“SpongeBone” Menopants*

Adam Fershko, MD, FACP

Kettering Health Network

*Postmenopausal Osteoporosis

Objectives

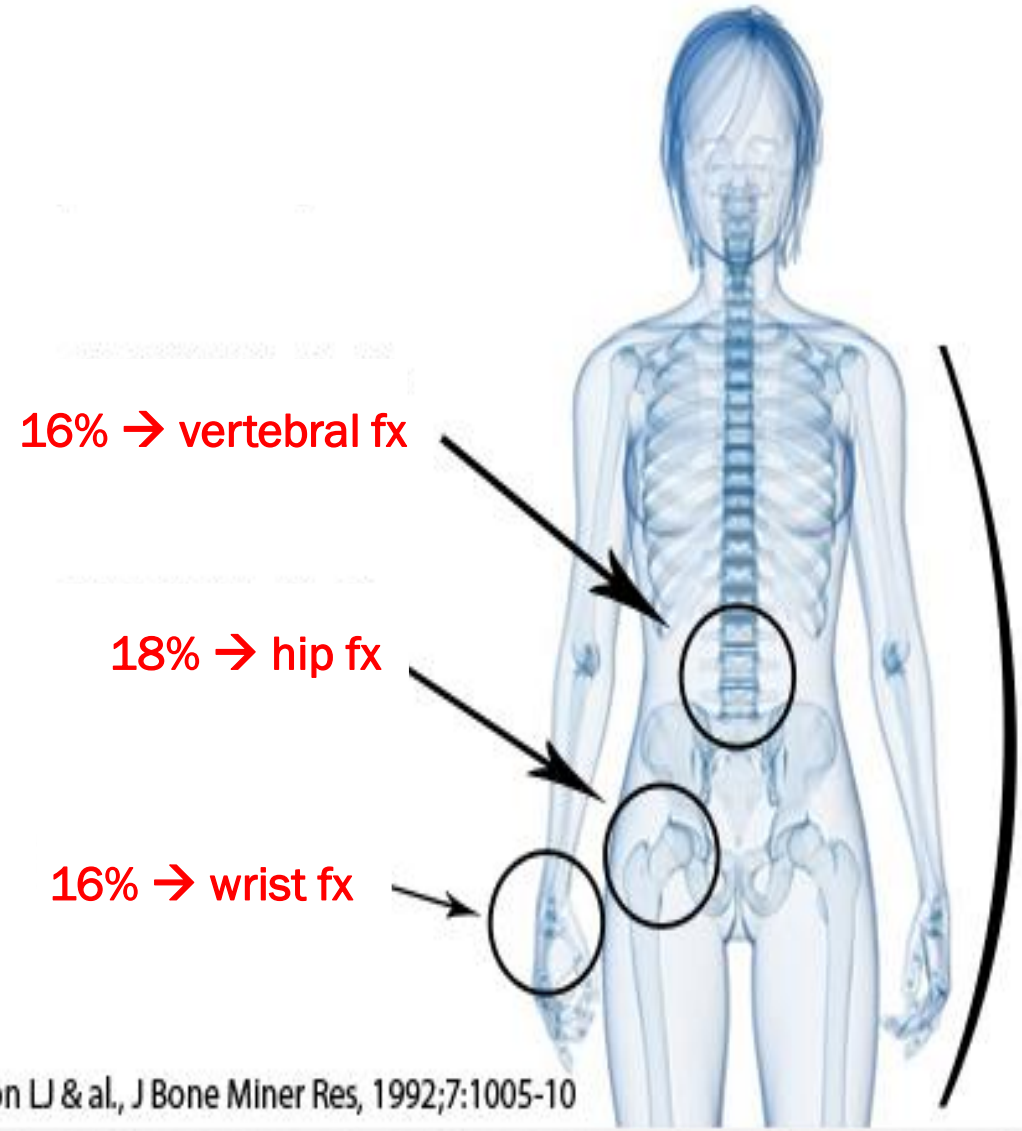
- Epidemiology
- Clinical significance
- Pathophysiology
- Screening and Diagnosis
- Treatment modalities
- Side effects

Background

- ~1.5 million osteoporotic fractures/year
- 10 million with osteoporosis
- 34 million with osteopenia
- Most → postmenopausal women
- Bone mass and bone quality
- Qualitative changes in microarchitecture
  - Bone remodeling in dynamic equilibrium
  - Peak BMD at age 30
- 50 year old WF
  - 15-20% →hip fx
  - 50% →any osteoporotic fx

Hip fracture

- Older women who have hip fracture have 2-3 fold increase in death in one year
- 1 month after surgery 10.5%
- 6 months 21.5%
- 1 year 27.3%

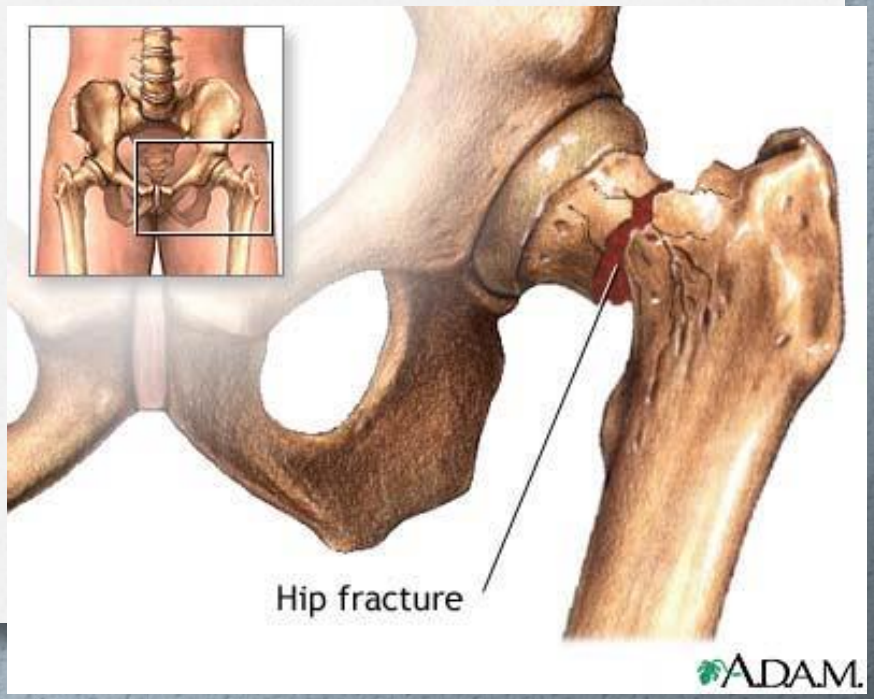


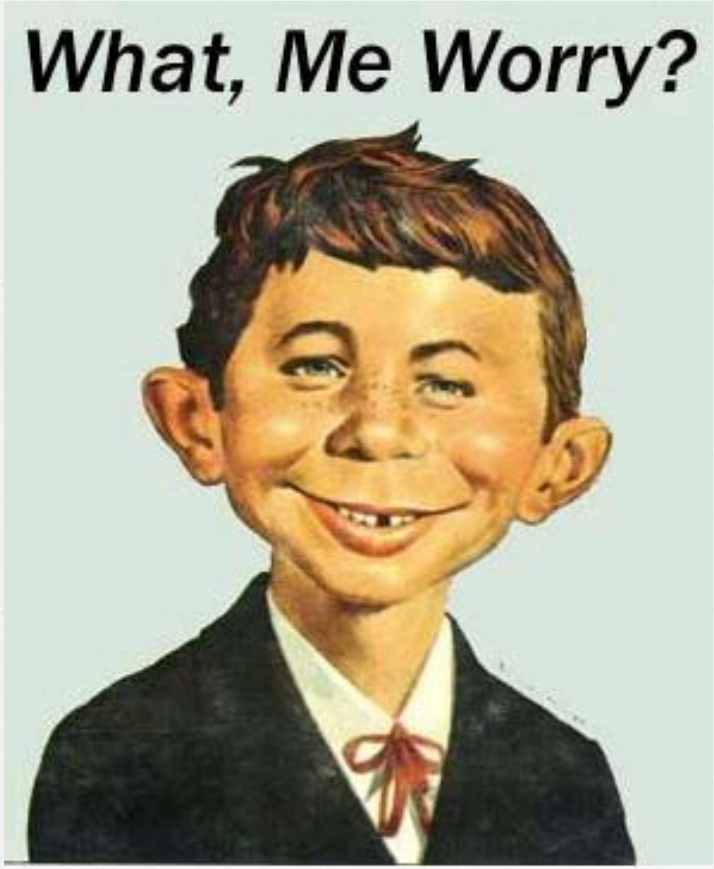
Melton LJ & al., J Bone Miner Res, 1992;7:1005-10

Complications of Osteoporosis

- Kyphosis
- Reduced FVC = each fracture ⇩ FVC by 9%
- Increased mortality rate – associated w hip fxs → 25% will die first year after hip fx
- 1/3 of vertebral fxs are painful
- Hip fracture → 1/3 long term ECF


www.eORIF.com

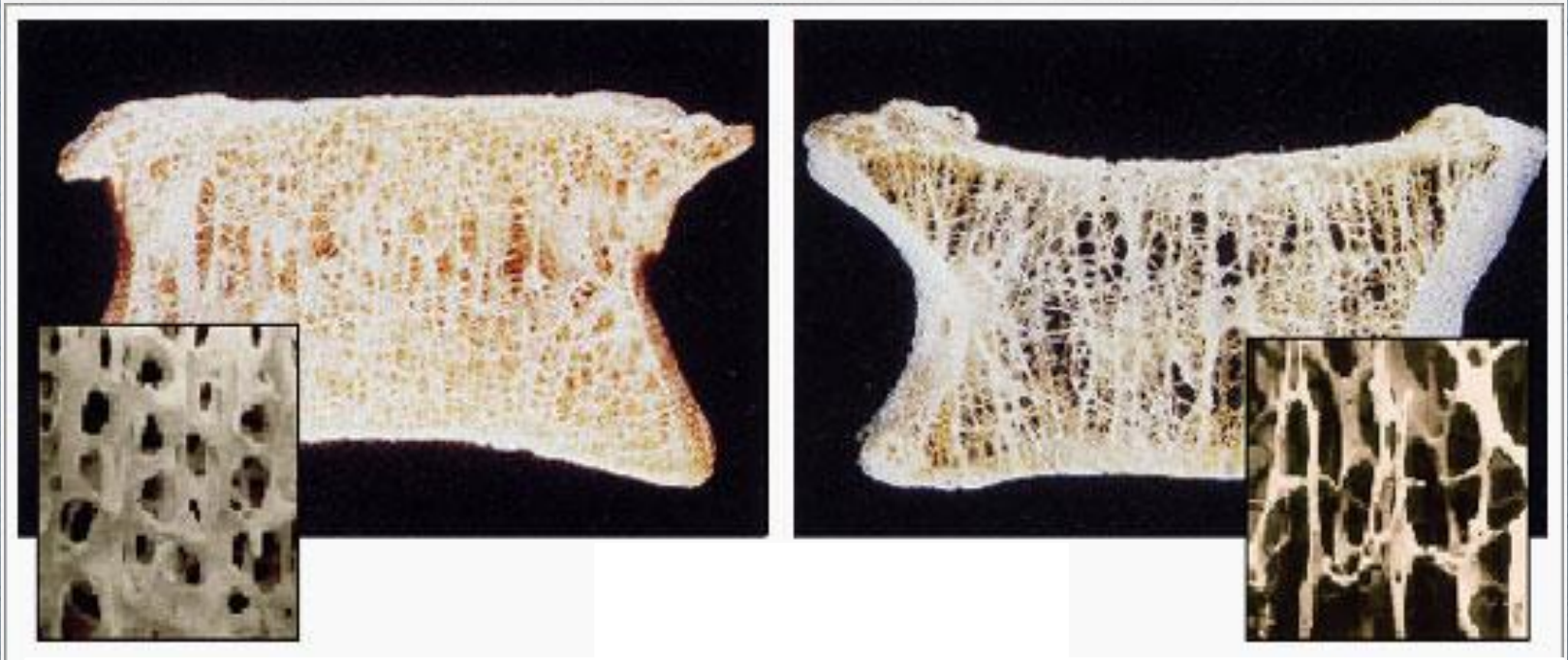

Hip fracture
A.D.A.M.


What, Me Worry?


Duff
BEER

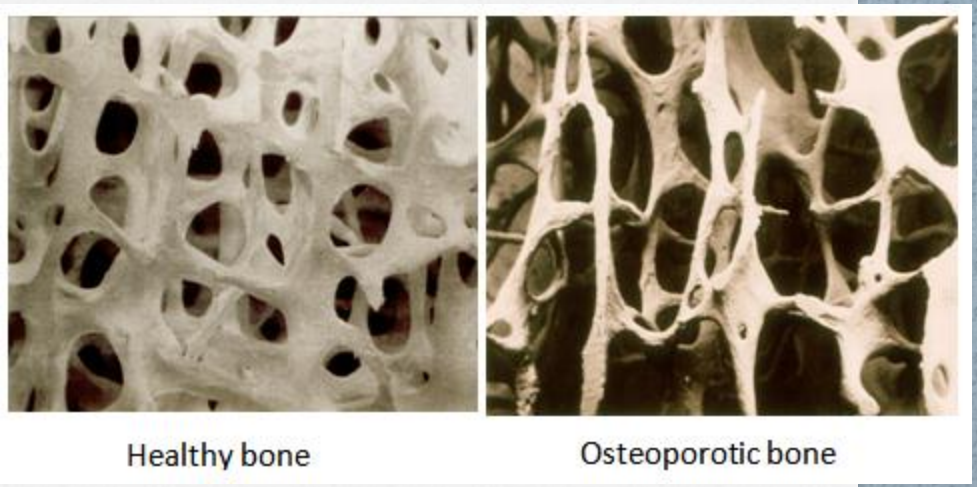
Risk Factors for Primary Osteoporosis

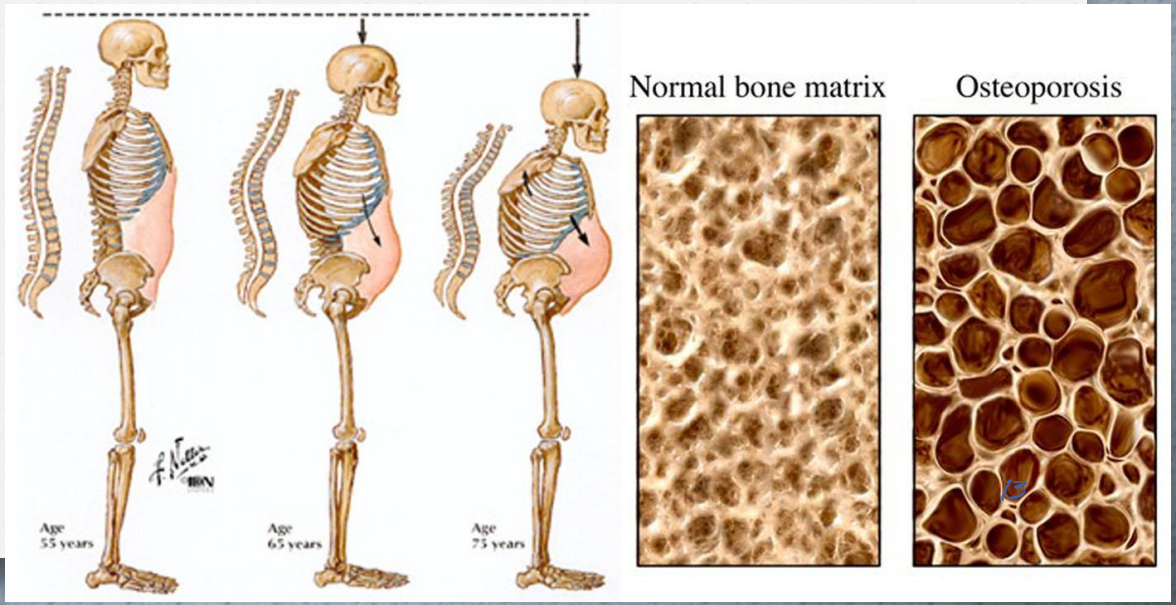
- Age
- BMD
- Caucasian or Asian
- Previous Fragility Fracture
- Family Hx
- Low BMI
- Life Style Factors
- Early/Surgical Menopause




Michigan State U Internal Medicine Clerkship


12


Healthy bone
Osteoporotic bone

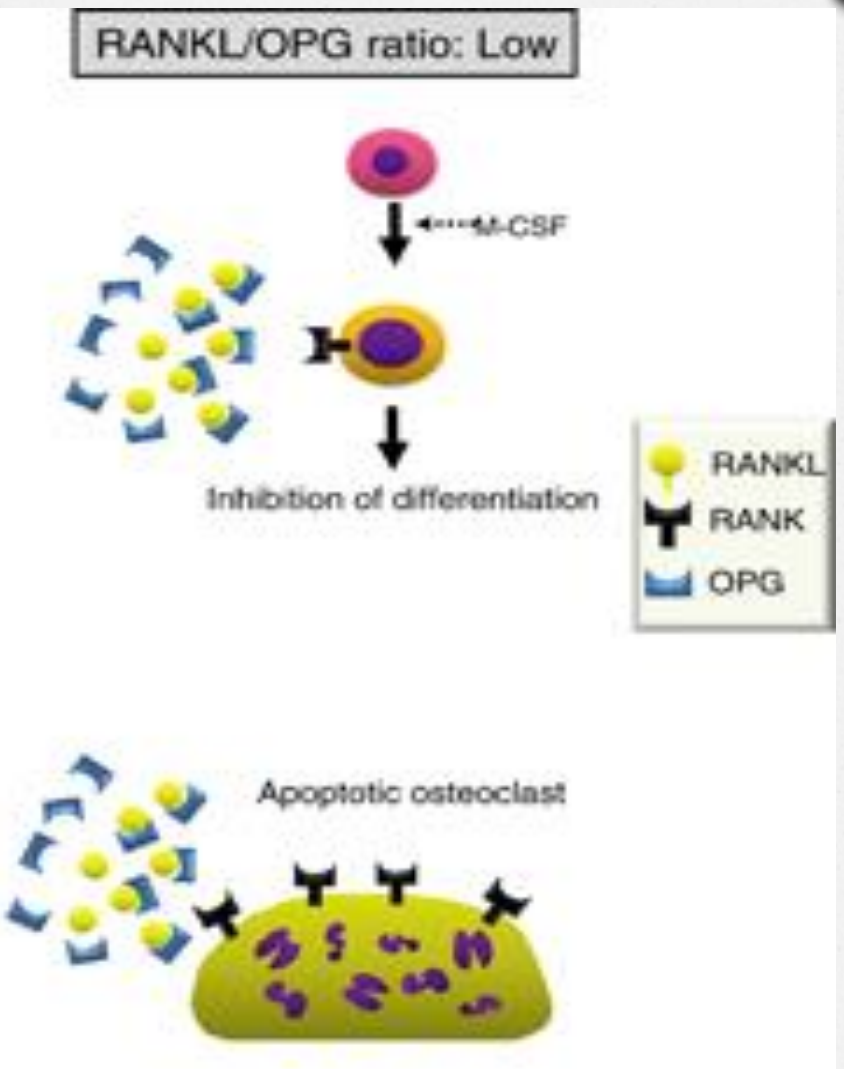

Age 55 years
Age 65 years
Age 75 years
Normal bone matrix
Osteoporosis

Pathophysiology

- Osteoclast
- Resorption
- T cell cytokines
- Differentiation of precursors
- RANKL
- RANK
- Osteoblasts
- Osteoprotegerin (OPG)

Postmenopause?

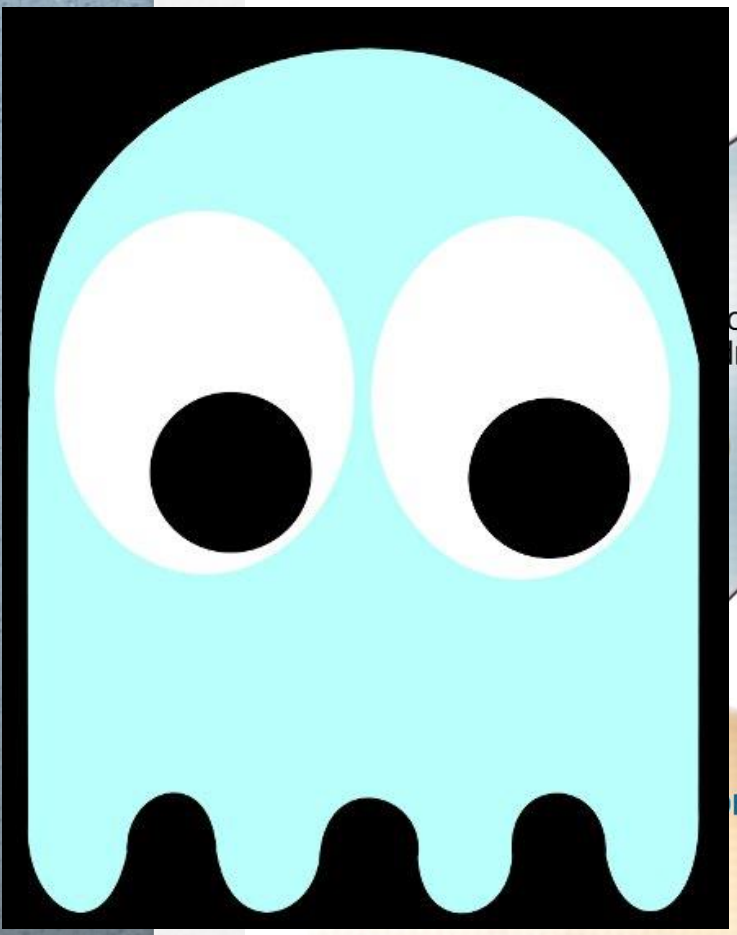
- Estrogen Deficiency
  - RANKL 
  - OPG 

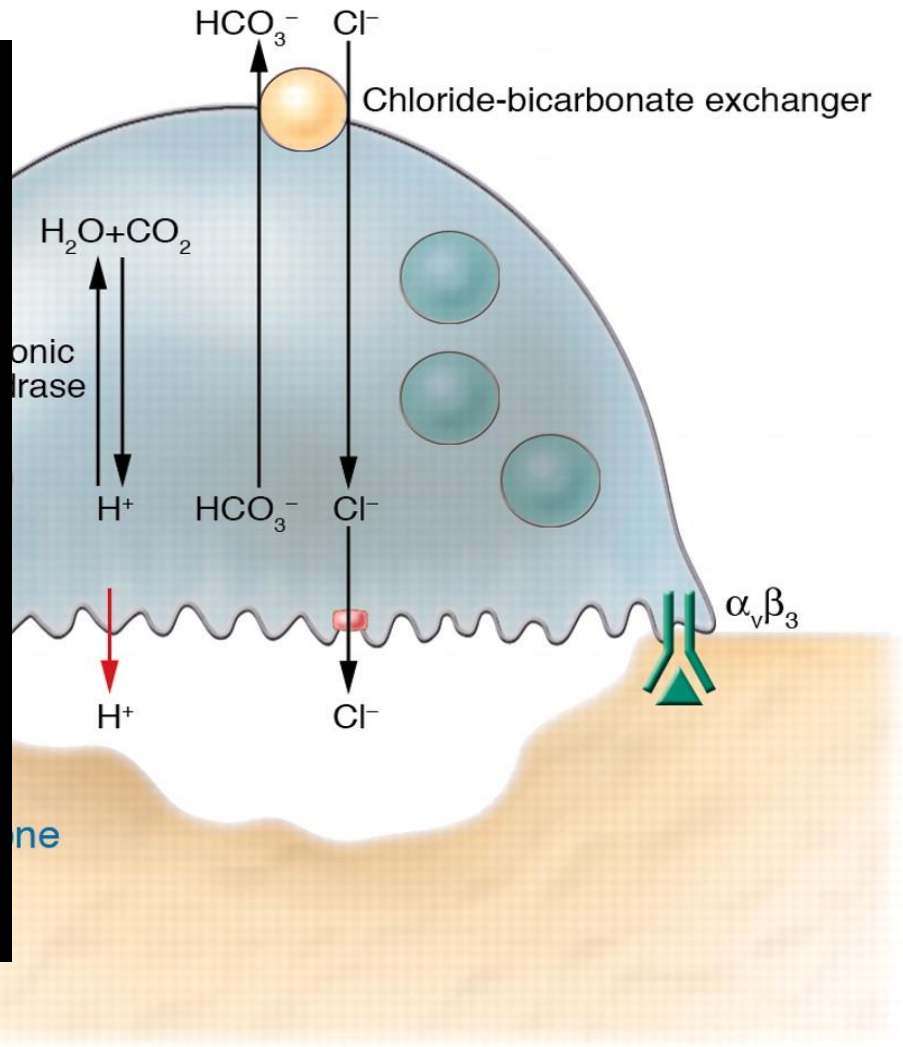

RANKL/OPG ratio: Low
M-CSF
Inhibition of differentiation
RANKL
RANK
OPG
Apoptotic osteoclast

Estrogen Replacement

Apoptosis of osteoclasts

Bone formation → stimulating type 1 collagen synthesis by osteoblasts




HCO_3^- Cl^-
Chloride-bicarbonate exchanger
H_2O+CO_2
onic
rase
H^+
HCO_3^- Cl^-
$\alpha_v\beta_3$
H^+
Cl^-
ne

did you know?
did-you-kno.tumblr.com

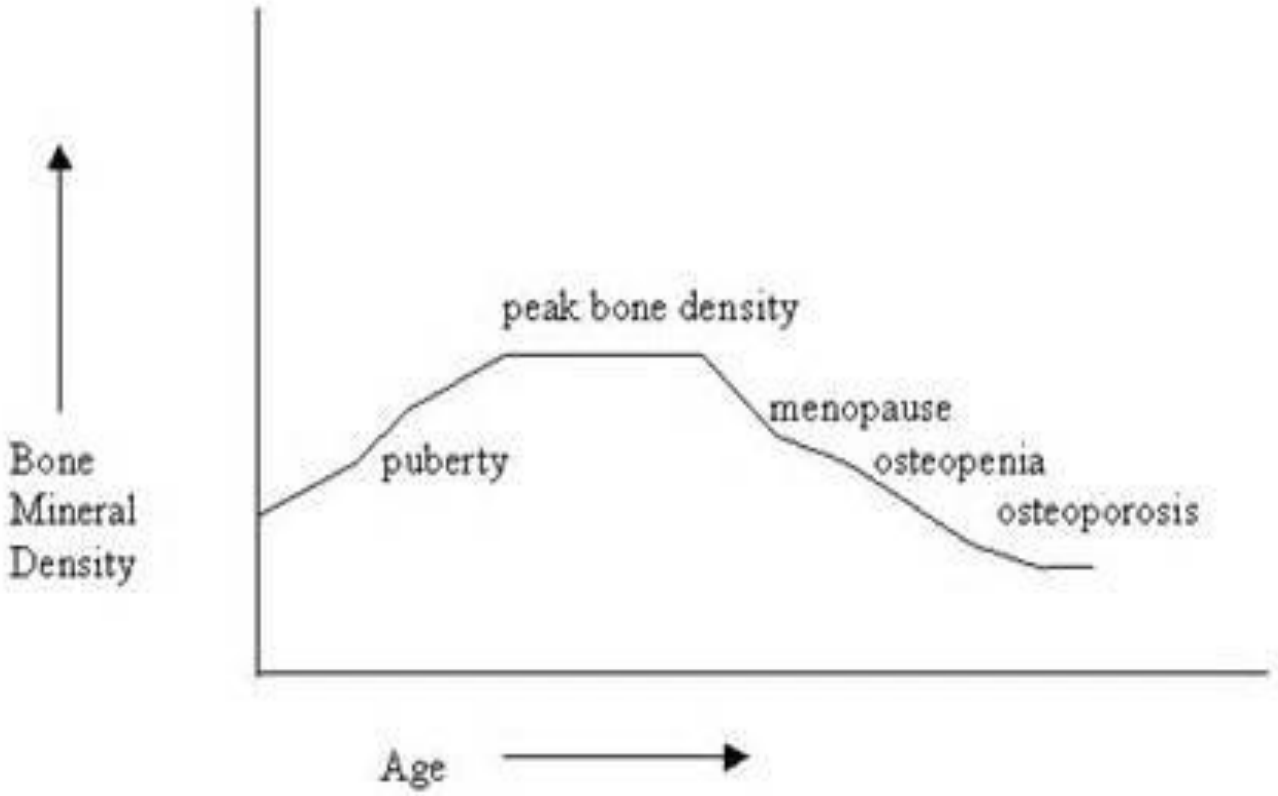
The four ghosts in Pacman are programmed to act differently: red chases you, pink just tries to position itself in a set way, blue tries to ambush you, orange is random.

did-you-kno.tumblr.com
didyouknowblog.com
facebook.com/didyouknowblog

Perimenopause

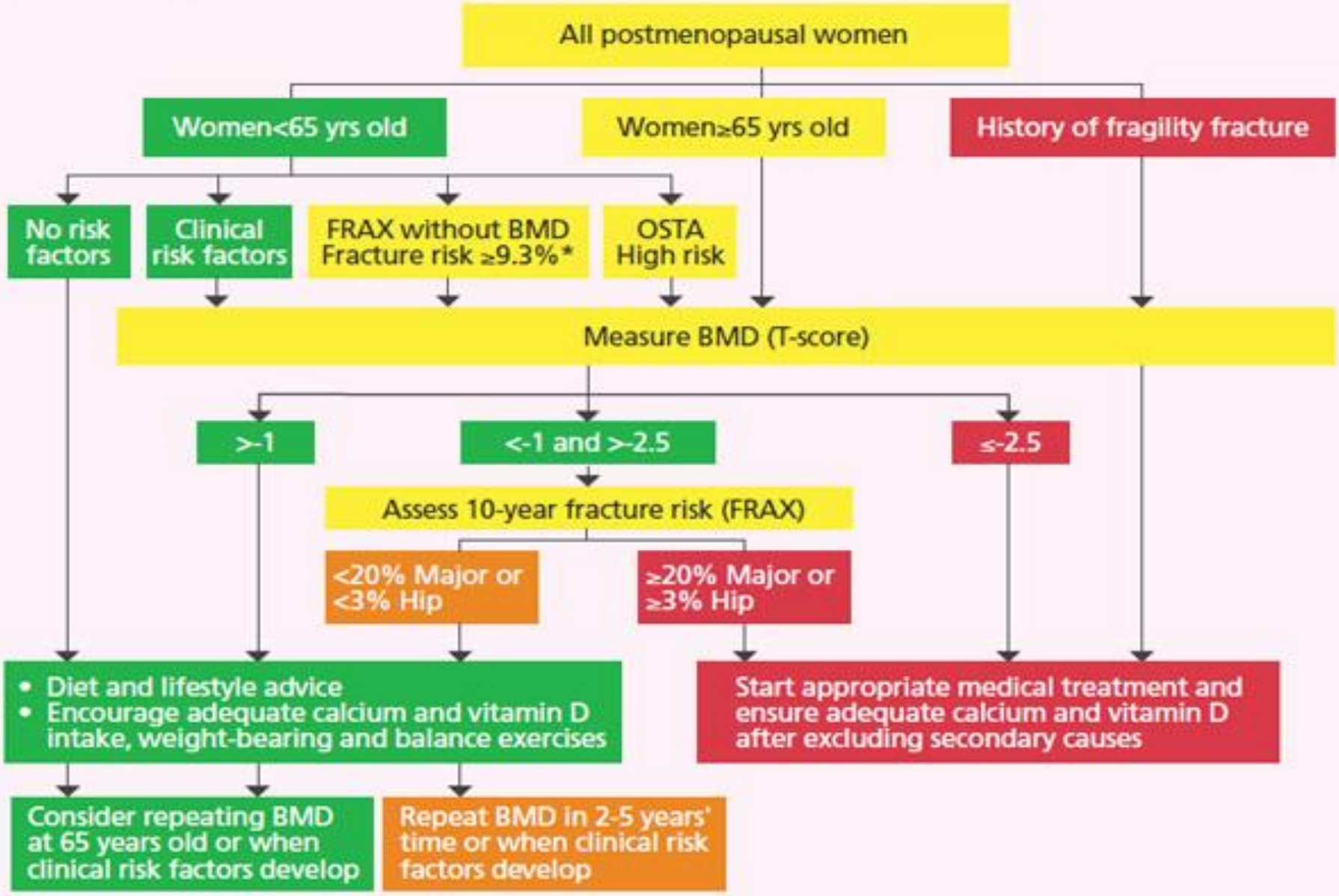
- Peak Bone mass → 25-35 yrs
- 5 years before menopause → femurs
- 4-8 years after menopause → accelerated phase of bone loss → continuous phase thereafter
- Accelerated phase → estrogen def
- Continuous phase → inc PTH because of decreased intestinal Ca absorption and increased urinary Ca excretion

Bone Mineral Density Decreases at Menopause




GOSH CHIP!
TELL ME SOMETHING I DON'T KNOW!
memegenerator.net

Strategies for Osteoporosis Screening



▲ Figure 1

Indications for BMD Testing. (2013).

	Women	Men
Age	65 and >	70 and >
Associated Risk factor for Low bone mass*	Post Menopausal Women < 65	< 70 Yrs
Clinical Risk factors **	during menopausal transition	
Adults	fragility fracture	
Adults	Disease or condition associated with low bone mass or loss	
Adults	medications associated with low bone mass or loss	
Anyone	being considered for pharmacological therapy	
Anyone	being treated, to monitor treatment effect	
Anyone	not receiving therapy in whom e/o bone loss would lead to treatment	
women discontinuing oestrogen should be considered for bone density testing according to indications listed above		

* Risk factors for low bone mass
Low body weight
Prior fracture
high risk medication use
disease / condition associated with bone loss.

** Clinical risk factors for
Low body weight
Prior fracture
high risk medication use

Prepared by Dr Deepak Jagiasharma as per
2013 Official Positions-ISCD

Diagnosis

- Fragility Fracture (regardless of T-score)

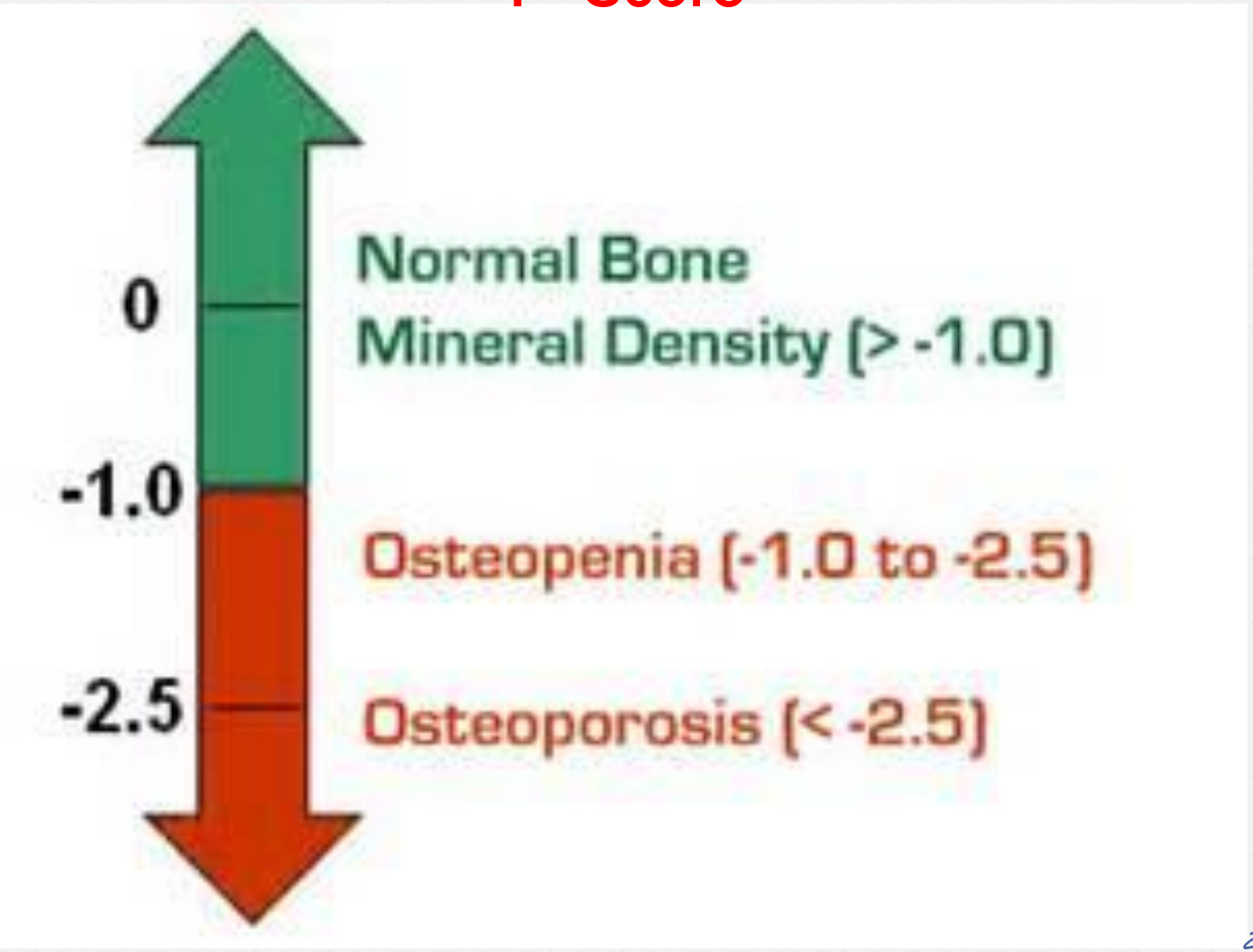
OR

- T-score (lowest value)


I'VE FALLEN AND I CAN'T GET UP!
GOOD

- **T-score**
  - BMD expressed as the number of standard deviations above or below the mean BMD of normal young adults (30 yrs old)
- **Z-score**
  - BMD expressed as the number of standard deviations above or below the mean BMD of adults of the same age and gender
- **Absolute BMD**
  - Acutal BMD → g/cm2
  - Used to calculate change over time

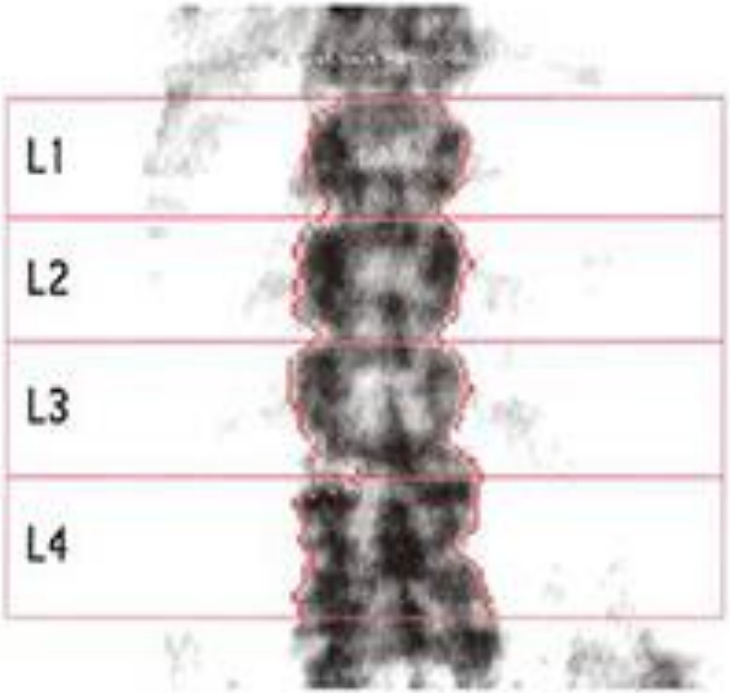
T - Score

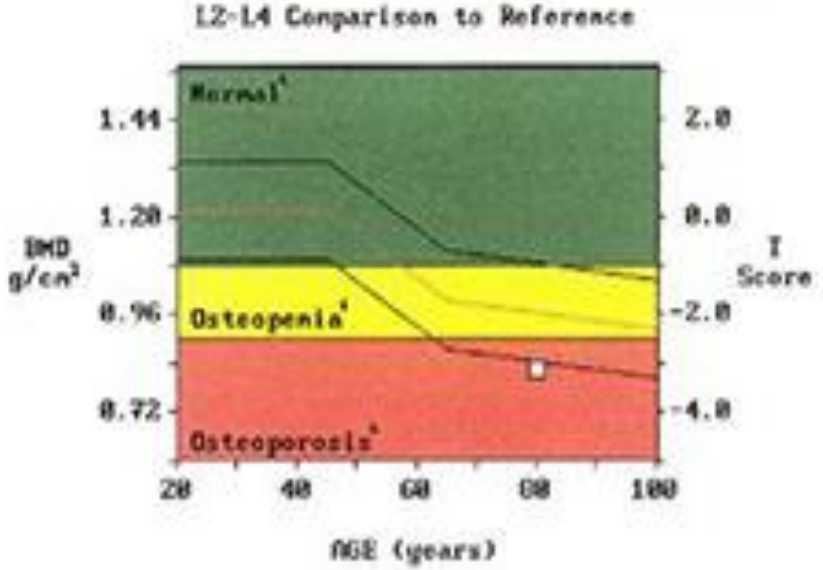

0
-1.0
-2.5
Normal Bone
Mineral Density (> -1.0)
Osteopenia (-1.0 to -2.5)
Osteoporosis (< -2.5)

AP SPINE BONE DENSITY

Facility:
80 years 05.08.1922
147 cm 68 kg White Female
Physician:

Acquired: 25.03.2003 (4.7d)
Analyzed: 25.03.2003 (4.7d)
Printed: 07.04.2003 (4.7d)
hall_e00.s77

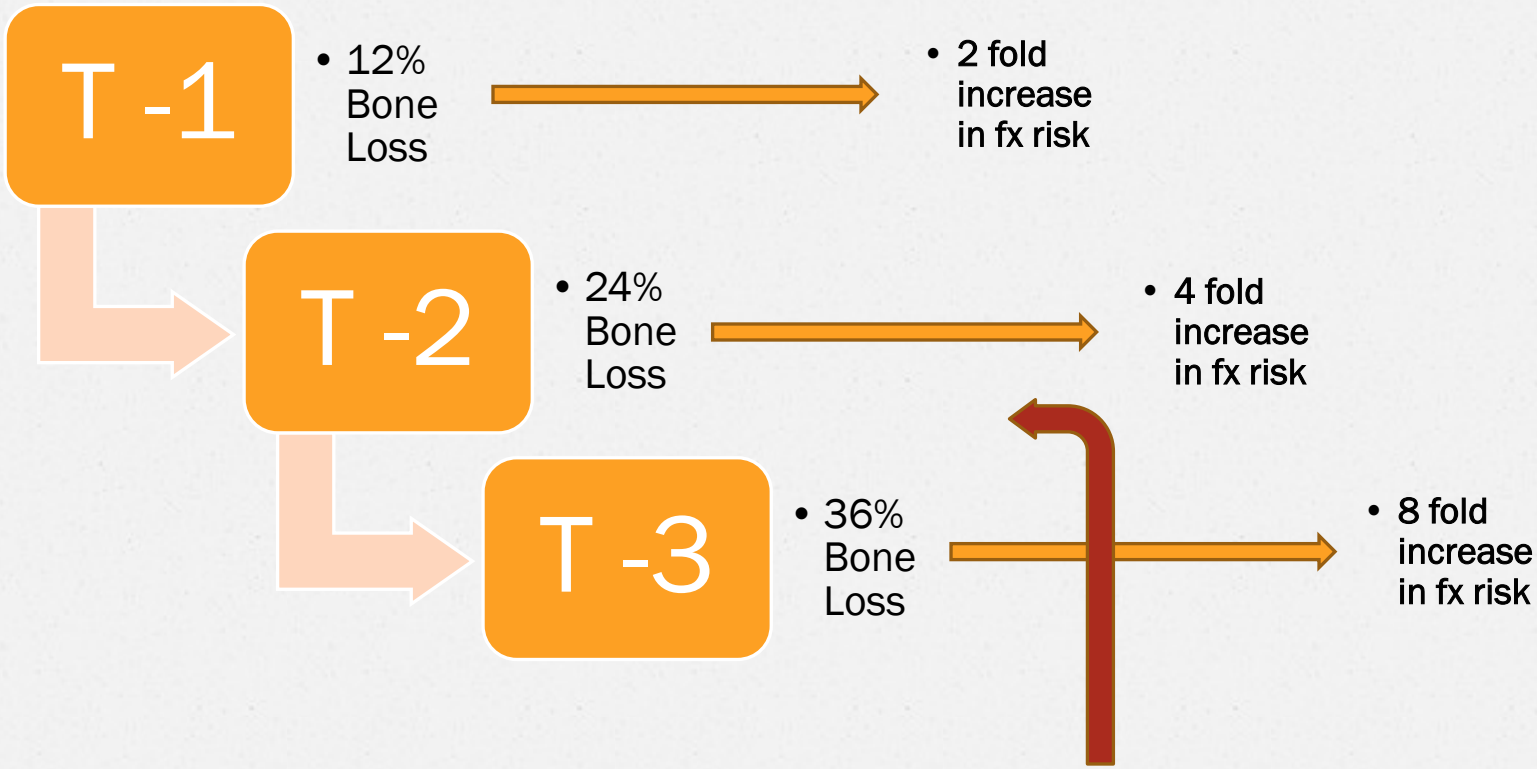




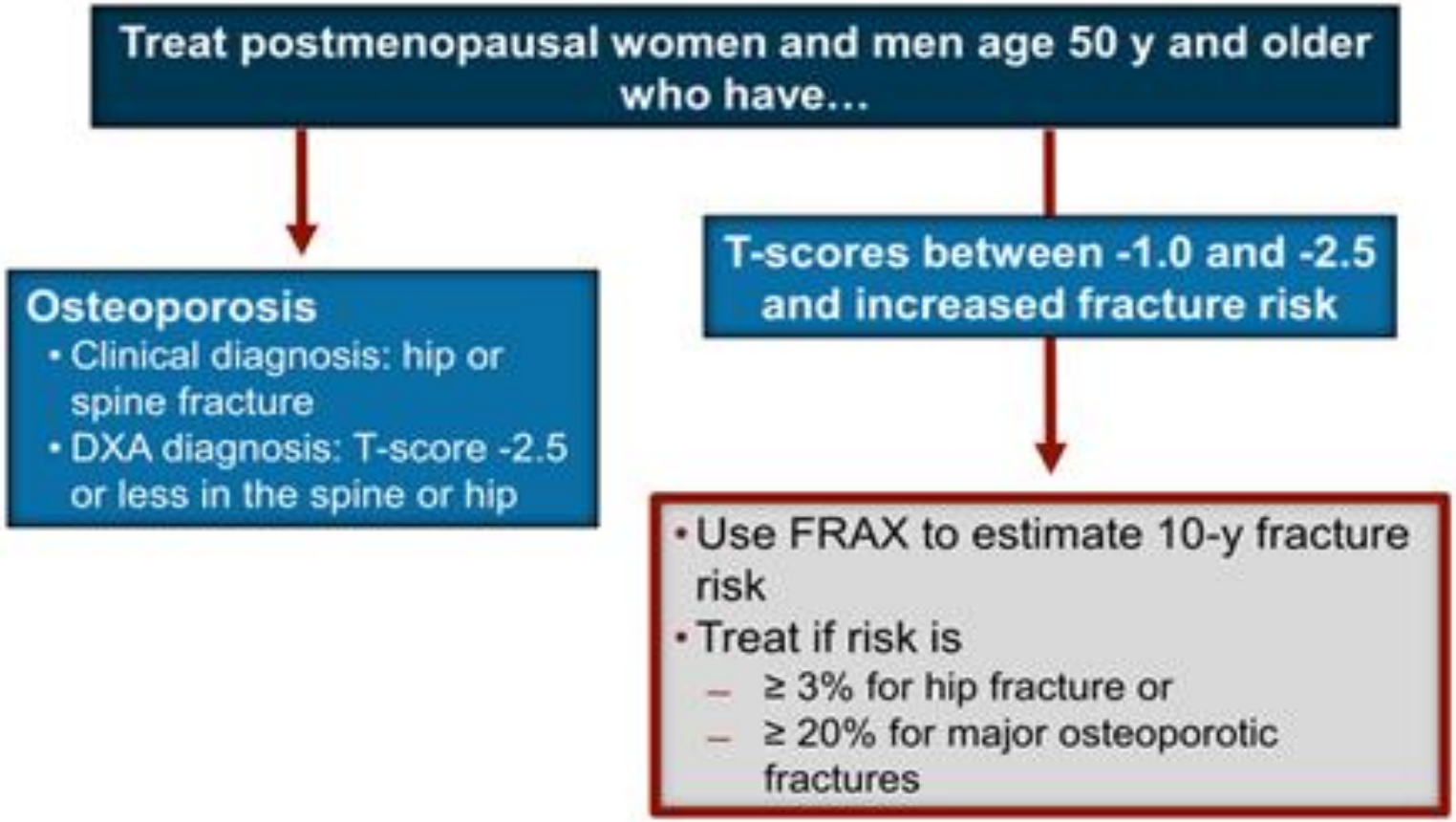
Region	BMD[1,7] g/cm²	Young-Adult[2] %	T-Score	Age-Matched[3] %	Z-Score
L2-L4[4]	0.823	69	-3.1	86	-1.2

Image not for diagnosis
0.75ma:Slow DPXMD 1.2x1.2mm 1.68mm
716555:413937 275.66:205.32:145.88
%Fat = 29.6(1.333)

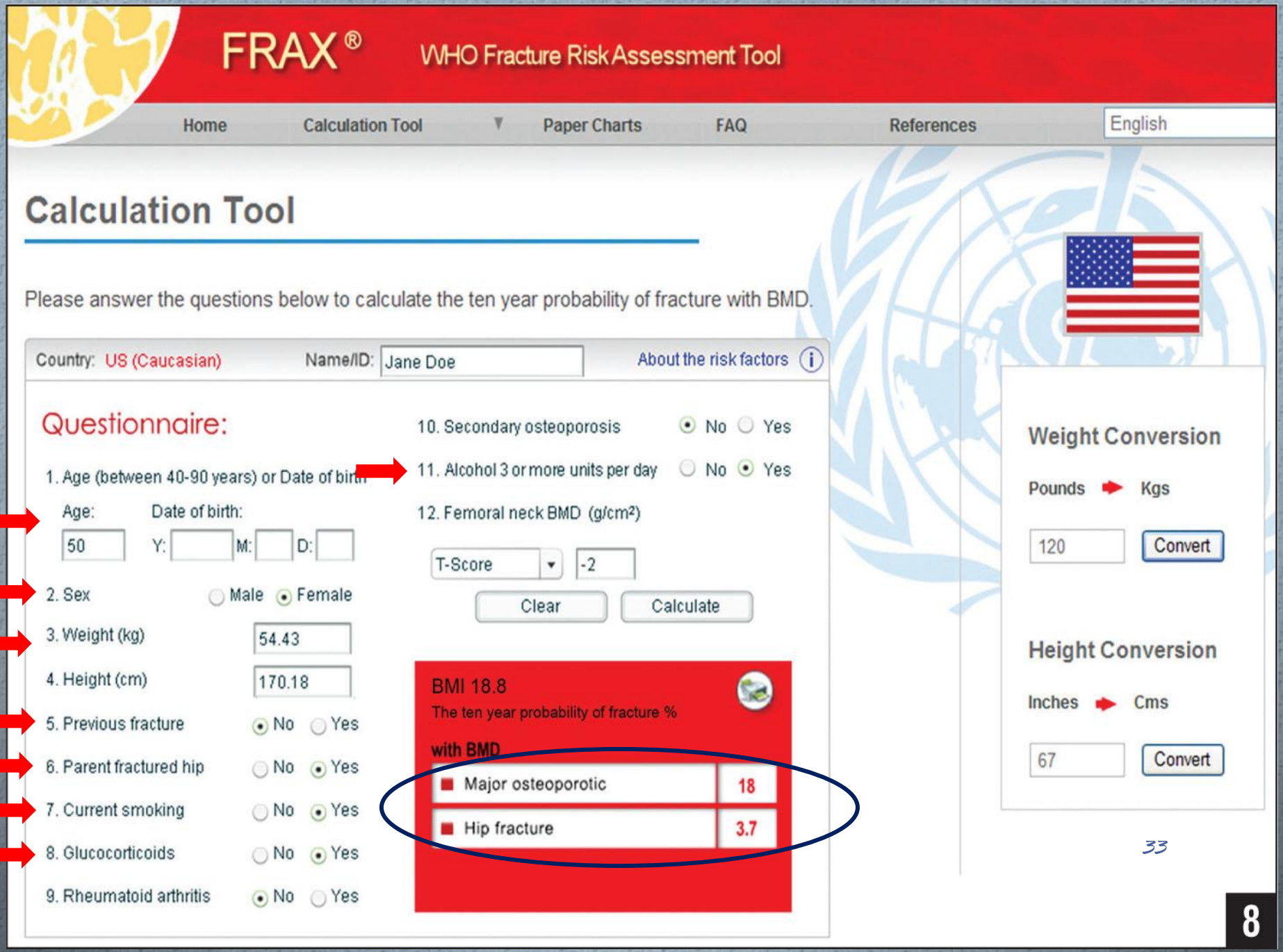
T-score Significance



National Osteoporosis Foundation Treatment Guidelines



National Osteoporosis Foundation, 2010.[8]


FRAX®
WHO Fracture Risk Assessment Tool
Home
Calculation Tool
Paper Charts
FAQ
References
English
Calculation Tool
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: US (Caucasian)
Name/ID: Jane Doe
About the risk factors
Questionnaire:
1. Age (between 40-90 years) or Date of birth
Age:
50
Date of birth:
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
54.43
4. Height (cm)
170.18
5. Previous fracture
No
Yes
6. Parent fractured hip
No
Yes
7. Current smoking
No
Yes
8. Glucocorticoids
No
Yes
9. Rheumatoid arthritis
No
Yes
10. Secondary osteoporosis
No
Yes
11. Alcohol 3 or more units per day
No
Yes
12. Femoral neck BMD (g/cm²)
T-Score
-2
Clear
Calculate
BMI 18.8
The ten year probability of fracture %
with BMD
Major osteoporotic
18
Hip fracture
3.7
Weight Conversion
Pounds
Kgs
120
Convert
Height Conversion
Inches
Cms
67
Convert

33

Treatment

- Goal of treatment → prevention
- For each 1 SD decrement (T score) in BMD risk of fracture increases by a factor of 2 to 3
- Check Vit D status
- Ca x Phos must be >24 to mineralize bone
- IF patient has low Z score must strongly consider secondary etio for osteoporosis

Conditions that Affect Bone Mass

- Menopause, hypogonadism, prolactinoma
- Hyperparathyroidism
- Hypercalciuria
- Hypercortisolism
- Hyperthyroidism
- Diabetes mellitus, type I
- Paralysis
- Malnutrition - Ca, vit D, protein/calorie, TPN
- Intestinal malabsorption (sprue, Crohn's, etc.)
- Gastrectomy
- Renal insufficiency
- Rheumatoid arthritis
- Multiple myeloma
- Mastocytosis
- Malignancies
- Chronic lung disease
- Alcoholism

Management

- Non-pharm options
  - Resistance and weight bearing exercise
    - Benefit on skeletal microarchitecture
  - Fall reduction
    - Balance programs – yoga and tai chi
    - Withdrawl of psychotropic meds
  - Counseling about cigarette smoking and excess EtOH use

Calcium and Vit D

- Postmenopausal women with osteoporosis
  - Ca 1000 to 1500 mg/day
  - Vit D 600 to 800 IU/day
- Only small reduction in fracture risk
  - Mostly in institutionalized elderly

So what are some good sources of dietary calcium?

Well Absorbed Dietary Sources of Calcium

- Plain low-fat yogurt 8oz → 448mg Ca
- Mozzarella 1.5oz → 333mg Ca
- 2% Low fat milk 1 cup → 293mg Ca
- Calcium fortified OJ → 261mg Ca
- Pink Salmon 3.0oz → 183mg Ca

N Engl J Med 2013;369:1537-43.

Table 3. Widely Available Calcium Supplements.

Formulation	Dose	Elemental Calcium Content	Comments
		percent	
Calcium carbonate	One or two 500-mg tablets taken orally two or three times daily with meals	40	Least expensive and most commonly used supplement; should be taken with meals, since acidity improves absorption; can cause constipation
Calcium citrate	One or two 950-mg or 1000-mg tablets taken orally two or three times daily	21	Less dependent on acidity for absorption, so it does not need to be taken with meals; may be used with agents for long-term gastric acid suppression
Calcium gluconate	500, 648, or 972 mg	9	Rarely used for fracture prevention
Calcium lactate	300 or 325 mg	13	Rarely used for fracture prevention
Bone meal, oyster shell, dolomite	Varies	30	Primarily contains calcium carbonate but may contain detectable lead and should be avoided during pregnancy

N Engl J Med 2013;369:1537-43

Pharmacologic Therapies

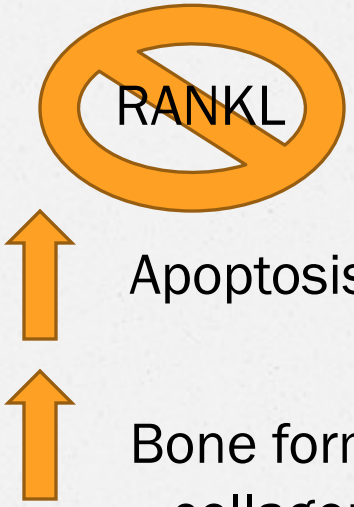
- Antiresorptive
  - Targeting osteoclast-mediated bone resoprtion
- Anabolic
  - Stimulating osteoblasts to form new bone

Table 5. Overview of FDA-Approved Medications for Osteoporosis

Drug (Brand)	Dosing	Route	Adverse Effects
Bisphosphonates			
Alendronate (Fosamax)	Treatment: 10 mg once daily or 70 mg once weekly Prevention: 5 mg once daily or 35 mg once weekly	Oral	Dyspepsia, abdominal pain, musculoskeletal pain
Ibandronate (Boniva)	Oral: 2.5 mg once daily or 150 mg once a month IV: 3 mg every 3 months	Oral, IV	Dyspepsia, back pain, musculoskeletal pain, headache, abdominal pain
Risedronate (Actonel, Atelvia)	IR: 5 mg once daily or 35 mg once weekly or 150 mg once a month DR: 35 mg once weekly	Oral	Rash, abdominal pain, dyspepsia, diarrhea, arthralgia
Zoledronic acid (Reclast)	5 mg once a year	IV	Acute reaction (flulike symptoms, fever, myalgia) may occur within 3 days of infusion; hypotension, fatigue, eye inflammation, nausea, vomiting, abdominal pain
Calcitonin			
Calcitonin (Fortical)	200 IU in 1 nostril daily alternating each day	Intranasal	Rhinitis, nasal irritation, dizziness, nasal dryness
Calcitonin (Miacalcin)	100 IU every other day 200 IU in 1 nostril daily alternating each day	SC, IM Intranasal	Injection site reactions, nausea, vomiting, abdominal cramping, flushing
Selective Estrogen Receptor Modulator			
Raloxifene (Evista)	60 mg once daily	Oral	VTE, arthralgia, leg cramps, flu syndrome, peripheral edema, hot flashes
Parathyroid Hormone Analogue			
Teriparatide (Forteo)	20 mcg once daily	SC	Transient hypercalcemia, nausea, rhinitis, arthralgia, pain
Monoclonal Antibody			
Denosumab (Prolia)	60 mg every 6 months	SC	Dermatitis, rash, mild bone/muscle pain, UTIs

DR: delayed-release; IM: intramuscular; IR: immediate-release; SC: subcutaneous; UTI: urinary tract infection; VTE: venous thromboembolism.
Source: Reference 7.

Estrogen Replacement



Apoptosis of osteoclasts

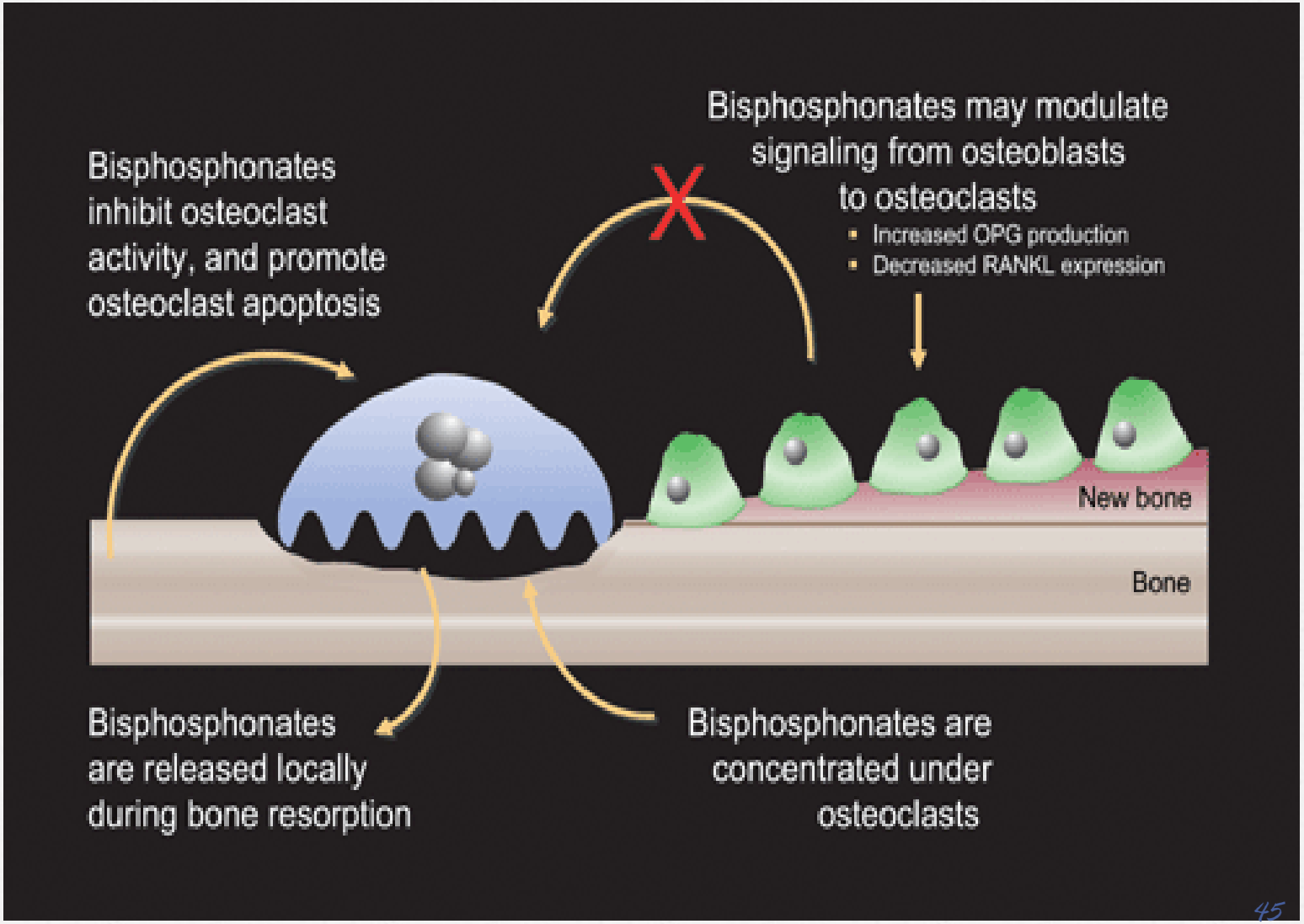
Bone formation → stimulating type 1 collagen synthesis by osteoblasts

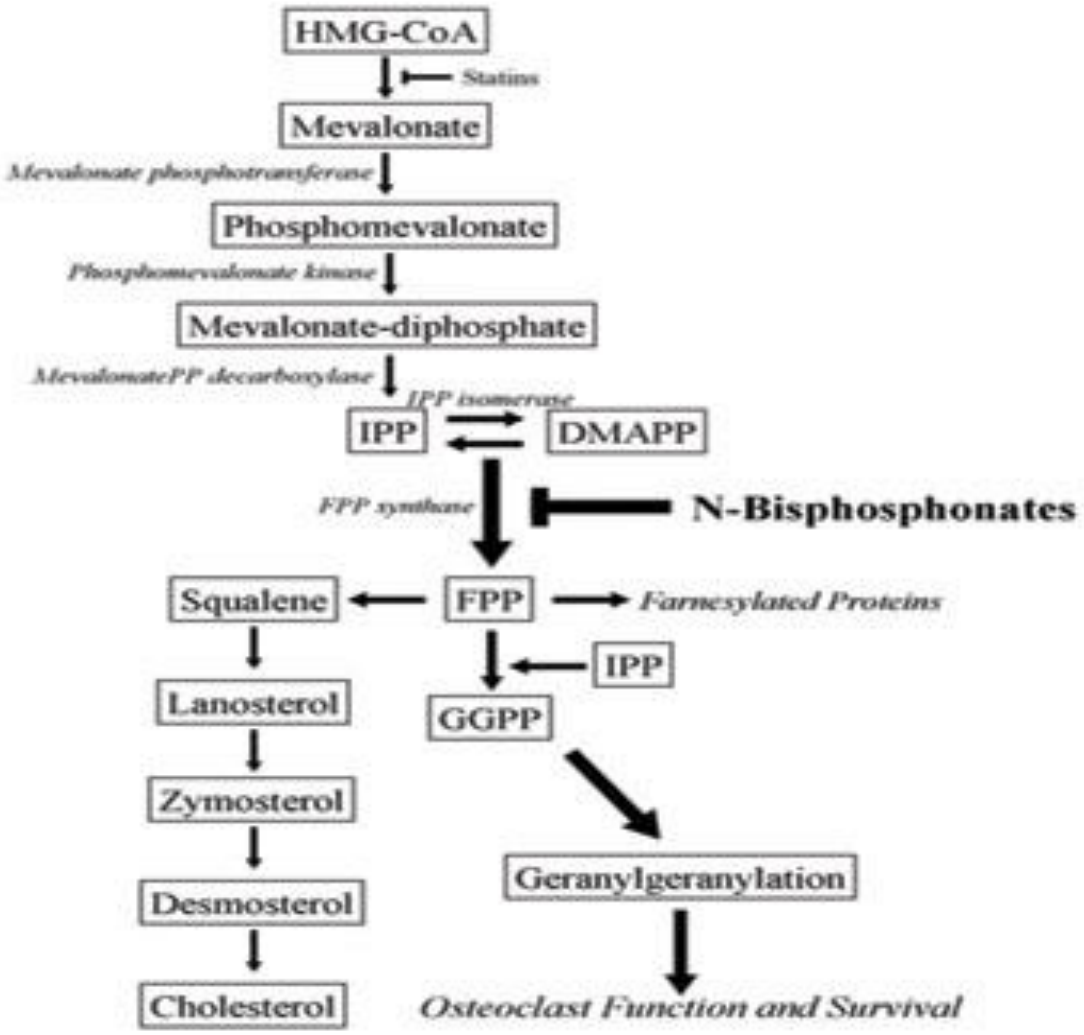
Estrogen and SERMs

- Low dose conjugated estrogens and ultra low dose estradiol
  - Breast ca, CVA, coronary and thrombotic risks
- Raloxifene – FDA approved
  - Decreases risk of vertebral fxs by 30%
  - No effect on nonvertebral or hip fxs

Bisphosphonates

- Oral and IV forms
- Majority of Rx for osteoporosis tx
- Generally safe
- Must have eGFR >35 ml/min and normal vitamin D level (otherwise can have significant hypoCa with BP tx)
- Mild hypoCa and muslce pain
- Esophagitis
- Two rare side effects
  - Atypical femoral neck fractures
  - Osteonecrosis of the jaw


Bisphosphonates may modulate signaling from osteoblasts to osteoclasts
Increased OPG production
Decreased RANKL expression
Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis
New bone
Bone
Bisphosphonates are released locally during bone resorption
Bisphosphonates are concentrated under osteoclasts


HMG-CoA
Statins
Mevalonate
Mevalonate phosphotransferase
Phosphomevalonate
Phosphomevalonate kinase
Mevalonate-diphosphate
MevalonatePP decarboxylase
IPP isomerase
IPP
DMAPP
FPP synthase
N-Bisphosphonates
Squalene
FPP
Farnesylated Proteins
IPP
Lanosterol
GGPP
Zymosterol
Geranylgeranylation
Desmosterol
Cholesterol
Osteoclast Function and Survival

- Oral Bisphosphonates (BPs)
  - Weekly doses (alendronate and risedronate)
  - Monthly doses (ibandronate and risendronate)
- IV BP
  - Zolendronate q1 year

Fracture Risk Reduction with Alendronate in Women with Osteoporosis: The Fracture Intervention Trial

We conclude that reductions in fracture risk during treatment with alendronate are consistent in women with existing vertebral fractures and those without such fractures but with bone mineral density in the osteoporotic range. Furthermore, reduction in risk is evident early in the course of treatment. This pooled analysis provides a more precise estimate of the antifracture efficacy of alendronate in women with osteoporosis than that in prior reports. (*J Clin Endocrinol Metab* 85: 4118–4124, 2000)

score of less than −2.5 at the femoral neck but without vertebral fracture. All analyses were prespecified in the data analysis plan.

The magnitudes of reduction of fracture incidence with alendronate were similar in both groups. The two groups were, therefore, pooled to obtain a more precise estimate of the effect of alendronate on relative risk of fracture (relative risk, 95% confidence interval): hip

alendronate are consistent in women with existing vertebral fractures and those without such fractures but with bone mineral density in the osteoporotic range. Furthermore, reduction in risk is evident early in the course of treatment. This pooled analysis provides a more precise estimate of the antifracture efficacy of alendronate in women with osteoporosis than that in prior reports. (*J Clin Endocrinol Metab* 85: 4118–4124, 2000)

The NEW ENGLAND JOURNAL of MEDICINE

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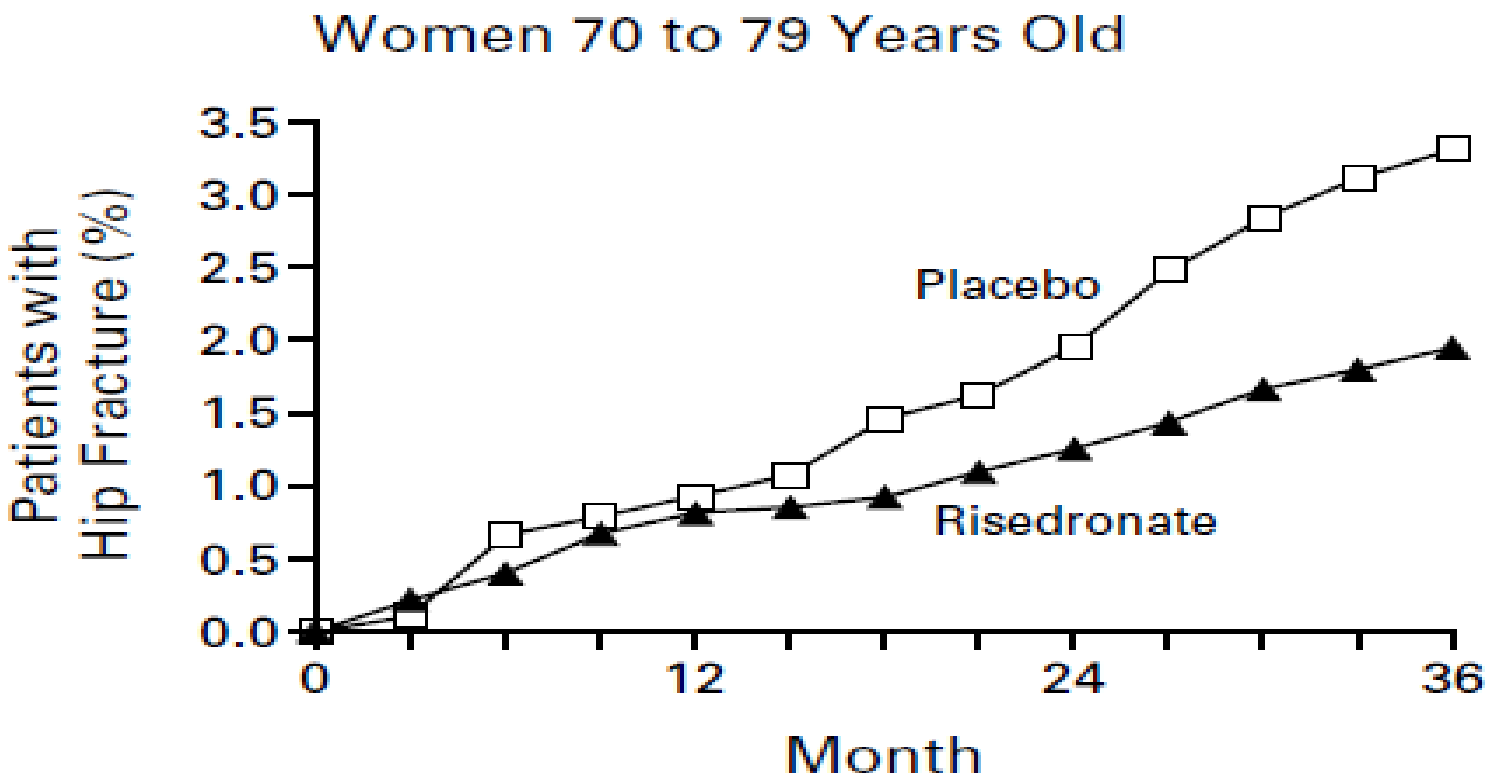


No. at Risk				
Risedronate	3624	3040	2681	2464
Placebo	1821	1526	1339	1210

- Low **adherence** to oral BPs
- Taken with a full glass of water
- **Empty** stomach
- **Up-right** x30 mins after
- Estimated that **<40%** of patients are still taking them after 1 year
- IV BPs – Zoledronic acid

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 3, 2007 VOL. 356 NO. 18

Once-Yearly Zoledronic Acid for Treatment

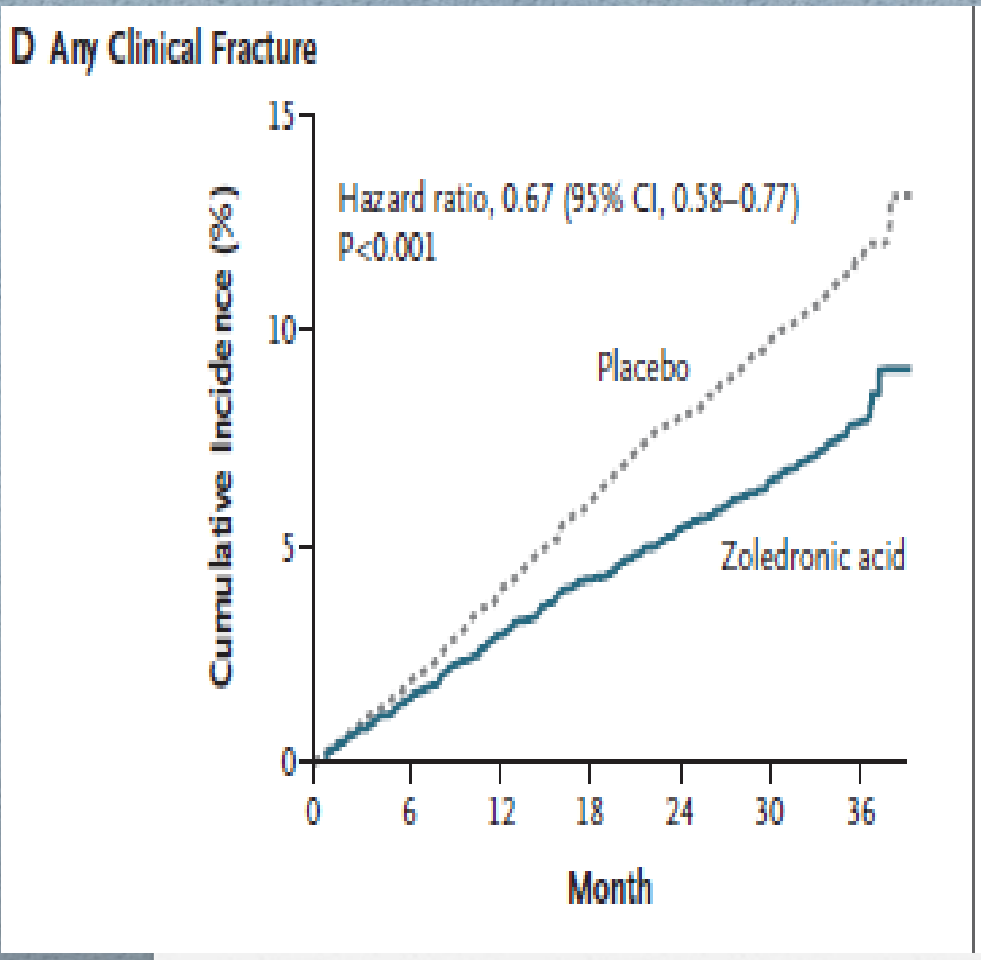
ABSTRACT

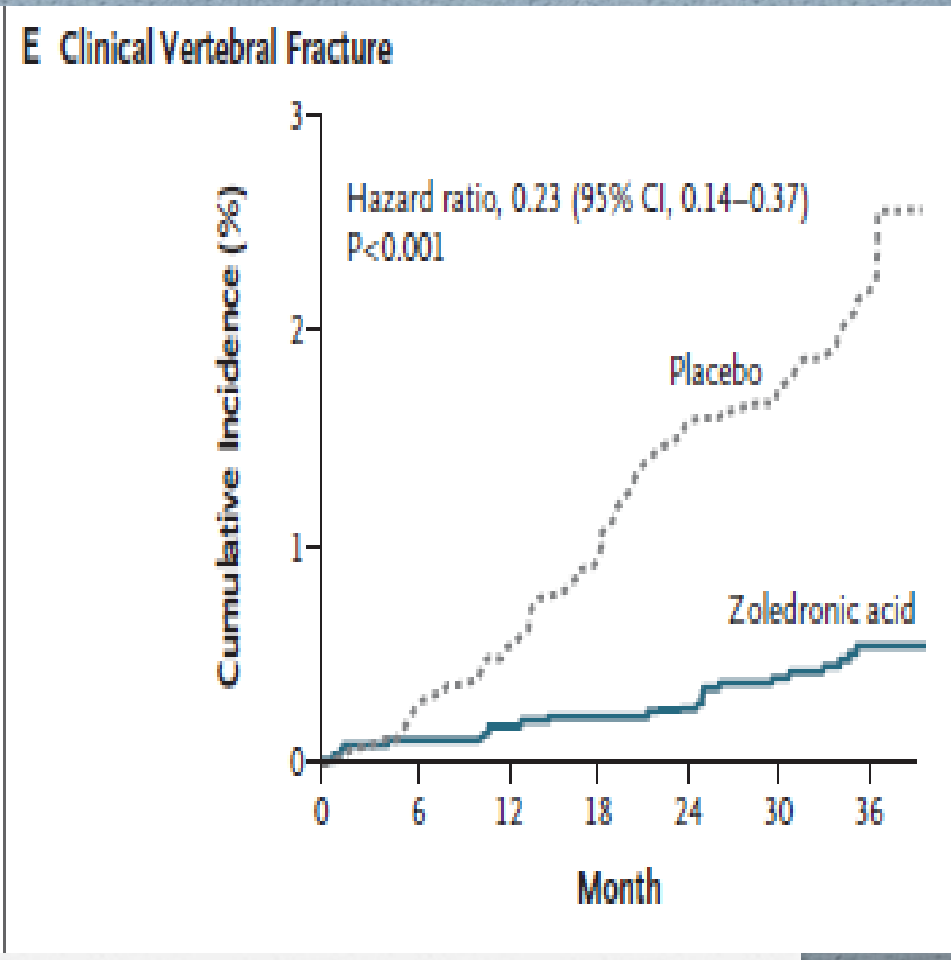
BACKGROUND

A single infusion of intravenous zoledronic acid decreases bone turnover and improves bone density at 12 months in postmenopausal women with osteoporosis. We assessed the effects of annual infusions of zoledronic acid on fracture risk during a 3-year period.

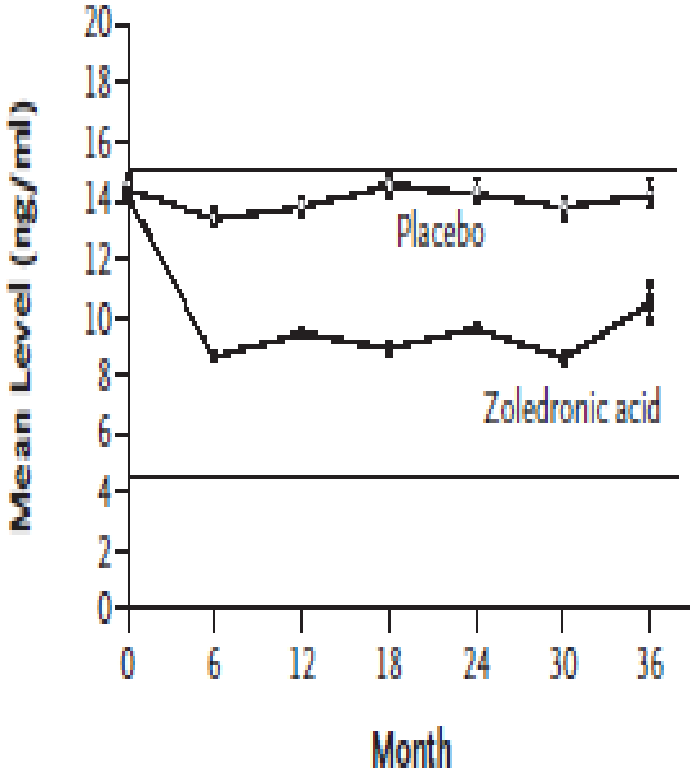
CONCLUSIONS

A once-yearly infusion of zoledronic acid during a 3-year period significantly reduced the risk of vertebral, hip, and other fractures. (ClinicalTrials.gov number, NCT00049829.)

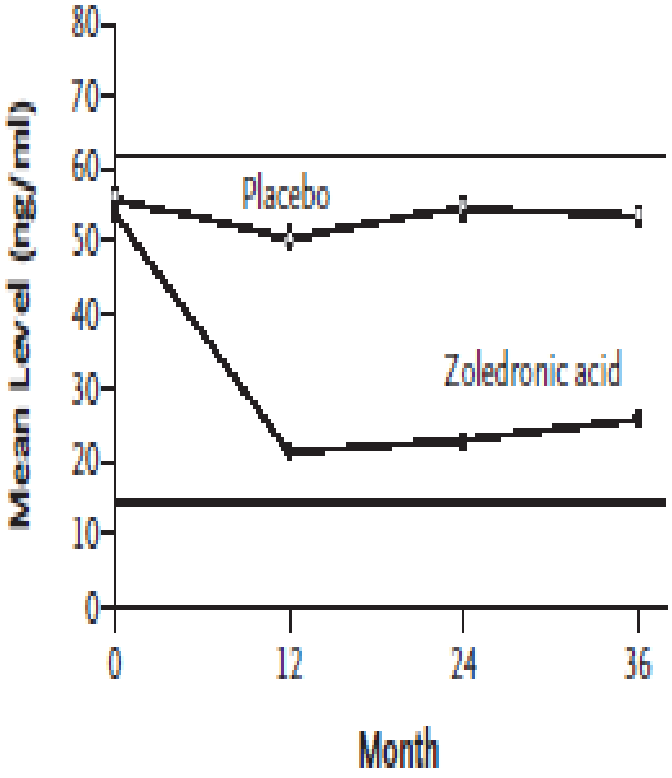

D Any Clinical Fracture
Cumulative Incidence (%)
15
10
5
0
Hazard ratio, 0.67 (95% CI, 0.58–0.77)
P<0.001
Placebo
Zoledronic acid
0
6
12
18
24
30
36
Month


E Clinical Vertebral Fracture
Cumulative Incidence (%)
3
2
1
0
Hazard ratio, 0.23 (95% CI, 0.14–0.37)
P<0.001
Placebo
Zoledronic acid
0
6
12
18
24
30
36
Month

E Serum Bone-Specific Alkaline Phosphatase



F Serum N-Terminal Propeptide

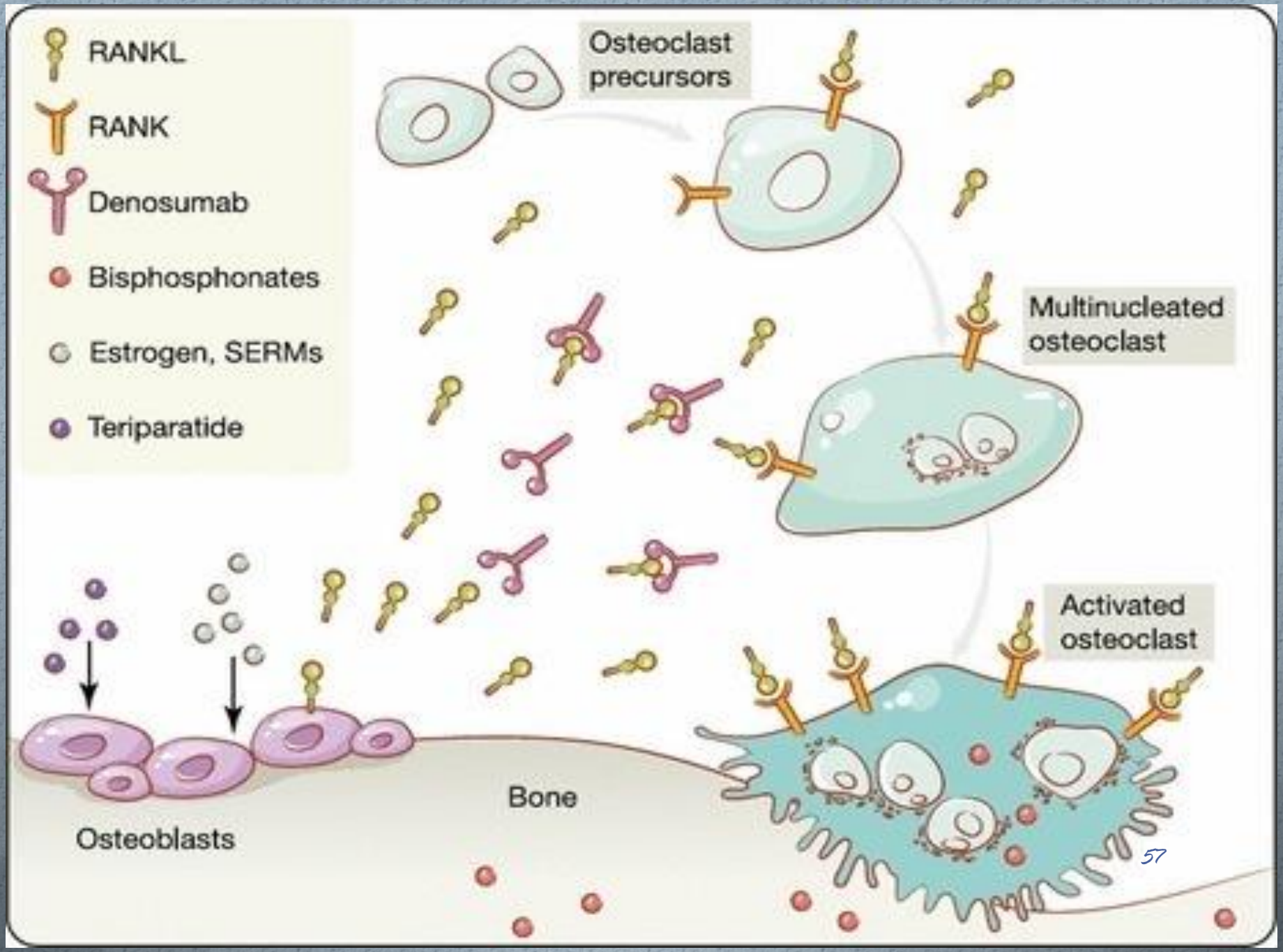


- Zolendronic acid can cause flu like sxs for up to 3 days after the first infusion in up to 1/3 of patients
  - Rarely after subsequent infusions
  - Give with acetaminophen – reduces by 50%

And now…
Return of our good ol' friends…
RANK and RANKL

Denosumab

- Biologic therapy
- Binds RANKL
  - Decreasing differentiation of osteoclasts
- Can be used with low eGFR
- Can, like BPs, cause atypical femur fxs and osteonecrosis of the jaw


RANKL
RANK
Denosumab
Bisphosphonates
Estrogen, SERMs
Teriparatide
Osteoclast precursors
Multinucleated osteoclast
Activated osteoclast
Bone
Osteoblasts

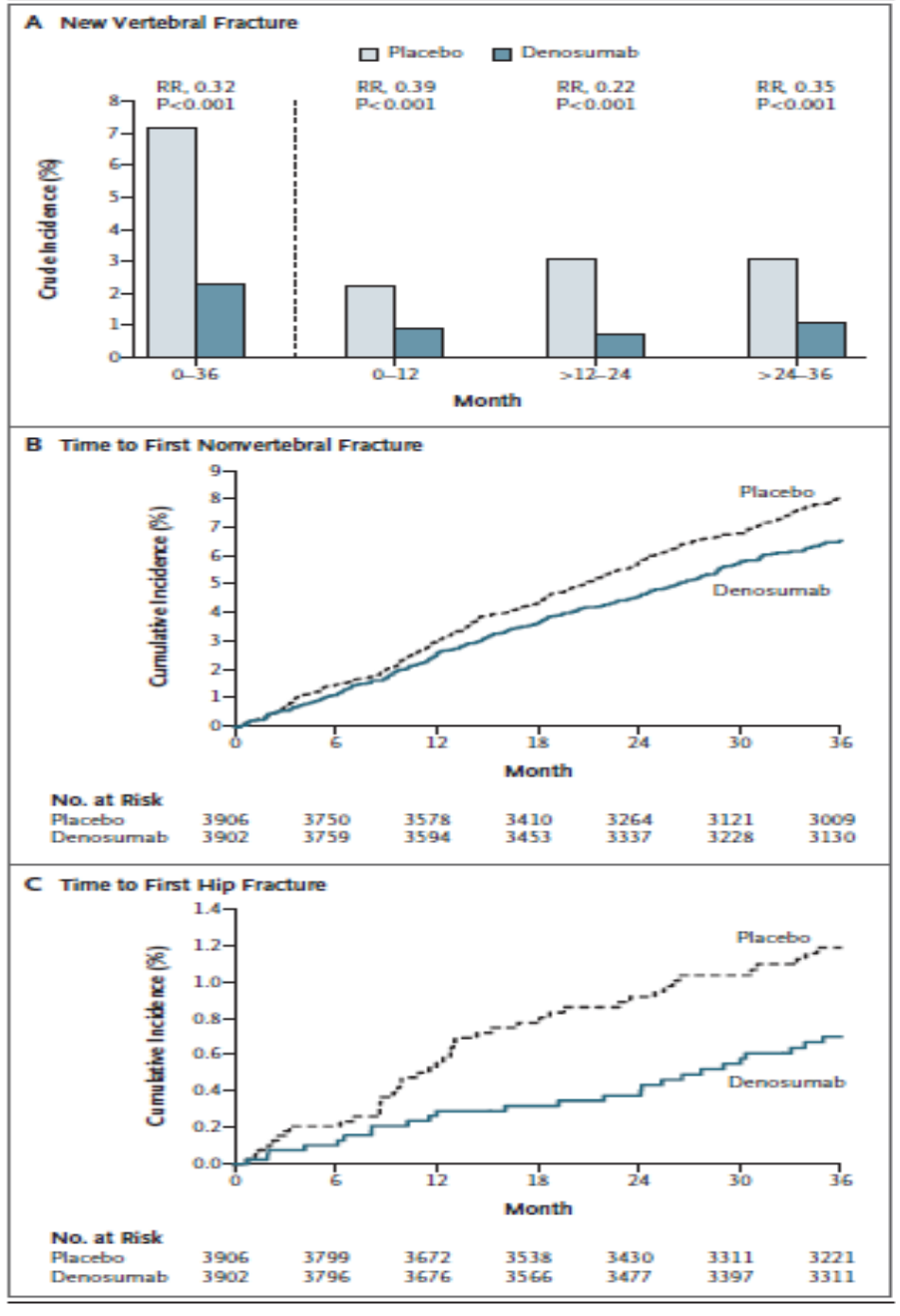
ORIGINAL ARTICLE

Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis

CONCLUSIONS

Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis. (ClinicalTrials.gov number, NCT00089791.)

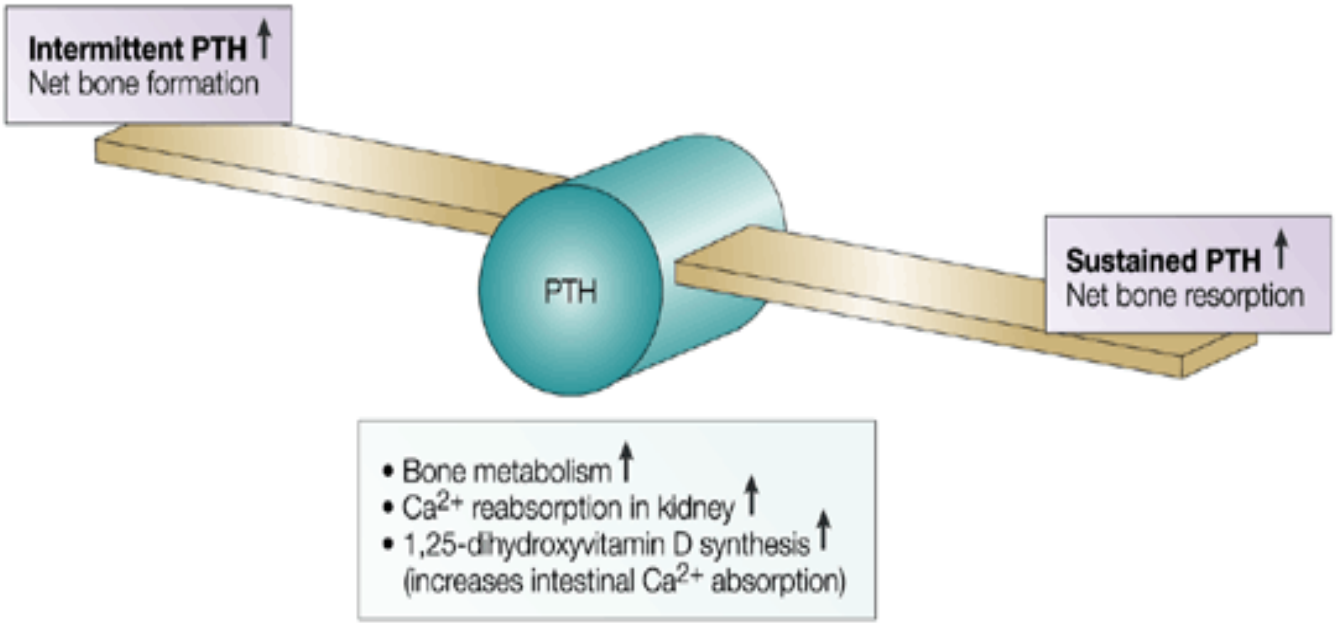
N ENGL J MED 361;8 NEJM.ORG AUGUST 20, 2009


A New Vertebral Fracture
Placebo
Denosumab
RR, 0.32
P<0.001
RR, 0.39
P<0.001
RR, 0.22
P<0.001
RR, 0.35
P<0.001
Crude Incidence (%)
0–36
0–12
>12–24
>24–36
Month
B Time to First Nonvertebral Fracture
Cumulative Incidence (%)
Placebo
Denosumab
Month
No. at Risk
Placebo 3906 3750 3578 3410 3264 3121 3009
Denosumab 3902 3759 3594 3453 3337 3228 3130
C Time to First Hip Fracture
Cumulative Incidence (%)
Placebo
Denosumab
Month
No. at Risk
Placebo 3906 3799 3672 3538 3430 3311 3221
Denosumab 3902 3796 3676 3566 3477 3397 3311

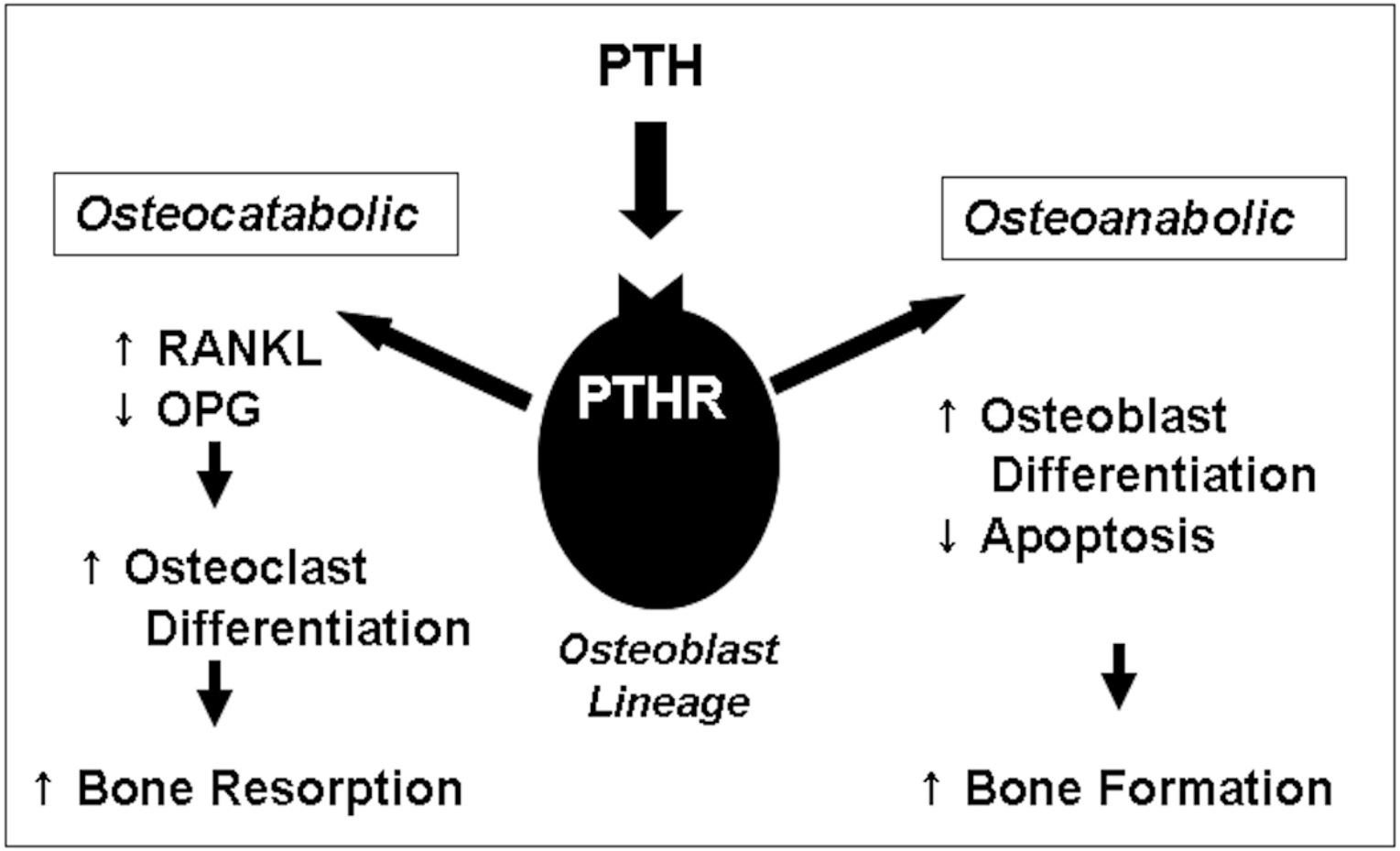
Teriparatide (PTH 1-34)

- Anabolic agent
  - Increasing bone formation
- Daily self injection
  - Approved for up to 2 years
- After discontinuation – benefit is quickly lost
  - Should be followed by an antiresorptive agent
- BBW → Osteosarcoma

- Teriparatide is amino acid sequence 1-34 of the human PTH molecule
- Chronically elevated PTH leads to bone resorption
- Intermittent exposure to PTH → activate osteoblasts more than osteoclasts
- Net effect of once daily teriparatide is stimulation of new bone formation



Nature Reviews | Drug Discovery


PTH
Osteocatabolic
Osteoanabolic
↑ RANKL
↓ OPG
PTHR
↑ Osteoblast Differentiation
↓ Apoptosis
↑ Osteoclast Differentiation
Osteoblast Lineage
↑ Bone Resorption
↑ Bone Formation

Curr Osteoporos Rep (2014) 12:385–395

Based on what we now know, in patients previously treated with bisphosphonates who suffer hip fractures or who have very low or declining hip BMD, strong consideration should be given to starting TPTD and continuing a potent antiresorptive agent (possibly switching to zoledronic acid or denosumab) to improve hip BMD and strength quickly. Furthermore, in treatment naïve individuals with very severe osteoporosis, such as those with spine and hip fractures, combination therapy with TPTD and denosumab or TPTD followed by combination treatment with a potent bisphosphonate or denosumab should be considered to maximize early increases in BMD throughout the skeleton (Cosman BoneKEy Rep 3, 2014)[1].

The NEW ENGLAND JOURNAL of MEDICINE

CONCLUSIONS

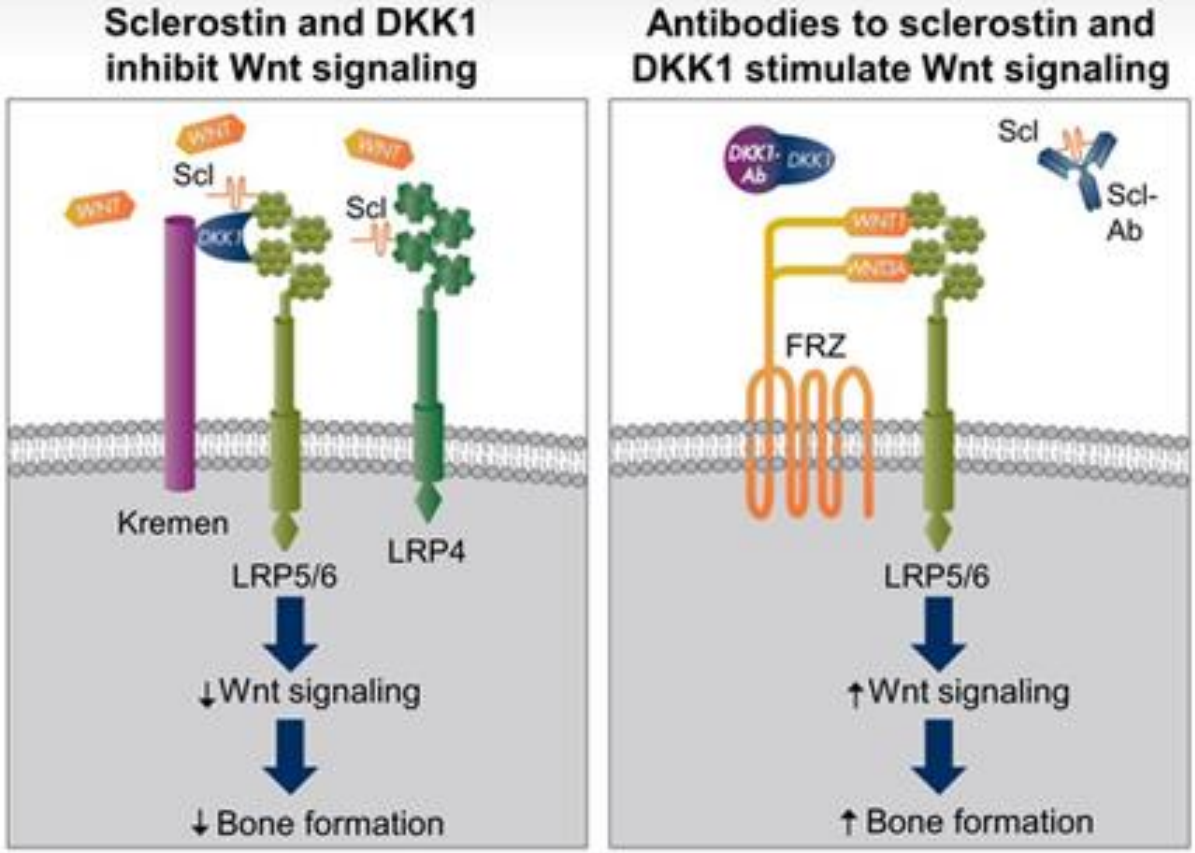
After one year of parathyroid hormone (1–84), densitometric gains appear to be maintained or increased with alendronate but lost if parathyroid hormone is not followed by an antiresorptive agent. These results have clinical implications for therapeutic choices after the discontinuation of parathyroid hormone.

N ENGL J MED 353;6 WWW.NEJM.ORG AUGUST 11, 2005

On the Horizon…

- Anti-sclerostin antibody → Romosozumab
  - Sclerostin – BMP antagonist; binding to LRP5/6 receptors and inhibiting the Wnt signaling pathway → decreased bone formation
  - Increased BD more than BP and teriparatide
  - Mild injection SEs
  - Monthly injections
  - On the market 2017…

Wnt Signaling Pathway



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D

Table 1. Risk of Atypical Femoral Fracture Associated with Bisphosphonate Use during the 3 Years (2005–2008) Preceding the Fracture.*

Variable	No. of Women	Cases of Atypical Fracture		Age-Adjusted Relative Risk (95% CI)	Age-Adjusted Absolute Risk (95% CI)
		No. of Atypical Fracture Cases	Crude Incidence *no./10,000 patient-yr*		
Bisphosphonate use					
Never	1, 437,820	13	0.09	1.0 (reference)	
Ever	83,311	46	5.5	47.3 (25.6–87.3)	0.0005 (0.0004–0.0007)
Duration of use					
<1.0 yr	15,672	3	1.9	18.4 (5.3–64.3)	0.0002 (0.0000–0.0004)
1.0–1.9 yr	21,406	4	1.9	17.0 (5.7–50.7)	0.0002 (0.0000–0.0004)
≥2.0 yr	46,233	39	8.4	67.0 (35.8–125.8)	0.0008 (0.0006–0.0011)
Time since last use					
<1.0 yr	83,311	42	5.0	42.9 (22.9–80.4)	0.0005 (0.0004–0.0007)
1.0–1.9 yr	70,036	1	0.1	3.5 (1.0–11.9)	<0.0001 (0.0000–0.0000)
≥2.0 yr	75,583	3	0.4	3.2 (1.0–10.1)	<0.0001 (0.0000–0.0001)

* CI denotes confidence interval.

n engl j med 364;18 nejm.1732 org may 5, 2011

Drug Holiday

- Temporary discontinuation for up to 5 years
- Benefits are generally retained for up to this amount of time
- Holiday only in those who are considered low risk
  - BMD and vertebral fx status
- Reinitiate tx no longer than 5 yrs after dc

Conclusions Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.

Trial Registration clinicaltrials.gov Identifier: NCT 00398931

JAMA. 2006;296:2927-2938 www.jama.com

Author Affiliations and Members of the FLEX Research Group are listed at the end of this article.
Corresponding Author: Dennis M. Black, PhD, University of California, San Francisco, Suite 5700, Lobby 4, 185 Berry St, San Francisco, CA 94107 (dblack@psg.ucsf.edu).

Summary

- Osteoporosis and fractures are common
- Phases of bone loss in menopause
  - Accelerated and Continuous
- Pathophysiology players in the game of osteoporosis
  - RANKL and RANK
  - OPG
  - RANKL/OPG ratios
  - Osteoblasts and Osteoclasts
  - New kid Sclerostin
- When to treat
  - T score of -2.5 or less,
  - hx of vertebral or hip fracture
  - FRAX score indicates increased fracture risk
- Non Pharm therapies
- Ca and Vit D
- Anabolic and Anti-resorptive therapies
- Biologic therapies
- Significant side effects
- Possibility of drug holidays

Getting old isn't all bad…

With Age comes skills

It's called MultiTasking

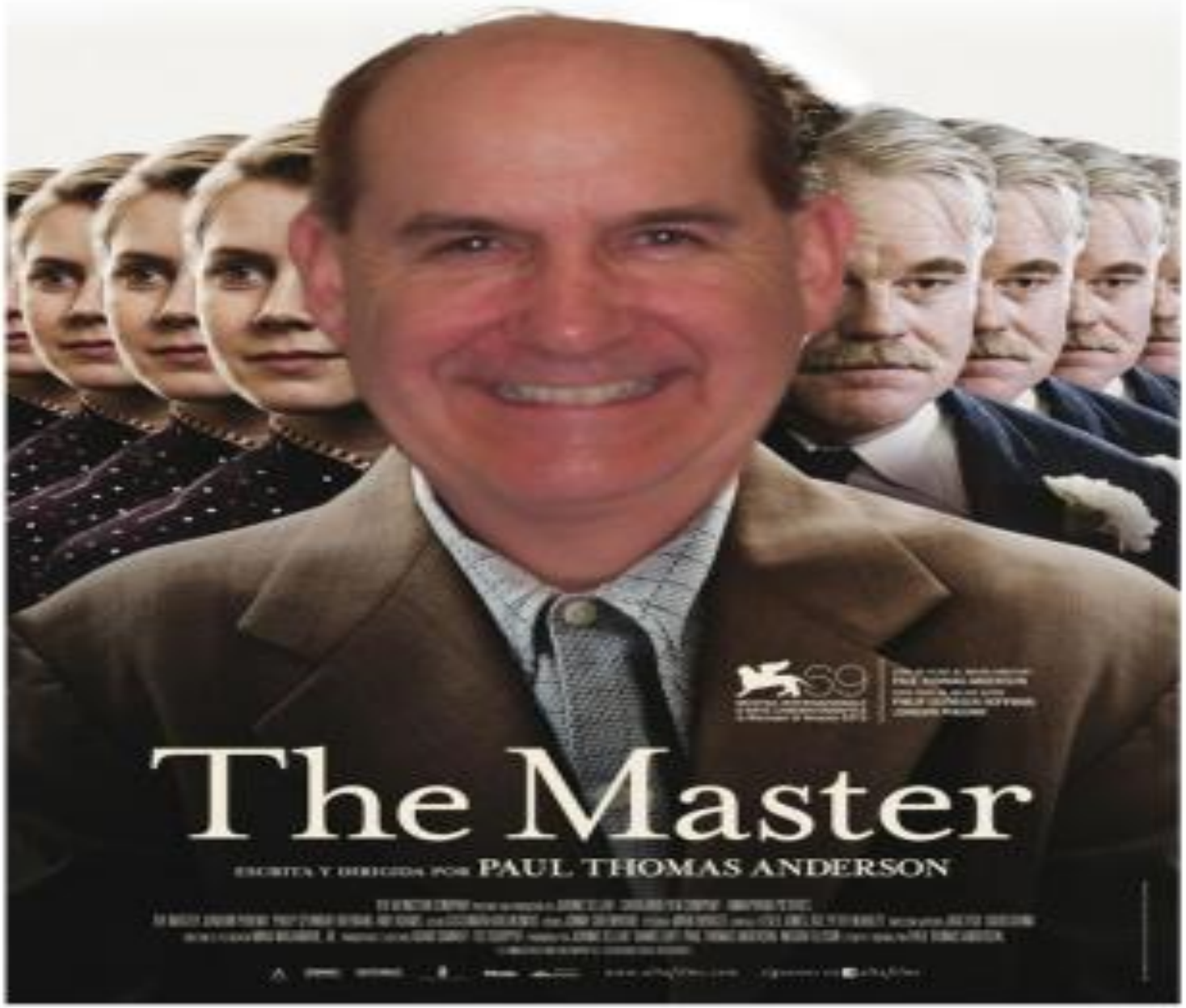
I CAN

LAUGH, COUGH,

SNEEZE, AND PEE ALL

AT THE SAME TIME.

Special thanks to Dr. Robert Hawkins…



APPENDIX

Osteoporos Int. 2014 Aug;25(8):2047-56. doi: 10.1007/s00198-014-2732-3. Epub 2014 May 7.

Calcium supplement intake and risk of cardiovascular disease in women.

Paik JM[1], Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, Taylor EN.

Author information

Open/close author information list

Abstract

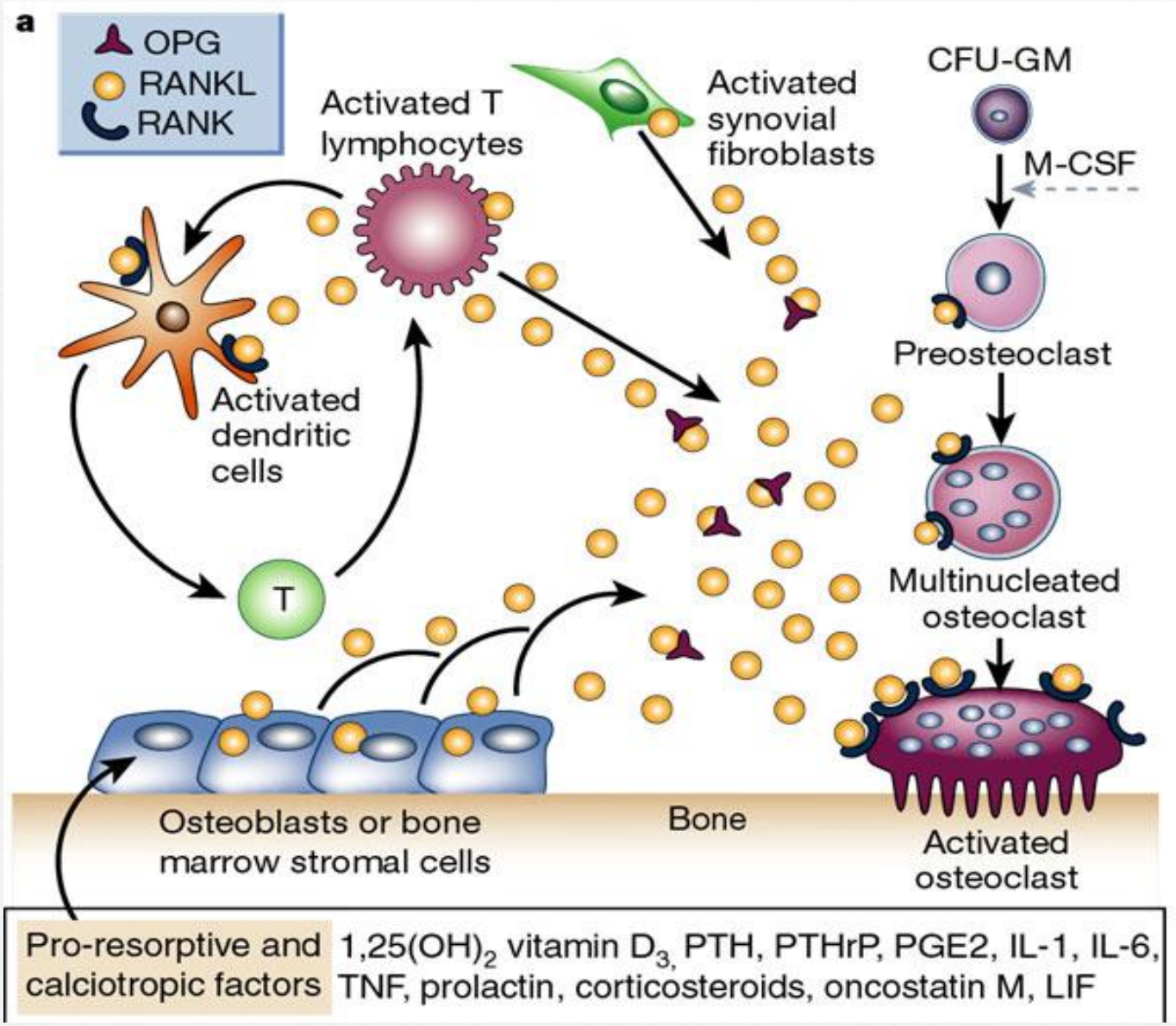
Some recent reports suggest that calcium supplement use may increase risk of cardiovascular disease. In a prospective cohort study of 74,245 women in the Nurses' Health Study with 24 years of follow-up, we found no independent associations between supplemental calcium intake and risk of incident coronary heart disease (CHD) and stroke.

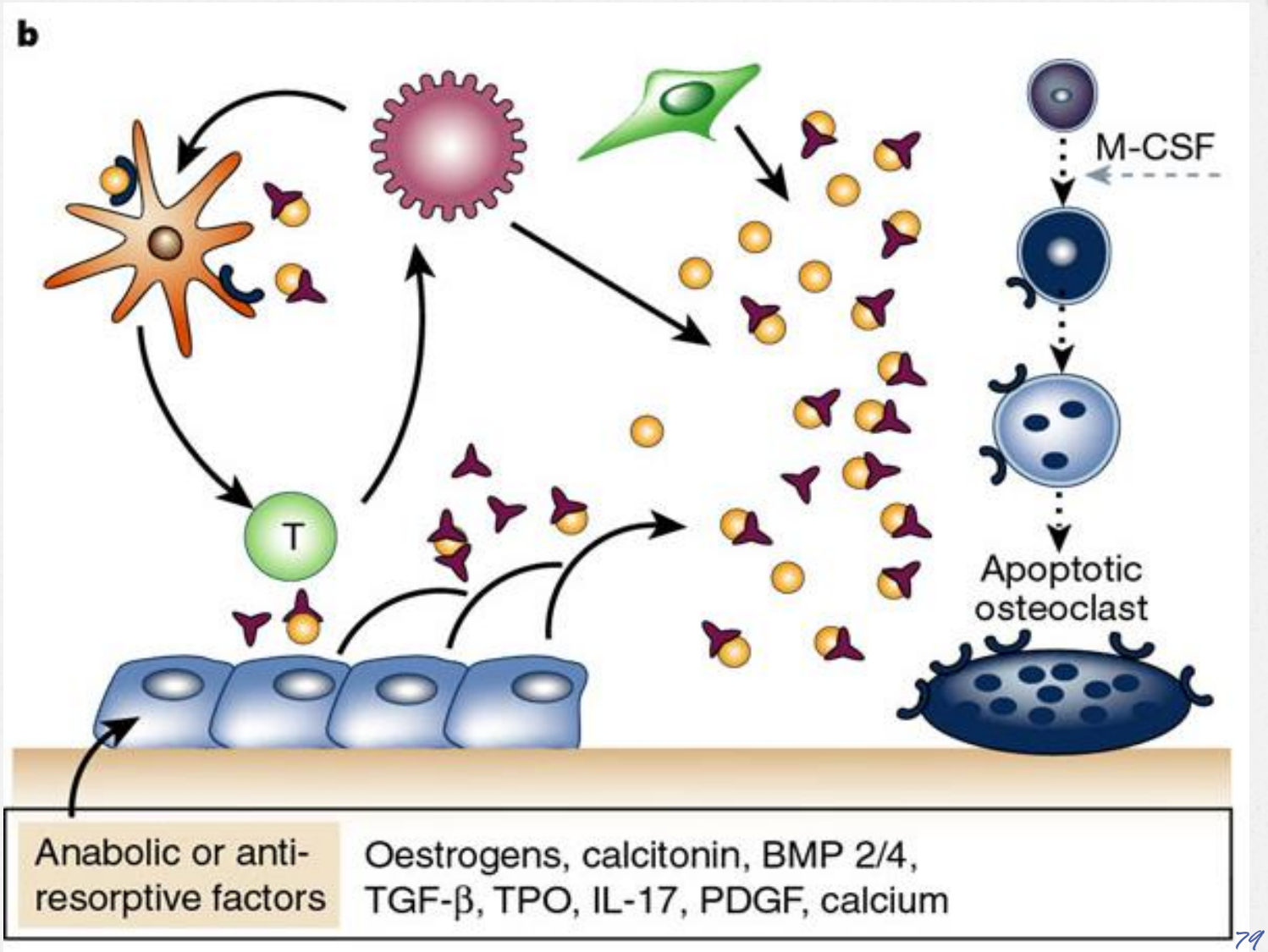
INTRODUCTION: Some recent reports suggest that calcium supplements may increase cardiovascular disease (CVD) risk. The objective was to examine the independent associations between calcium supplement use and risk of CVD.

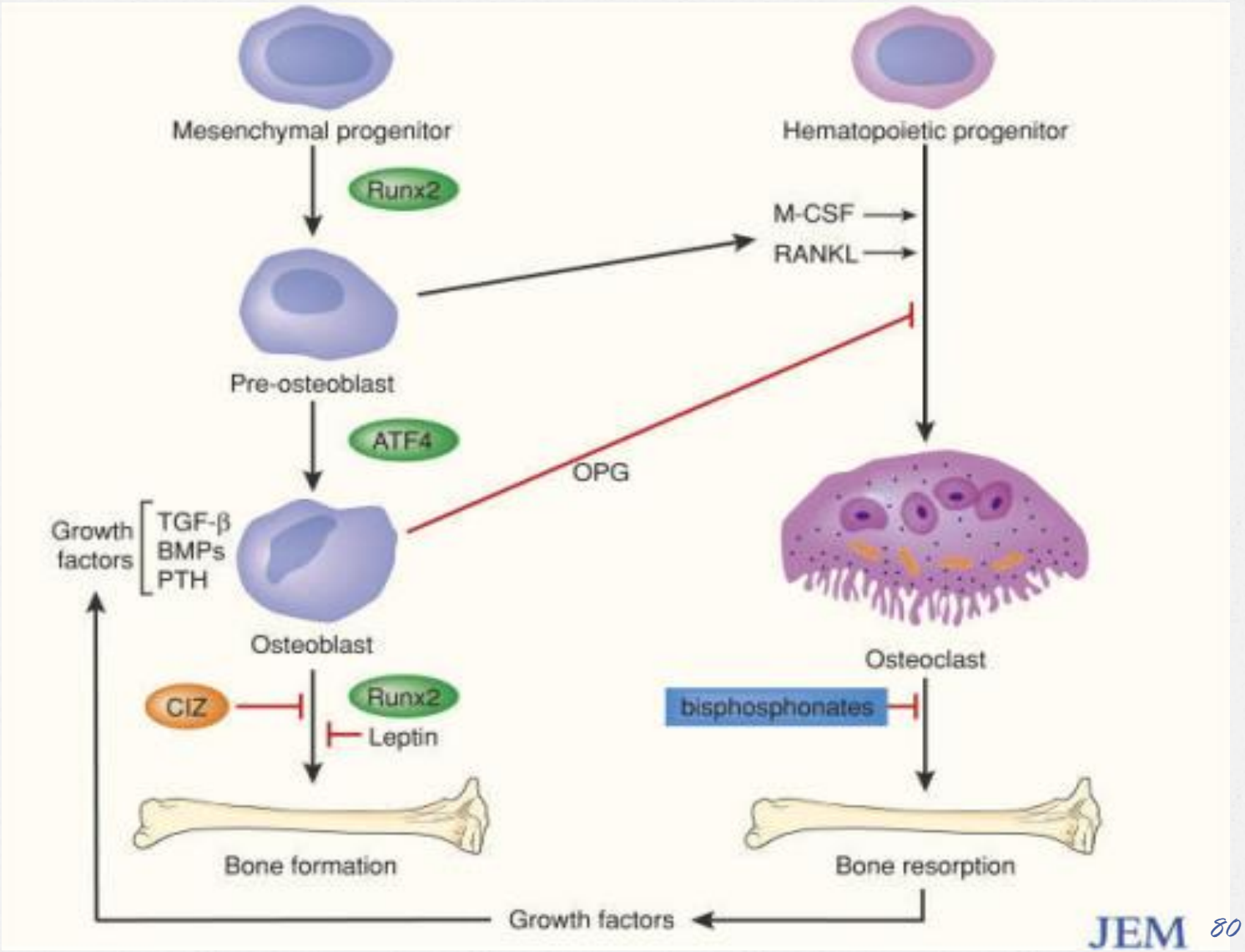
METHODS: We conducted a prospective cohort study of supplemental calcium use and incident CVD in 74,245 women in the Nurses' Health Study (1984-2008) free of CVD and cancer at baseline. Calcium supplement intake was assessed every 4 years. Outcomes were incident CHD (nonfatal or fatal MI) and stroke (ischemic or hemorrhagic), confirmed by medical record review.

RESULTS: During 24 years of follow-up, 4,565 cardiovascular events occurred (2,709 CHD and 1,856 strokes). At baseline, women who took calcium supplements had higher levels of physical activity, smoked less, and had lower trans fat intake compared with those who did not take calcium supplements. After multivariable adjustment for age, body mass index, dietary calcium, vitamin D intake, and other CVD risk factors, the relative risk of CVD for women taking >1,000 mg/day of calcium supplements compared with none was 0.82 (95% confidence interval [CI] 0.74 to 0.92; p for trend <0.001). For women taking >1,000 mg/day of calcium supplements compared with none, the multivariable-adjusted relative risk for CHD was 0.71 (0.61 to 0.83; p for trend < 0.001) and for stroke was 1.03 (0.87 to 1.21; p for trend = 0.61). The relative risks were similar in analyses limited to non-smokers, women without hypertension, and women who had regular physical exams.

CONCLUSIONS: Our findings do not support the hypothesis that calcium supplement intake increases CVD risk in women.


a
OPG
RANKL
RANK
Activated T lymphocytes
Activated synovial fibroblasts
CFU-GM
M-CSF
Preosteoclast
Activated dendritic cells
T
Multinucleated osteoclast
Osteoblasts or bone marrow stromal cells
Bone
Activated osteoclast
Pro-resorptive and calciotropic factors
1,25(OH)2 vitamin D3, PTH, PTHrP, PGE2, IL-1, IL-6, TNF, prolactin, corticosteroids, oncostatin M, LIF


b
M-CSF
T
Apoptotic
osteoclast
Anabolic or anti-
resorptive factors
Oestrogens, calcitonin, BMP 2/4,
TGF-β, TPO, IL-17, PDGF, calcium


Mesenchymal progenitor
Runx2
Pre-osteoblast
ATF4
Growth factors
TGF-β
BMPs
PTH
Osteoblast
CIZ
Runx2
Leptin
Bone formation
Hematopoietic progenitor
M-CSF
RANKL
OPG
Osteoclast
bisphosphonates
Bone resorption
Growth factors

JEM

Table 2. Well-Absorbed Dietary Sources of Calcium.*

Type of Food	Serving Size	Elemental Calcium per Serving	Calories per Serving
		mg	*kcal*
Dairy products			
Plain low-fat yogurt	8.0 oz	448	154
Low-fat yogurt with fruit	8.0 oz	384	238
Mozzarella, part skim milk	1.5 oz	333	108
Cheddar cheese	1.5 oz	307	171
2% Low-fat milk	1 cup	293	122
Low-fat cottage cheese	1 cup	206	194
Fruits and vegetables			
Calcium-fortified orange juice	6.0 oz	261	88
Raw kale	1 cup	100	33
Raw bok choy	1 cup	74	9
Raw broccoli	1 cup	43	31
Canned fish			
Sardines	3.0 oz	325	177
Pink salmon	3.0 oz	183	110
Grains			
Fortified, ready-to-eat cereals	1 cup	100–1333	100–160
Fortified, cooked oat cereals	1 cup	187	159
Commercially prepared white or wheat bread	1 slice	30–73	69–74

* These foods contain low levels of oxalic and phytic acid. Data are from the National Nutrient Database for Standard Reference of the U.S. Department of Agriculture.[7]

81

N Engl J Med 2013;369:1537-43.

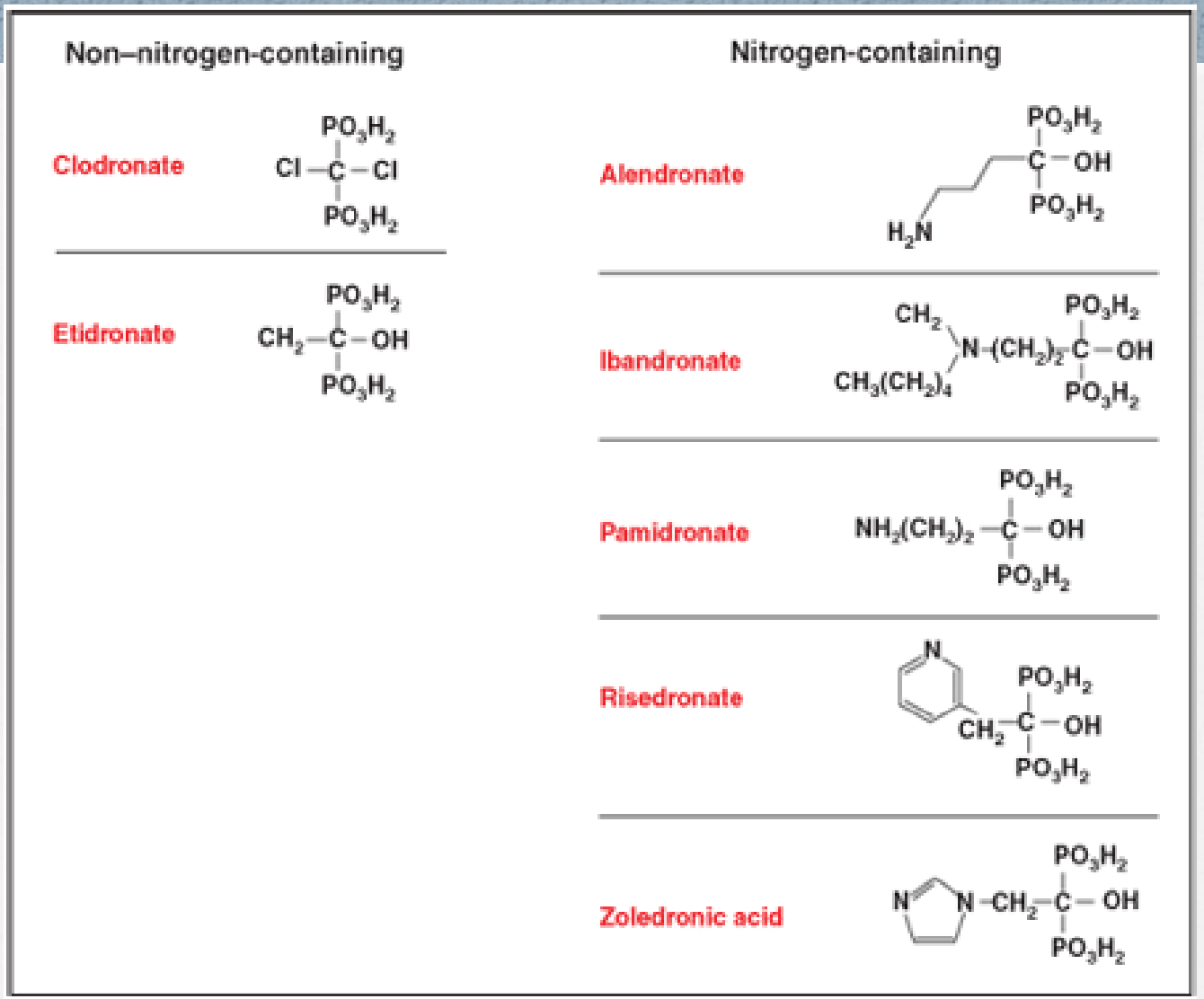
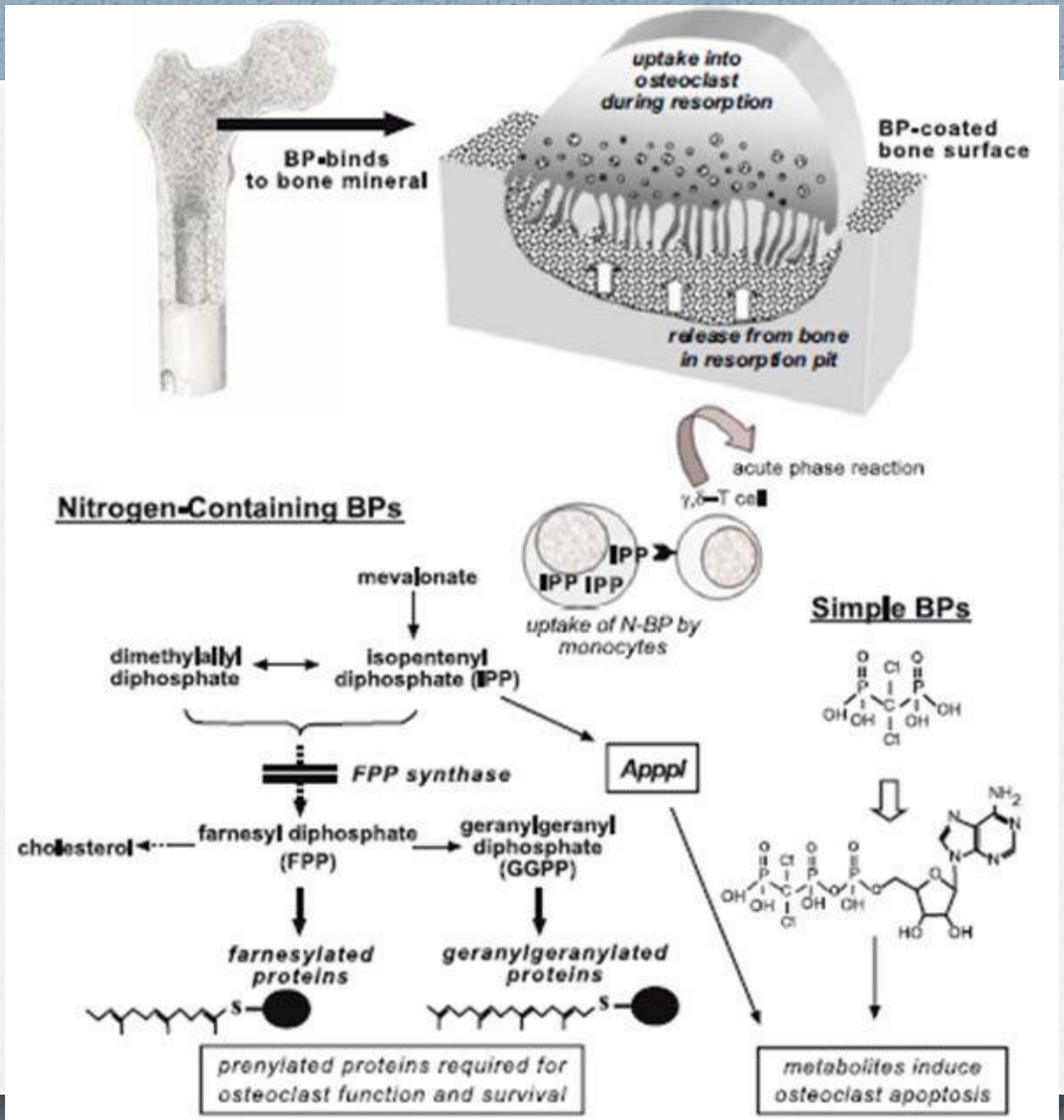


Figure 4: Bisphosphonate Structure—Bisphosphonates are structurally related to the mineralized bone matrix component pyrophosphate and belong to two general classes. The more potent nitrogen-containing bisphosphonates possess one or more nitrogen atoms in their variable side chains around the central carbon atom. Adapted from Reszka et al.[38]


BP binds to bone mineral
uptake into osteoclast during resorption
BP-coated bone surface
release from bone in resorption pit
acute phase reaction
γ,δ-T cell
IPP
IPP IPP
uptake of N-BP by monocytes
Nitrogen-Containing BPs
mevalonate
dimethylallyl diphosphate
isopentenyl diphosphate (IPP)
FPP synthase
ApppI
Simple BPs
cholesterol
farnesyl diphosphate (FPP)
geranylgeranyl diphosphate (GGPP)
farnesylated proteins
geranylgeranylated proteins
prenylated proteins required for osteoclast function and survival
metabolites induce osteoclast apoptosis

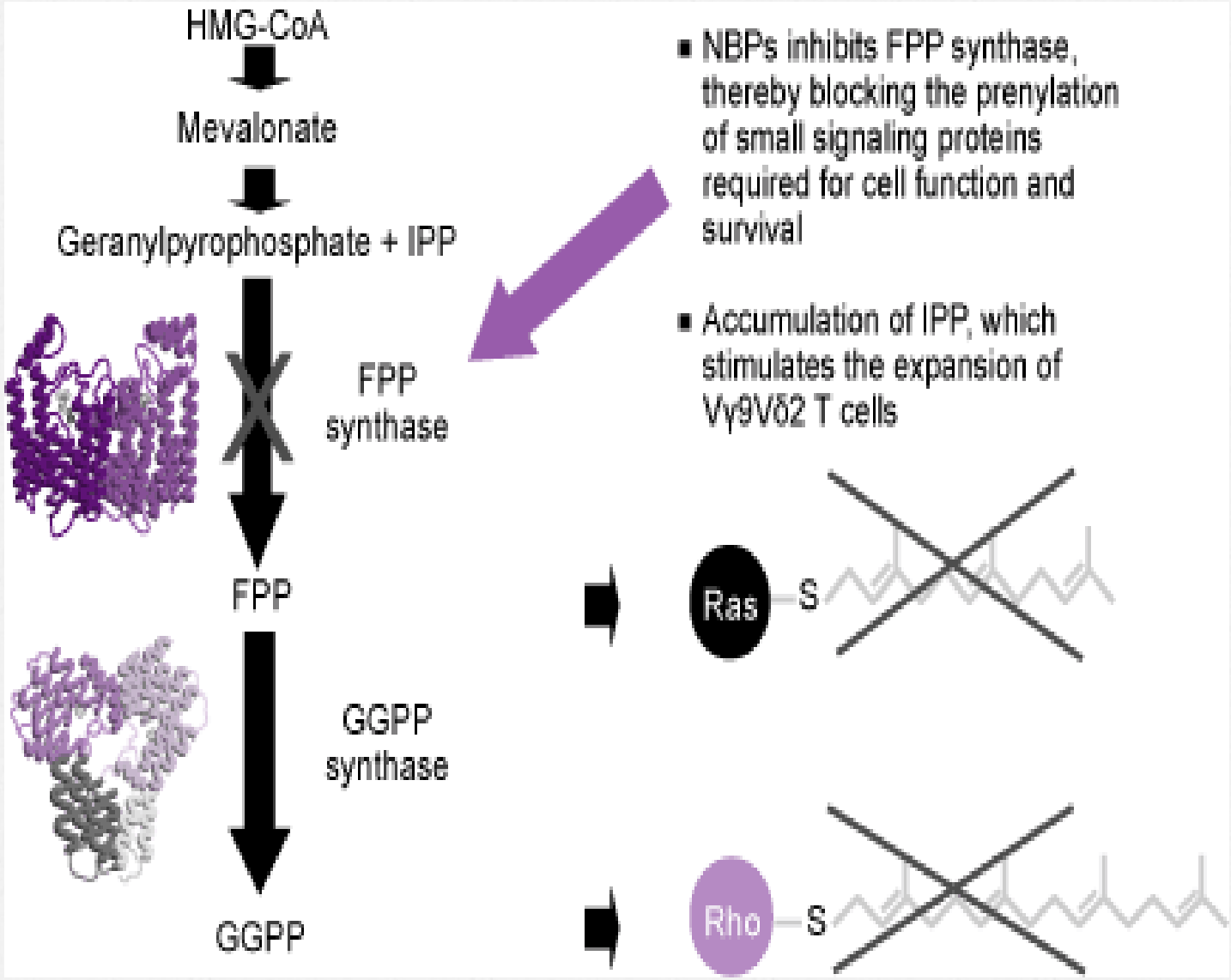

HMG-CoA
Mevalonate
Geranylpyrophosphate + IPP
FPP synthase
FPP
GGPP synthase
GGPP
NBPs inhibits FPP synthase, thereby blocking the prenylation of small signaling proteins required for cell function and survival
Accumulation of IPP, which stimulates the expansion of Vγ9Vδ2 T cells
Ras
S
Rho
S

TABLE 4. Number needed to treat with alendronate for 5 yr to prevent selected types of fracture

Fracture class	Women with existing vertebral fracture (Vertebral Fracture Arm)	Women without vertebral fracture and T score <-2.5 (Clinical Fracture Arm/low BMD)
Any radiologic vertebral	8	29
Any clinical	13	11
Any nonvertebral	21	12
Hip	46	66

TABLE 3. RR of alendronate *vs.* placebo in combined osteoporotic group (existing vertebral fracture at baseline or femoral neck T score of -2.5 or less)

Fracture class	RR (95% CI)	*P*
Radiologic vertebral	0.52 (0.42, 0.66)	<0.001
Multiple vertebral (radiologic)	0.13 (0.07, 0.25)	<0.001
Clinical vertebral	0.55 (0.36, 0.82)	0.003
Any clinical	0.70 (0.59, 0.82)	<0.001
Nonvertebral	0.73 (0.61, 0.87)	<0.001
Nonvertebral (osteoporotic)	0.64 (0.51, 0.80)	0.002
Hip	0.47 (0.26, 0.79)	0.005
Wrist	0.70 (0.49, 0.98)	0.038

Case 1

- 38 year old female with family history of mother with osteoporosis (mother just had hip fracture at age 68)
- She does not have prior steroid use, PPI use, rheumatoid arthritis, tobacco or alcohol
- She had fracture of clavicle during high impact motor vehicle accident
- DEXA scan was done after she requested it when her mother had recent fracture.
- Z score was -2.7
- What is the next step?

- Check for causes of low bone density
  - Check routine labs including CMP and 25-OH Vit D.
  - Check urinary calcium excretion
    - Can use low dose hydrochlorthiazide if high
  - Check for problems with absorption
    - Such as IBD or Celiac Disease
  - Consider 24 hour urine cortisol if cushinoid

Case 2

- 41 year old premenopausal female with history of SLE who has been on long courses of steroids and has had hip fracture after fall from standing position a year ago. She has chronically been on PPI for GI prophylaxis.
- She does not have family history of fracture/osteoporosis or rheumatoid arthritis
- Denies EtOH or tobacco use
- Labs: creatinine 0.9, Calcium normal, 25-OH Vit D 15
- DEXA scan with Z score of -3.6 at spine and -3.4 at hip.
- What are the next steps?

- Replace Vitamin D
  - 50,000 units weekly for 8-12 weeks, then 1000-2000 units/day
- Advise Calcium 1000-1400 mg daily (supplement + diet)
- Teriparatide may be worth considering as initial treatment to increase bone density given several fractures

Case 3

- 82 year old male with end stage kidney disease with osteoporosis with T score of -3.2 at lumbar spine and -2.9 at femoral neck.
- He has kyphosis with vertebral compression fractures on x-ray of thoracic spine.
- Estimated GFR 22, 25-OH-Vit D 40, calcium normal, PTH mildly elevated.
- What is the treatment choice?

- Denosumab (Prolia)
- Cannot use bisphosphonates given low eGFR.
- Avoid Teriparatide given elevated PTH
- For men, in general would be worth to check testosterone level and consider replacement therapy.