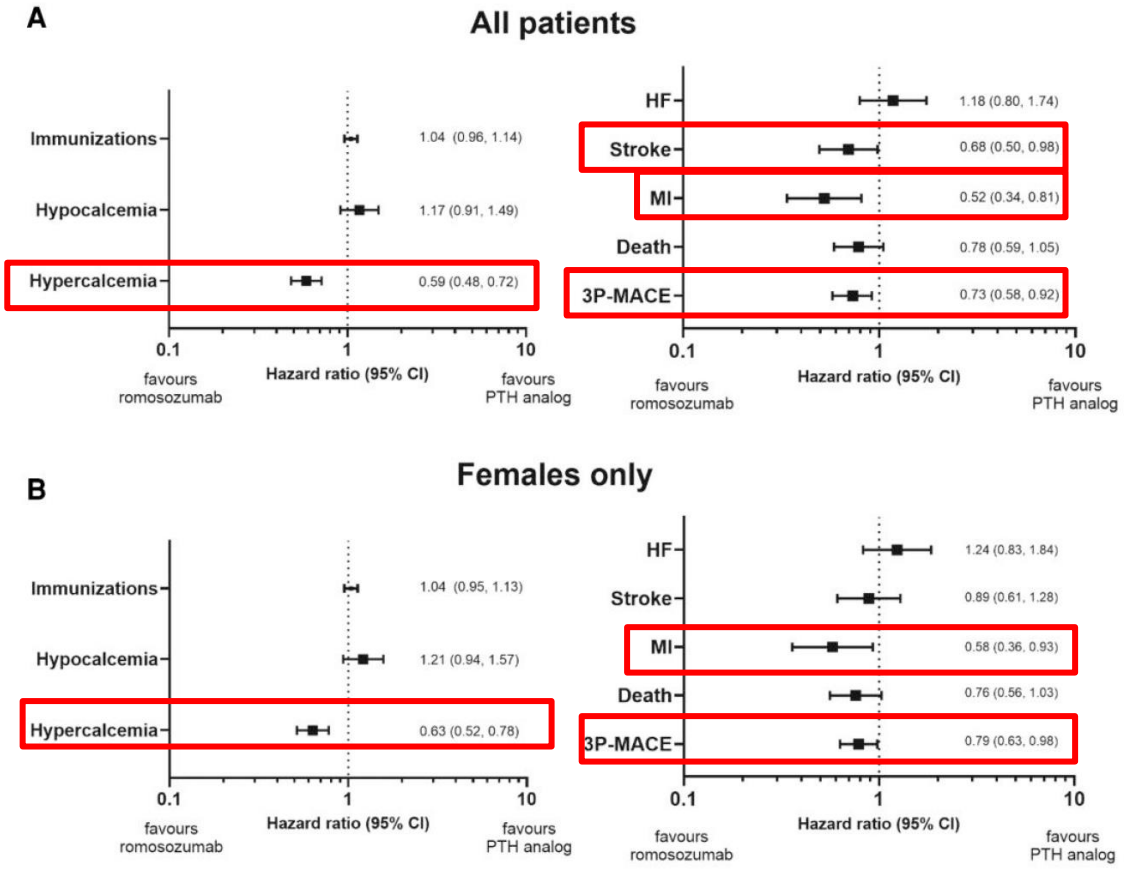
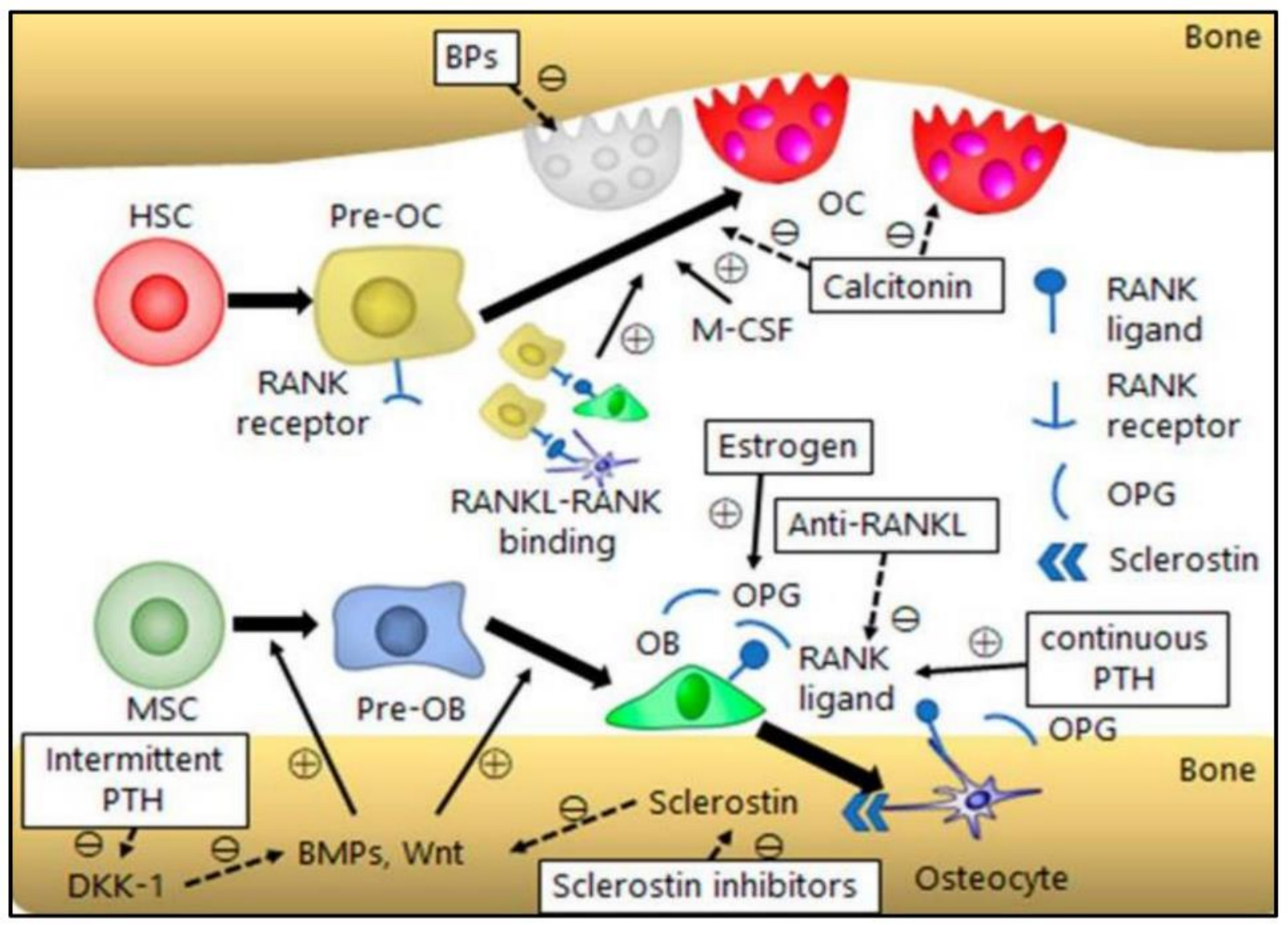


Figure 1. Outcomes over 1-year follow-up for romosozumab vs PTH analogue using Kaplan-Meir analysis with log-rank test. A, All patients; N = 5610 per group. B, Women only; N = 5292 per group. 3P-MACE, 3-point major adverse cardiovascular events; HF, heart failure; MI, myocardial infarction; PTH, parathyroid hormone.

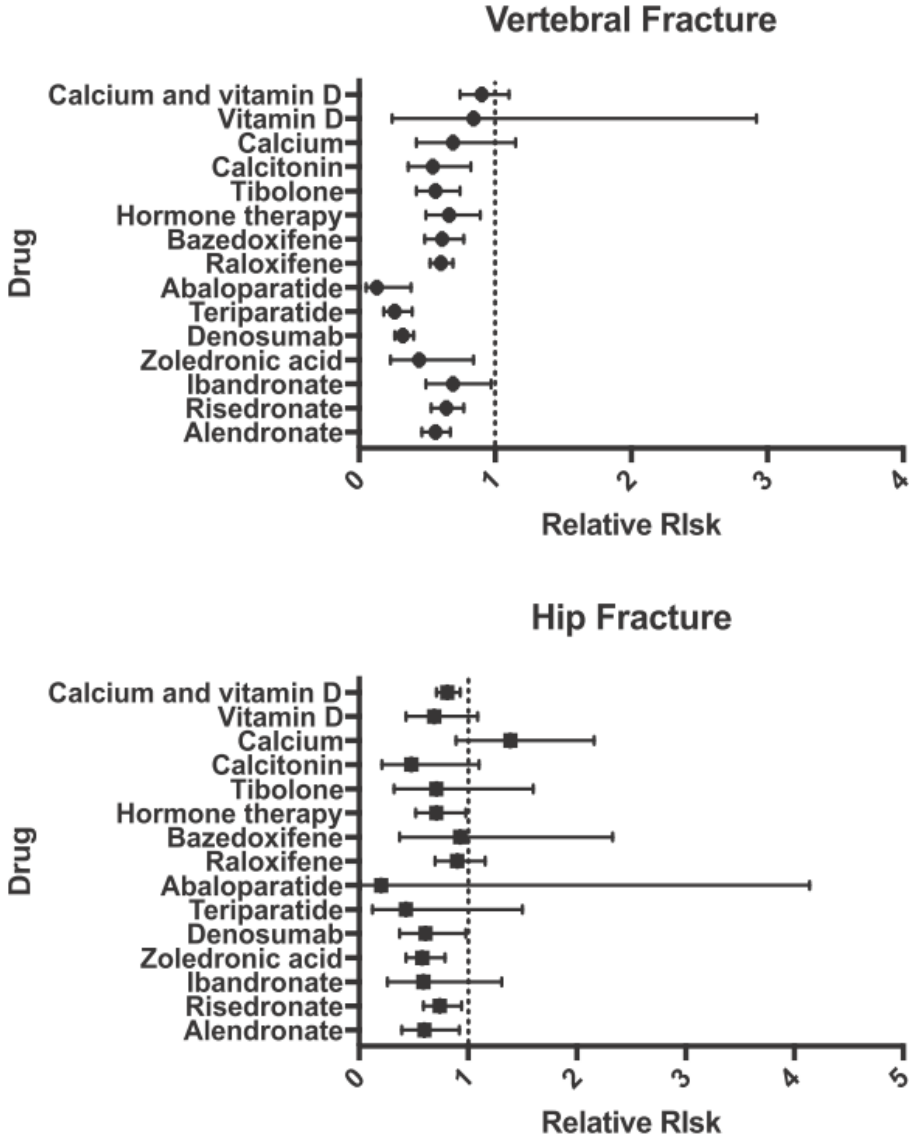
---J Clin Endocrinol Metab. 2024 Mar 14:dgae173.

Mechanism of Osteoporosis therapies



---Int J Mol Sci 2021;22:8182.

Summary of Treatments for Postmenopausal Osteoporosis



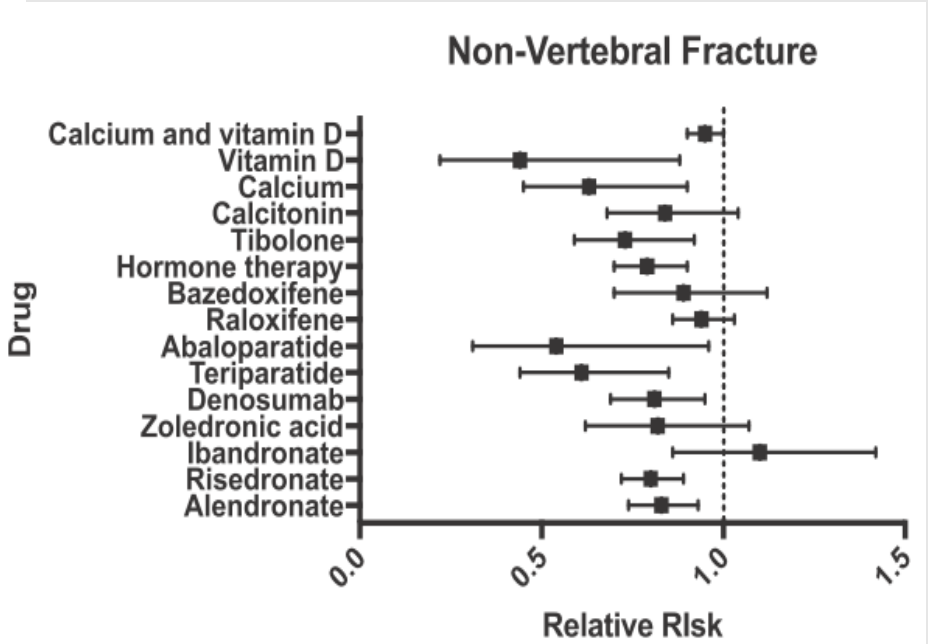
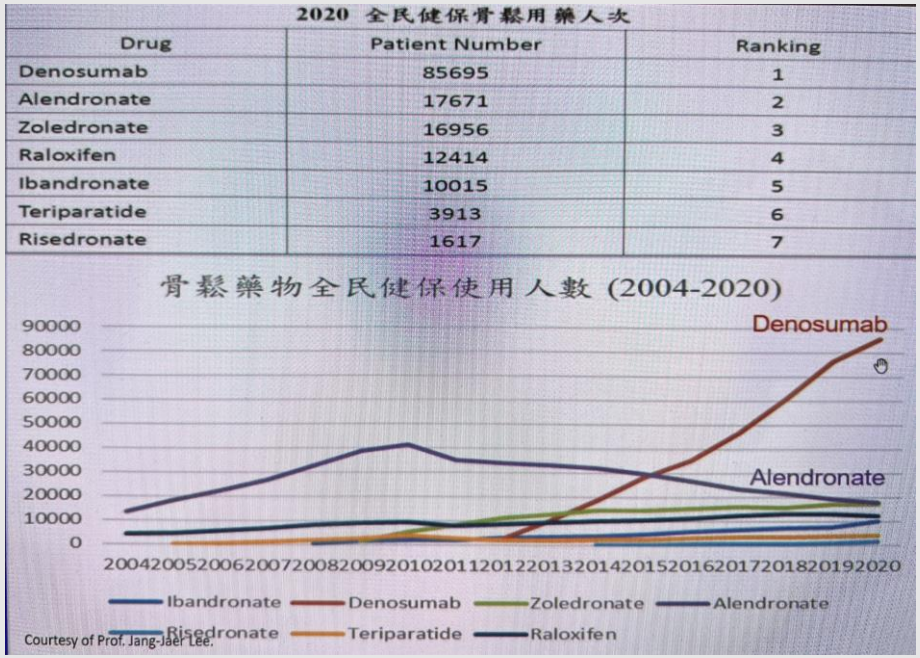


Figure 1. Relative risks of vertebral, hip, and nonvertebral fractures (and 95% CIs) in response to the treatments for postmenopausal osteoporosis, calculated directly and compared with placebo. Note that the evidence is based on a direct meta-analysis of 107 trials of drugs in postmenopausal women with primary osteoporosis in which the trial duration lasted for 3 to 120 mo. In this analysis, each agent was compared with placebo and so direct comparisons should not be made between treatments based on this figure. (12). [Adapted with permission from data presented in Moreno PB, Kapoor E, Asi N, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. J Clin Endocrinol Metab. 2019;104(5):1623–1630].

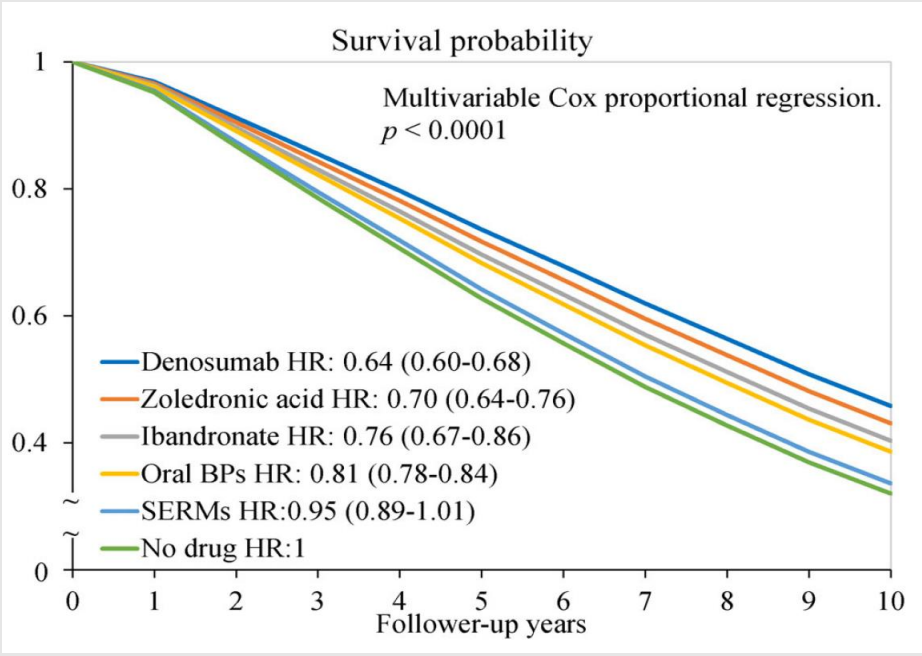
Current Status of anti-osteoporosis drugs in Taiwan

2020 全民健保骨鬆用藥人次

Drug	Patient Number	Ranking
Denosumab	85695	1
Alendronate	17671	2
Zoledronate	16956	3
Raloxifen	12414	4
Ibandronate	10015	5
Teriparatide	3913	6
Risedronate	1617	7



The Impact of Various Anti-Osteoporosis Drugs on All-Cause Mortality After Hip Fractures: A Nationwide Population Study



---J Bone Miner Res. 2022 Aug;37(8):1520-1526.

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline

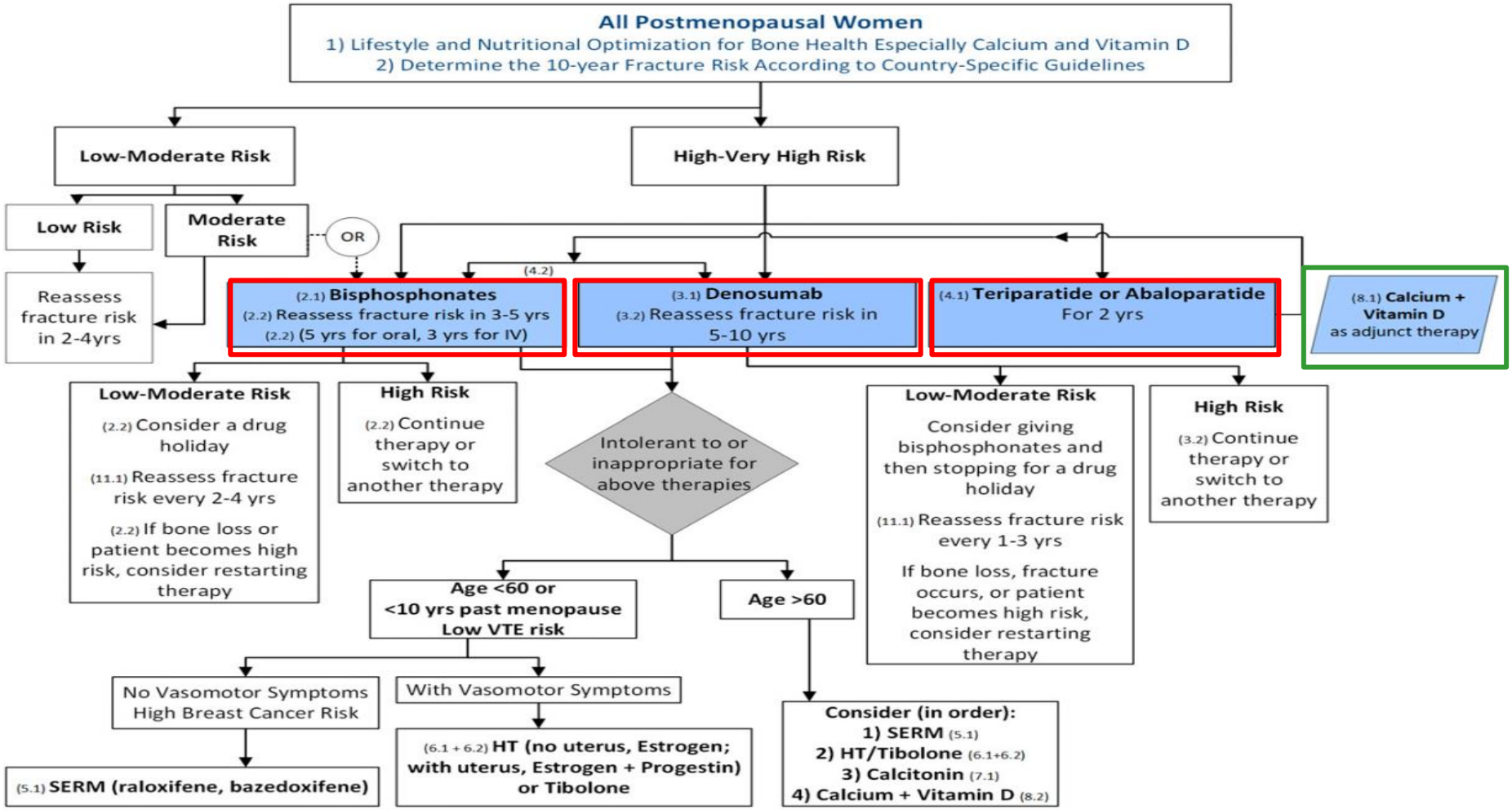
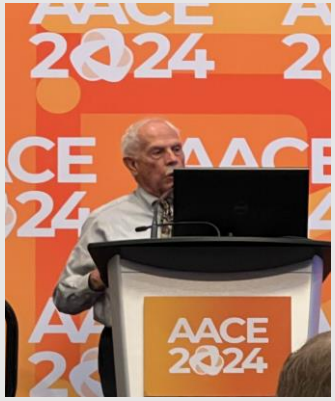


Figure 2. Algorithm for the management of postmenopausal osteoporosis. Note that in this algorithm, we considered that a determination of fracture risk would include measurement of lumbar spine and hip BMD and inserting the total hip or femoral neck BMD value into the FRAX tool. Using that FRAX algorithm, we define the following risk categories: "low risk" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, and 10-year hip fracture risk <3% and 10-year risk of major osteoporotic fractures <20%; "moderate risk" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, or 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%; "high risk" includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of −2.5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and "very high risk" includes multiple spine fractures and a BMD T-score at the hip or spine of −2.5 or below.

J Clin Endocrinol Metab, May 2019, 104(5):1595–1622

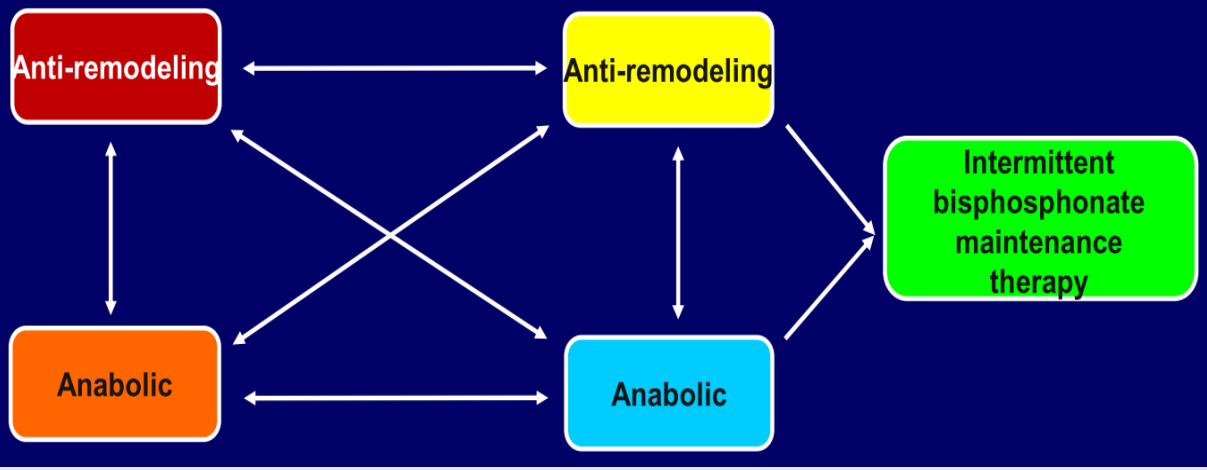
Osteoporosis Treatment: Sequences & Holidays
---Michael McClung---



Transitions and Holidays in Osteoporosis Therapy

Background:

- Osteoporosis requires life-long management
- On-treatment BMD (total hip) correlates with current fracture risk;
  - appropriate "target" is total hip T-score of -2.0 or better
- Optimal management must be individualized but will involve sequential use of different classes of osteoporosis drugs



Bisphosphonate

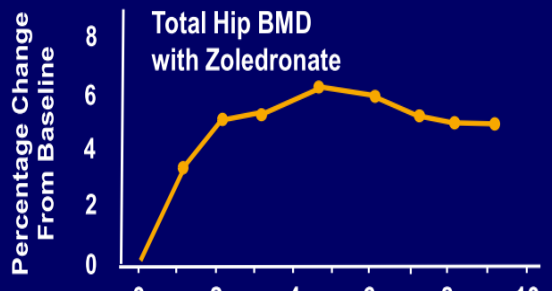
Bisphosphonate Holidays: When and How?

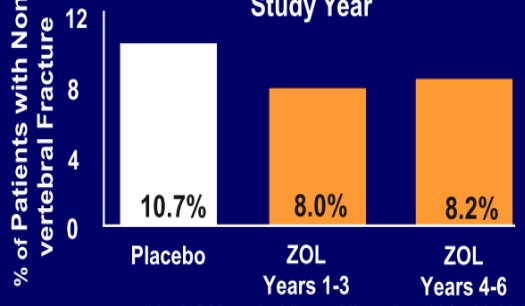
Key Points:

- BMD gain and fracture risk reduction plateau after 3-5 years of bisphosphonate therapy
  - no incremental benefit of therapy beyond 5 years
- Risk of atypical femoral fracture(AFF) increases with long-term bisphosphonate therapy (~1/1000 after 8-10 years)
  - AFF risk decreases upon stopping therapy

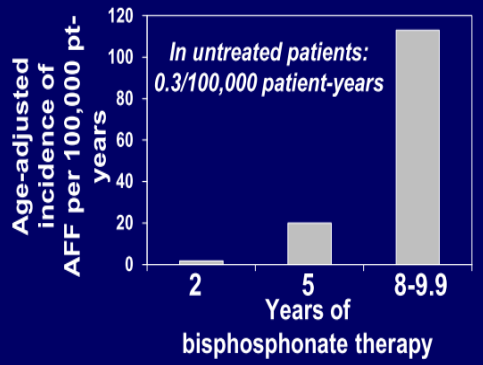
There is no justification for continuing bisphosphonates for more than 5 years at a time

McClung M. Personal opinion





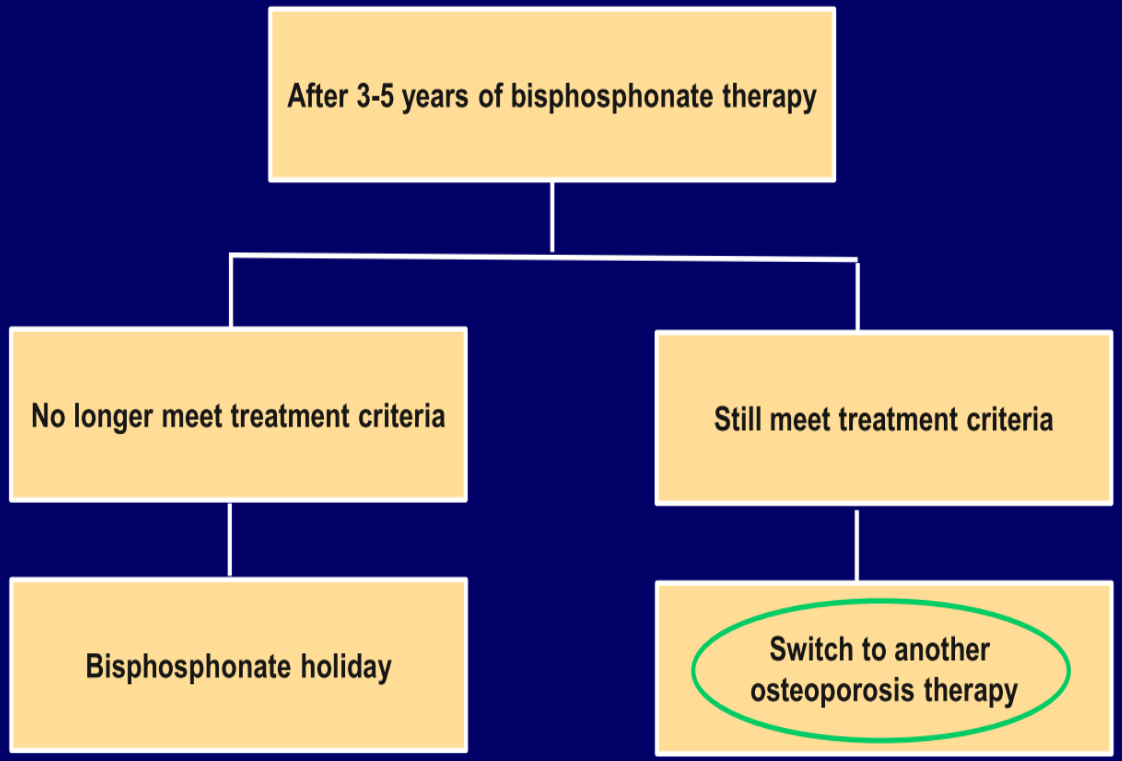
Black DM et al. *J Bone Miner Res* 2015;30:934-44



Dell RM et al. *J Bone Miner Res* 2012;27:2544-50

Operationalizing a Bisphosphonate Drug Holiday

- If a patient no longer meets criteria for treatment after 3-5 years of bisphosphonate therapy, temporary discontinuation of therapy – with appropriate monitoring – is justified
- Patients who still meet treatment criteria should be switched to another drug

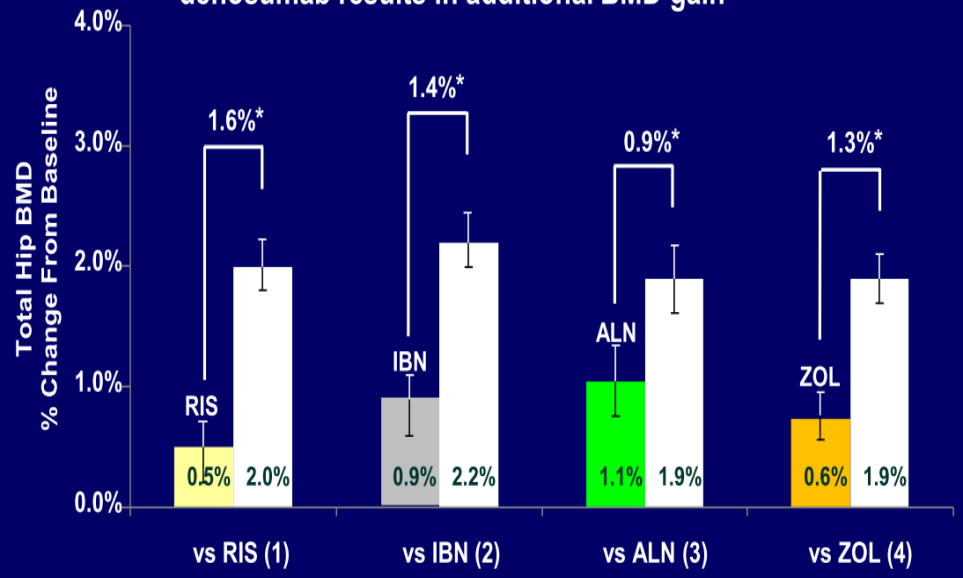


McClung MR. Personal opinion

Switching from Bisphosphonate to Another Therapy

Bisphosphonate to denosumab

Switching from bisphosphonate to denosumab results in additional BMD gain

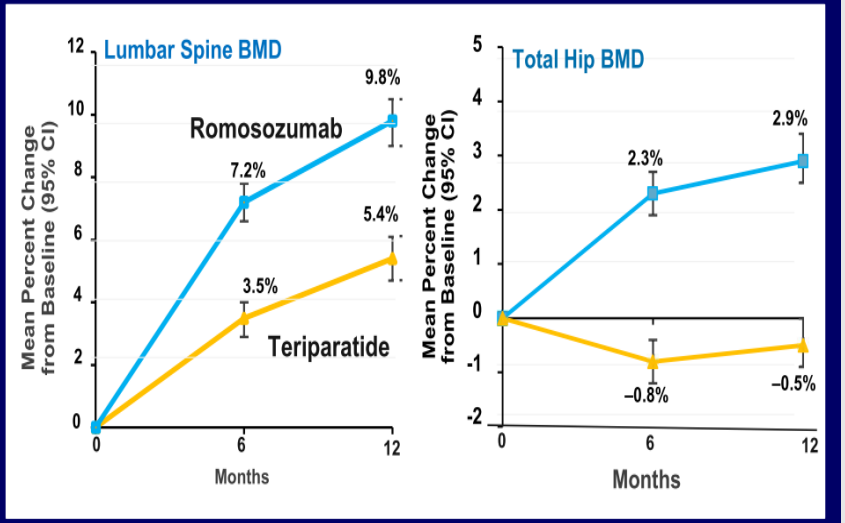


Data are least-squares means and 95% confidence intervals.
*$p < 0.0001$ denosumab vs bisphosphonate

1. Roux C et al. *Bone* 2014;58:48-54
2. Recknor C et al. Obstet Gynec 2013;121:1291-9
3. Kendler DL et al. *J Bone Miner Res* 2010;25:72-81
4. Miller PD et al. *J Clin Endo Metab* 2016;101:3163-70

Bisphosphonate to osteoanabolic therapy

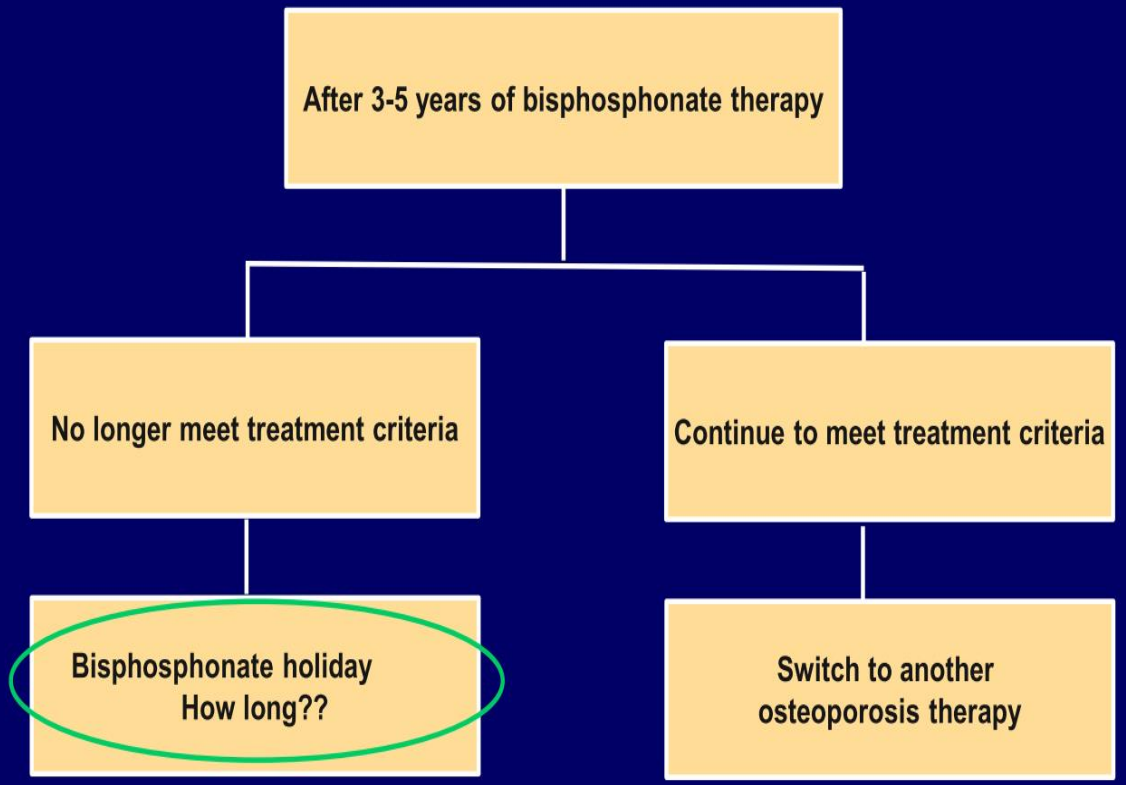
Switching from bisphosphonate to anabolic agents results in additional BMD gain, more with romosozumab than with teriparatide



Langdahl B et al. *Lancet* 2017;390:1585–94

Operationalizing a Bisphosphonate Drug Holiday

- If a patient no longer meets criteria for treatment after 3-5 years of bisphosphonate therapy, temporary discontinuation of therapy – with appropriate monitoring – is justified
- Patients who continue to meet treatment criteria should be switched to another drug



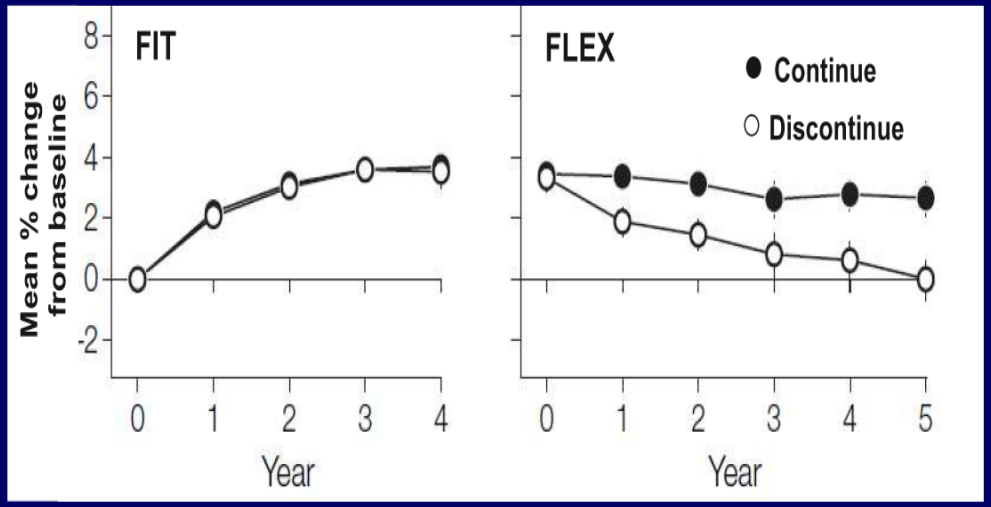
McClung MR. Personal opinion

Bisphosphonate Holiday: How Long?

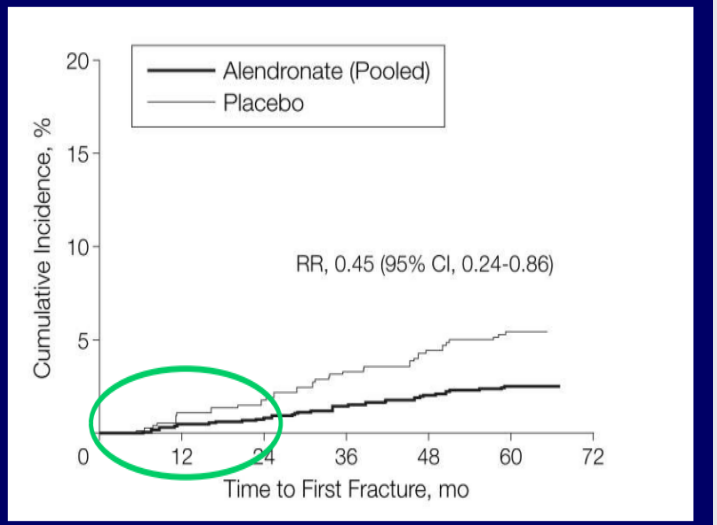
Key Points:

- Upon stopping bisphosphonate therapy, BMD is lost slowly and vertebral fracture protection is lost after 2-3 years
- Patients should be evaluated after 2 years and then intermittently McClung MR. Personal opinion

Total Hip BMD



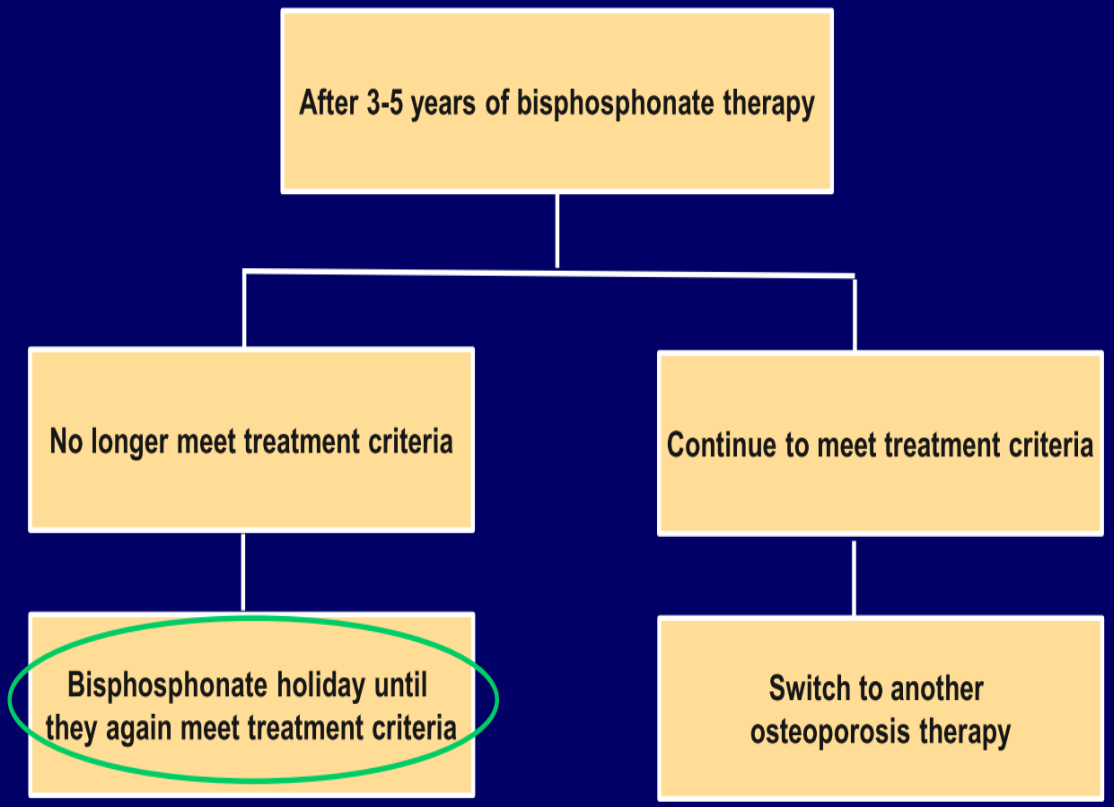
Clinical Vertebral Fractures



Black DM et al. *JAMA* 2006;296:2927-38

Operationalizing a Bisphosphonate Drug Holiday

- If a patient no longer meets criteria for treatment after 3-5 years of bisphosphonate therapy, temporary discontinuation of therapy – with appropriate monitoring – is justified
- Patients who continue to meet treatment criteria should be switched to another drug



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Bisphosphonate Holiday

Take Home Points:

- There is no incremental benefit of bisphosphonate therapy beyond 5 years
- There is no justification for use of a bisphosphonate for more than 5 years at a time
- For patients with osteoporosis at moderate fracture risk, bisphosphonate therapy for 3-5 years may result in their no longer meeting criteria for treatment
  - temporary interruption of therapy with monitoring every 2 years may be considered
  - re-start a therapy when they again meet criteria for treatment
- For patients remaining at high risk after 3-5 years of bisphosphonates, continuing bisphosphonate therapy provides no incremental benefit, and a switch to either denosumab or to an osteoanabolic agent would be warranted
- The concept of “drug holiday” does not pertain to non-bisphosphonate osteoporosis therapies

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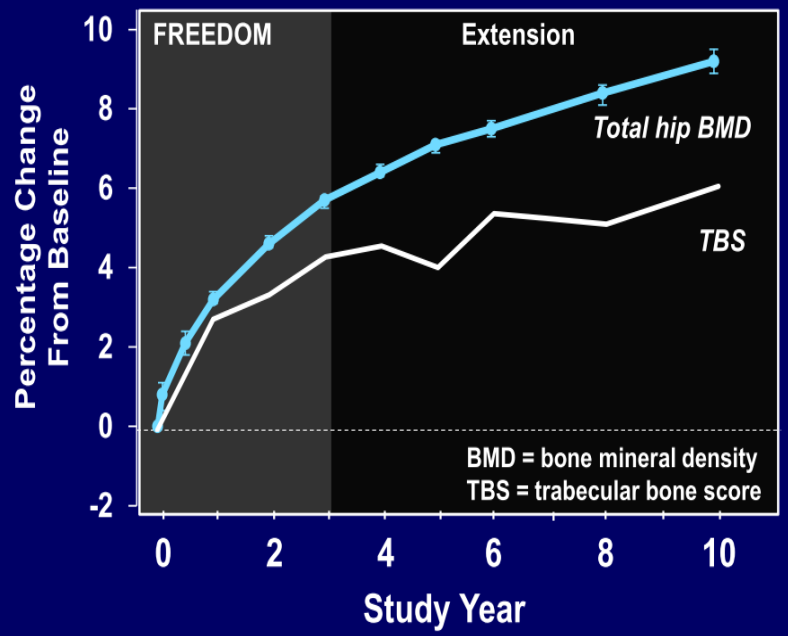
Denosumab

Long-term Denosumab Therapy

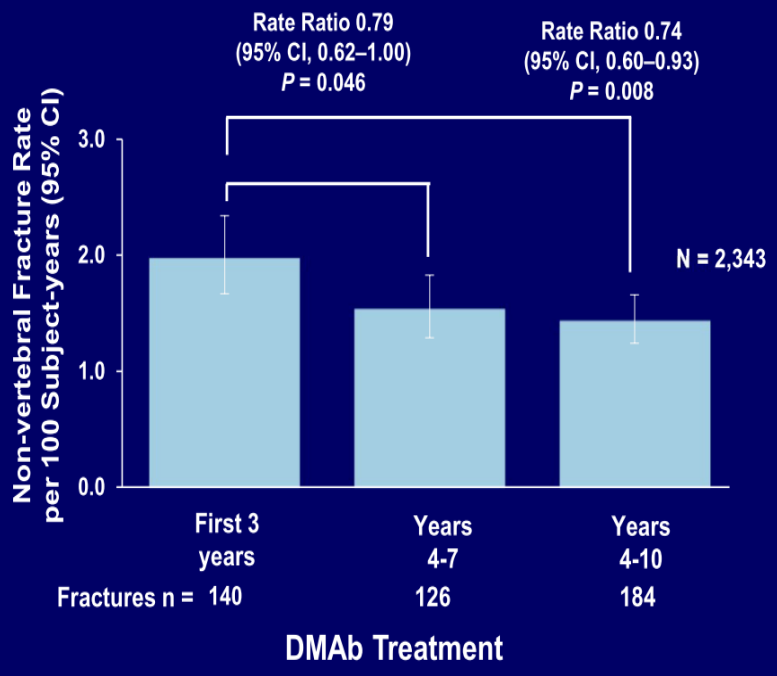
Over 10 years, BMD and trabecular bone score increase progressively



Bone HG et al. *Lancet Diabetes Endocrinol* 2017;5:513-23

Hans D et al. *Osteoporos Int* 2023;34:1075-84

Over 10 years, vertebral fracture risk reduction is maintained, and non-vertebral fracture risk improves beyond 3 years of therapy



Ferrari S et al. *J Clin Endocrinol Metab* 2019;104:3450-61

Long-term Denosumab Safety

- Over 10 years, there were no duration-dependent adverse events

Exposure-adjusted Subject Incidence (%) of Adverse Events in Cross-over Group (Rates per 100 Subject-years)

	Placebo (N = 3883)	DMab years 4-10 (N = 2206)
Serious adverse events	10.4	10.1
Infections	30.7	20.7
Serious infections	1.3	1.4
Malignancy	1.6	2.0
Death	0.8	0.8

- Osteonecrosis of the jaw*: 13 cases = 5.2/10,000 patient-years — *One per 40 fractures prevented*
- Atypical femoral fracture*: 2 cases = 0.8/ 5.2/10,000 patient-years — *One per 281 fractures prevented*

*NOTE: all oral adverse events and femoral shaft fractures adjudicated

Bone HG et al. *Lancet Diabetes Endocrinol* 2017;5:513-23

Discontinuing Denosumab Therapy

Take Home Points:

- There is no limit to the duration of denosumab therapy
  - no evidence of loss of effectiveness with long-term use
  - no duration-dependent adverse events over 10 years
- If therapy is discontinued, steps must be taken to prevent or limit the expected rebound in bone remodeling

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- After short-term therapy, oral alendronate or one dose of zoledronate is usually sufficient to prevent the rebound in bone remodeling, rapid bone loss and loss of vertebral fracture prevention
- Raloxifene and risedronate are less effective

Managing the Discontinuation of Denosumab

ECTS recommendations:

Denosumab < 2.5 years
Low risk for spine fracture

↓

Oral bisphosphonate for 1-2 years or 1 dose of zoledronate

Monitor with BMD and CTX

↓

Denosumab > 2.5 years
High risk for spine fracture

↓

IV Zoledronate 6 months after last dose of denosumab

Monitor CTX at 3 and 6 months, BMD at 6 months

↓

Re-treat with zoledronate if evidence of rebound in bone resorption (CTX above premenopausal reference range) or bone loss

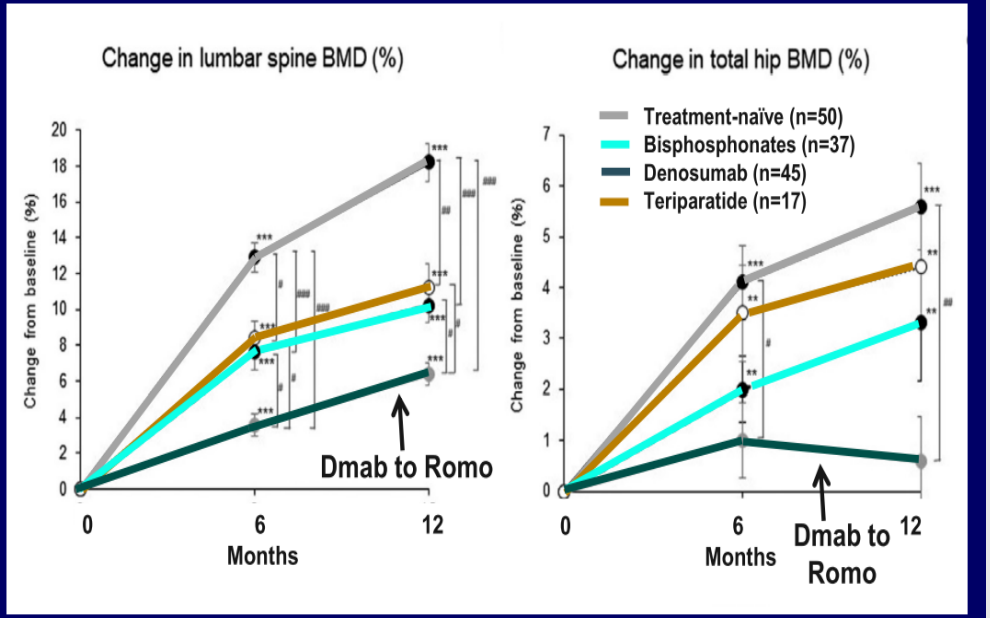
Adapted from Tsourdi E, et. al. *J Clin Endocrinol Metab.* 2021; 106:264-81

Denosumab to Osteoanabolic Therapy

- Switching from denosumab to teriparatide (and presumably abaloparatide) does NOT prevent the rebound in remodeling, and significant bone loss occurs
- Switching from short-term denosumab to romosozumab results in stable or increased BMD

- BMD response to romosozumab for 12 months was evaluated in patients with various previous treatments: bisphosphonates 2.5 years; denosumab 2 years; teriparatide 11 months
- BMD remained stable or increased slightly

- *No data yet about effect of that sequence after long-term denosumab*



Adapted from Ebina K et al. *Osteoporos Int* 2022;33:1807-13

Managing the Discontinuation of Denosumab

Patients who cannot or will not take a bisphosphonate:

Options include

a) continue denosumab

b) raloxifene or no additional therapy if risk for vertebral fracture is very low

c) consider transition to romosozumab for 12 months with careful monitoring

d) reduce dose to 30 mg Q 6 months for 12 months before discontinuing

(Cheung A et al. ASBMR 2022)

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Managing the Discontinuation of Denosumab

Take Home Points:

- There is no limit to the duration of denosumab therapy
- If therapy is discontinued, steps must be taken to prevent or limit the expected rebound in bone remodeling
- Preventing rebound remodeling and its consequences can be accomplished easily after short-term denosumab therapy
- Managing discontinuation with bisphosphonates after long-term denosumab therapy simply takes planning and monitoring
- Concern about denosumab discontinuation should not preclude the use of denosumab

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Osteoporosis Guidelines Recommend Choosing Initial Treatment Based on Current Fracture Risk

RISK CATEGORIES			
Low	**Moderate**	**High**	**Very High**
Postmenopausal women with low BMD but few or no other risk factors, especially if they are recently estrogen deficient, are candidates for prevention therapy	Younger postmenopausal women with lumbar spine BMD consistent with osteoporosis without prior fracture; low risk for hip fracture	Osteoporosis in spine or hip; low bone mass with remote history of non-spine, non-hip fracture or multiple other risk factors	Recent (within 1-2 years) fracture; very low BMD (<-3.0) or very high fracture probability by FRAX (>30% MOF or 4.5% hip fracture) hip region
RECOMMENDED DRUGS			
Hormone therapy	Raloxifene	Bisphosphonates	Osteoanabolic agents * teriparatide abaloparatide romosozumab
Low-dose bisphosphonates		Denosumab	

* to be followed by an anti-remodeling drug

McClung MR et al. *Menopause* 2021:28:973-97
Camacho PM et al.. *Endocr Pract* 2020;26(Suppl 1):1-46
Kanis JA et al. *Osteoporos Int* 2020;31:1-12

Why Should Osteoanabolic Drugs Be the Initial Treatment for Osteoporosis?

Key Point:

- It is intuitive that improving the structural derangement of osteoporosis first with an osteoanabolic agent and then maintaining that better structure would be better than simply preserving the poor structure of patients with osteoporosis with an anti-remodeling drug

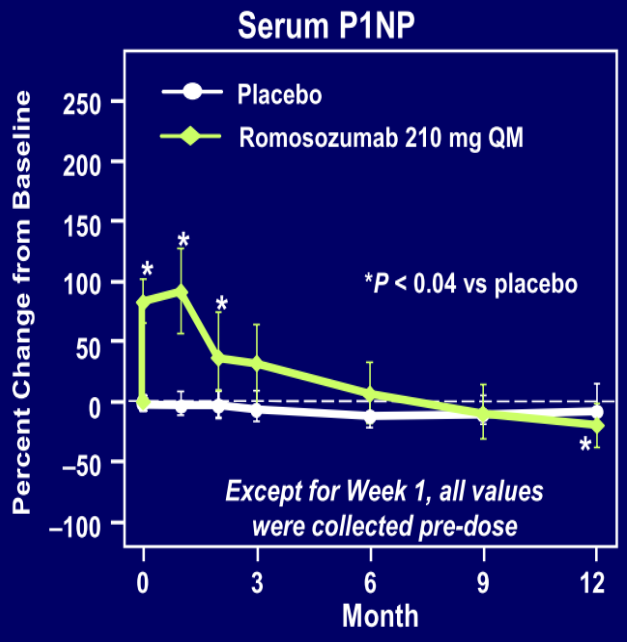
- That intuition has been proven correct
  - larger faster increases in BMD; larger if anabolic given first vs second
  - improved bone architecture
  - superior to anti-remodeling drugs to reduce fracture risk
  - benefits persist for at least 2 years after transition to an anti-remodeling drug

If cost was not an issue, beginning therapy with an osteoanabolic agent should be considered in every patient with osteoporosis

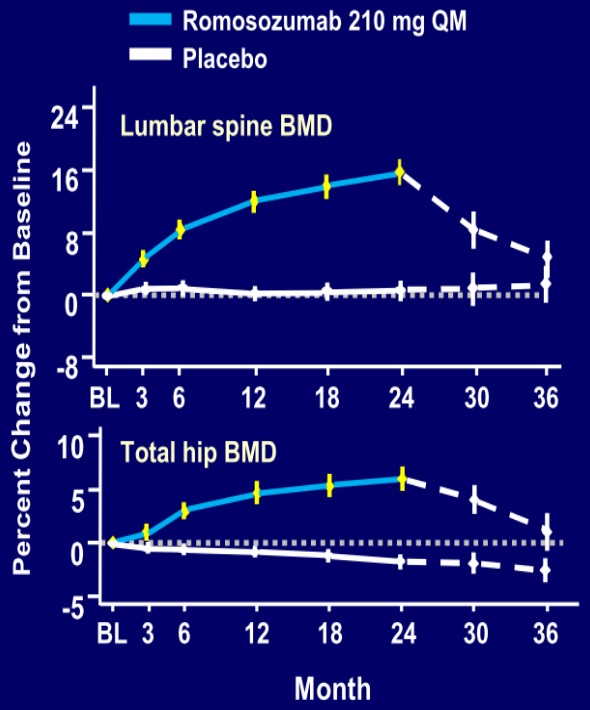
Transition: Osteoanabolic to Anti-remodeling Therapy

FDA Guidance: ***(After a course of romosozumab,) if osteoporosis therapy remains warranted, continued therapy with an antiresorptive drug should be considered***

- **Reasons for transition:**
  - **Anabolic effects wane – follow-on Rx needed to maintain benefit**



Data are medians and IQRs

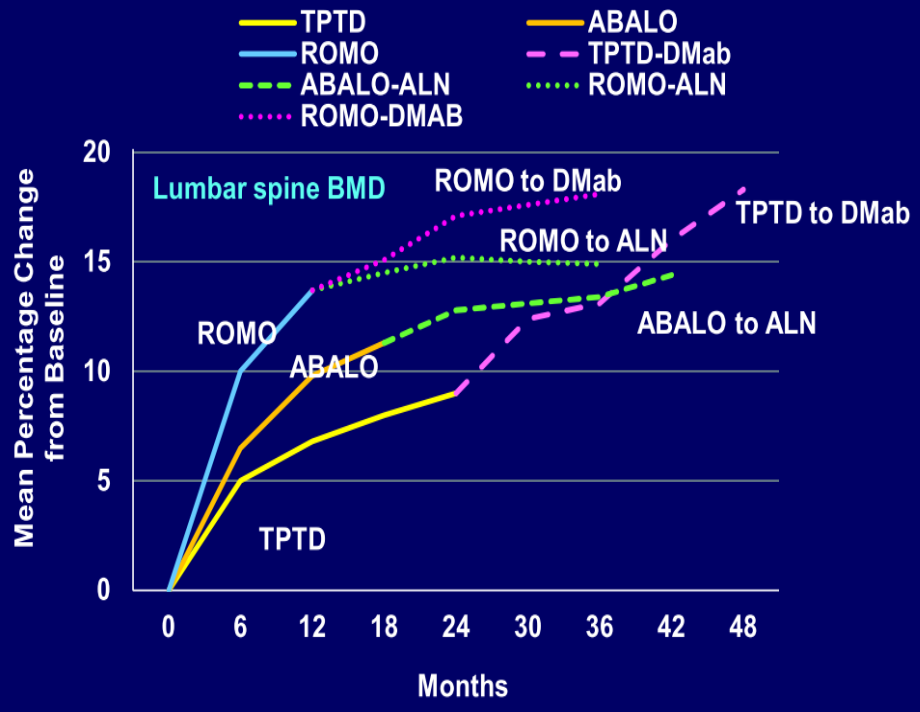


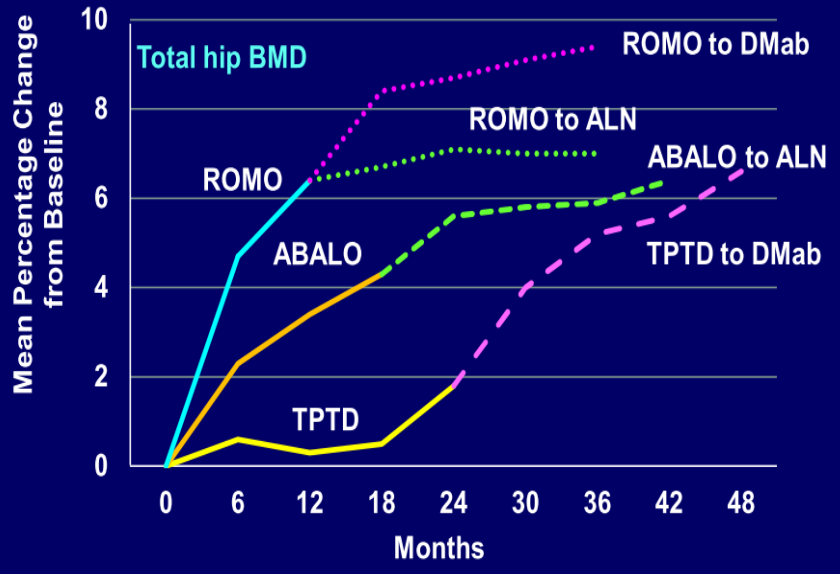
McClung MR et al. *J Bone Miner Res* 2018;33:1397-1406

Transition: Osteoanabolic to Anti-remodeling Therapy

Key Point:

- **BMD increase is larger with denosumab than with a bisphosphonate**





TPTD = teriparatide; ABALO = abaloparatide; ROMO = romosozumab;
DMab = denosumab; ALN = alendronate

Transition from Anabolic to Anti-remodeling Drug

Take Home Points:

- Almost every course of an osteoanabolic therapy needs to be followed by an anti-remodeling drug for at least 1-2 years
  - *Exception:* use of teriparatide in premenopausal osteoporosis

  - Switching to a bisphosphonate maintains BMD
  - Switching to denosumab results in additional BMD gain

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Long-term Maintenance Therapy

Key Points:

- Osteoporosis requires long-term if not life-long management
- Upon achieving treatment goals with osteoanabolic, denosumab or bisphosphonate therapy, a strategy for long-term maintenance with intermittent bisphosphonate can be used

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  - The risk of AFF is very low during the first few years of bisphosphonate therapy
  - That risk decreases quickly during the 2 years following bisphosphonate discontinuation
  - BMD and fracture risk remain quite stable during the first few years off alendronate or zoledronate therapy (may not be true for risedronate or ibandronate)

Intermittent Bisphosphonate Maintenance Therapy

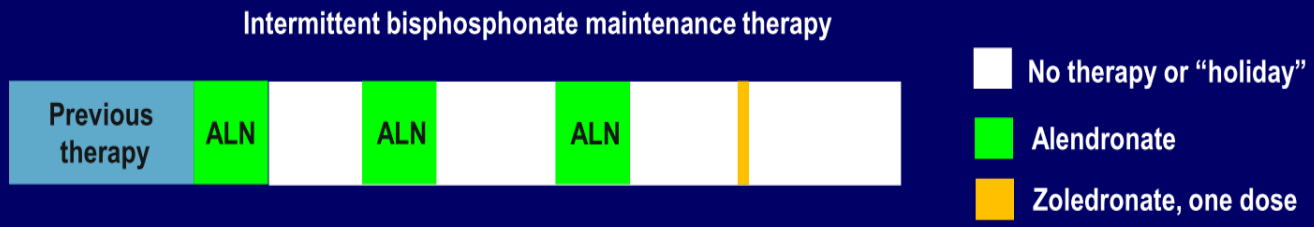
Key Points:

- Once a patient achieves modest fracture risk or a treatment "target", treatment can shift from trying to attain higher BMD or lower fracture risk to maintenance therapy
- This can be achieved with short, intermittent courses of an oral bisphosphonate such as alendronate or with infrequent doses (e.g., Q 3-5 years) of zoledronate

Grey A et al, *J Bone Miner Res* 2022;37:3-11

  - Re-treatment could be considered if BMD loss was noted, if a fracture occurred or if other risk factors developed – *if the patient again met criteria for therapy*

- In theory, this could maintain BMD and bone strength, prevent additional deterioration of skeletal structure without exposing the patient to the risk of atypical fracture observed with long-term bisphosphonate therapy



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Combination and Sequential Therapies

TABLE 4 | Combination therapies.

Anabolic agents	Anti-resorptive drugs	Methods	Conclusions
PTH (1–84)	Alendronate (Black et al., 2003)	Randomly assigned patients to daily treatment with parathyroid hormone (1–84) (100 μg), alendronate (10 mg), or both for 12 months	i) There was no evidence of synergy between parathyroid hormone and alendronate ii) The anabolic effects of parathyroid hormone may be reduced when use of alendronate simultaneously
PTH (1–84)	Ibandronate (Schafer et al., 2012)	Participants received either 6 months of concurrent PTH and ibandronate, followed by 18 months of ibandronate (concurrent) or two sequential courses of 3 months of PTH followed by 9 months of ibandronate (sequential) over 2 years	i) BMD did not increase more than with either treatment alone ii) Concurrent monthly ibandronate may blunt the effects of PTH(1–84)
Teriparatide	Zoledronic Acid (Cosman et al., 2011)	Randomly assigned patients to receive a single intravenous infusion of zoledronic acid 5 mg plus daily teriparatide 20 mg *via* subcutaneous injection, zoledronic acid alone, or placebo infusion plus daily teriparatide 20 mg for 1 year	A beneficial effect of co-administration of teriparatide and zoledronic acid treatment was shown as compared to teriparatide or zoledronic acid monotherapy
Teriparatide	Denosumab (Tsai et al., 2013; Tsai et al., 2019)	Patients were assigned in a 1:1:1 ratio to receive 20 μg teriparatide daily, 60 mg denosumab every 6 months, or both	Combined teriparatide and denosumab increased BMD more than either agent alone
		Participants were randomly assigned (1:1) to receive teriparatide 20 μg (standard dose) or 40 μg (high dose) daily for 9 months. At 3 months, both groups were started on denosumab 60 mg every 6 months for 12 months	Combined treatment with teriparatide 40 μg and denosumab increased BMD more than standard combination therapy

TABLE 5 | Sequential therapies.

Initial agents	Subsequent agents	Methods	Conclusions
Teriparatide	Denosumab	Subjects were switched from both the combination and teriparatide groups to denosumab, and subjects in the denosumab group were switched to teriparatide. In all groups, 24 months of additional treatment were given. (Leder et al., 2015b)	In postmenopausal osteoporotic women switching from teriparatide to denosumab, BMD continued to increase
Denosumab	Teriparatide		In postmenopausal osteoporotic women switching from denosumab to teriparatide results in progressive or transient bone loss
Abaloparatide	Alendronate (Bone et al., 2018)	Patients who had been randomized to either placebo or abaloparatide (80 μg daily) for 18 months were subsequently treated with oral alendronate (70 mg weekly) for an additional 24 months	Sequential abaloparatide followed by alendronate had a greater reducion in the risk of fractures and BMD increased more
Romosozumab	Denosumab (Lewiecki et al., 2019)	Patients received romosozumab or placebo (month 0–12) followed by denosumab (month 12–36)	BMD were further augmented and fracture risk was reduced by switching from romosozumab to denosumab

---Front. Pharmacol. 2021;12:717065.

Take home messages

- Osteoporosis requires long-term if not life-long management

- Initial therapy – and the sequence of subsequent therapies – should be based on the patient's current risk of fracture

  - osteoanabolic therapies are the most effective choices
  - bisphosphonate should be limited to no more than 5 years at a time
  - denosumab is more effective than bisphosphonates – and is the best option for long-term improvement in bone density
  - all non-bisphosphonate therapies requires an interval of bisphosphonate therapy to maintain benefit
  - If patients achieve moderate risk, intermittent bisphosphonate therapy would be the appropriate long-term maintenance therapy

Thanks for your attention!!!