Managing Osteoporosis and Reducing Fractures

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My goals:

1. The key messages are:
   - No falling!
   - Vitamin D is sometimes needed
   - Practice, practice, practice (i.e. exercise)
2. Use of bisphosphonates for 5 years and then reassess
   - Know when to use
   - Know what to look out for
3. Consider options beyond bisphosphonates
   - Combination therapy
   - Biologics

USPSTF Guidelines for screening

Screening women for osteoporosis, 2 year interval (Grade B, 100% covered by ALL plans)

Women ≥ 65 years

Women ≤ 60 years whose 10 year fracture risk ≥ 65 year old white women without RF

Screening men for osteoporosis, 2 year interval (Grade Indeterminate, NOT covered)

Men whose 10 year fracture risk is ≥ 65 year old white women without RF

Bone Densitometry: DXA
(Quantitative Digital Radiography)

"z" Score: S.D. difference vs. age and sex matched individuals

"t" Score: S.D. difference vs. early life

- Vertebral fracture risk increases 2 - 2.4 times for each S.D. of bone loss

- Non-vertebral fracture risk increases 1.7 times for each S.D. of bone loss

WHO categories of osteoporosis

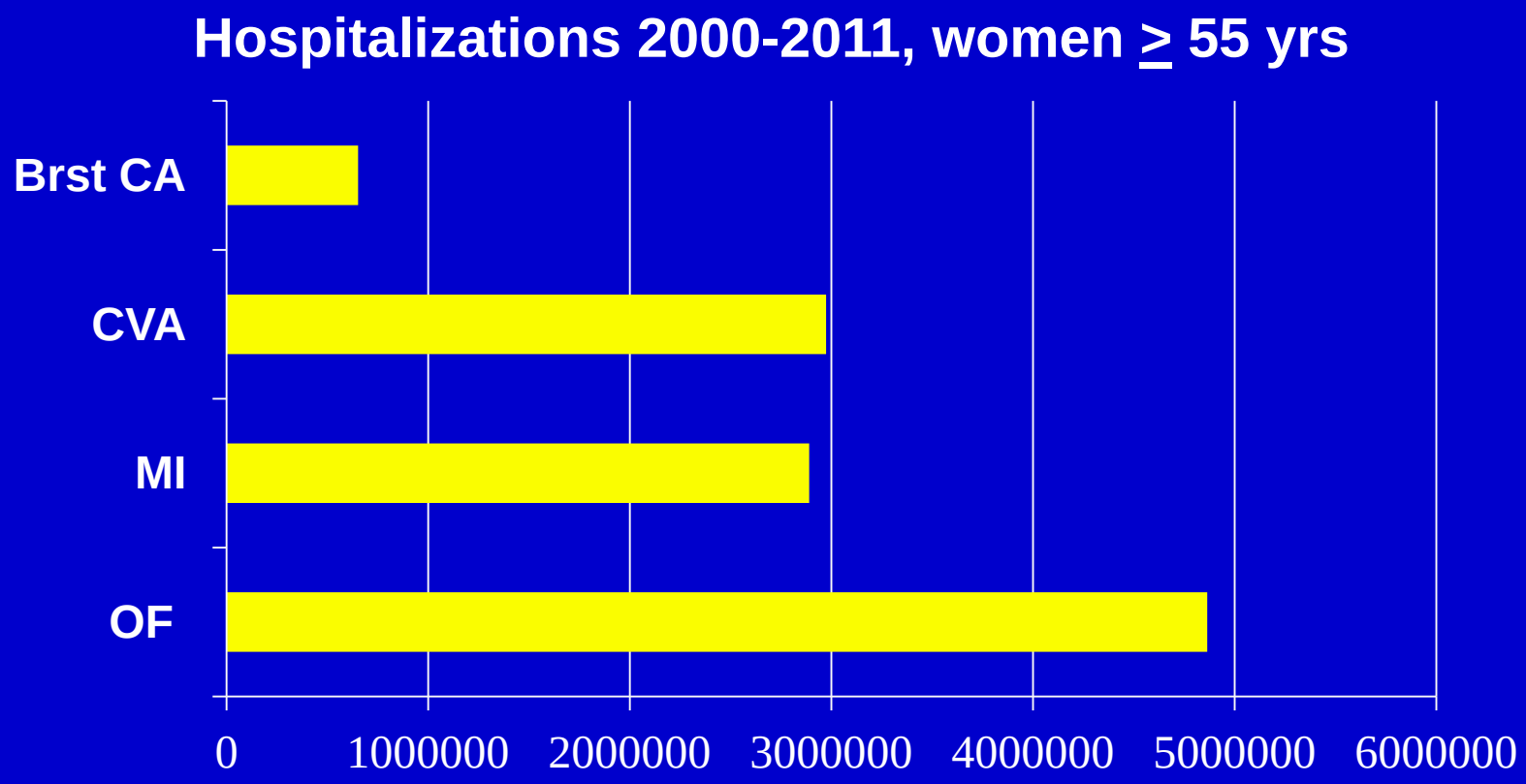
Osteopenia: BMD -1 to -2.5 S.D. below healthy mean (30-40 yr)

Osteoporosis: BMD ≤ - 2.5 S.D. below healthy mean

Severe osteoporosis: Osteoporosis with a non-violent fracture

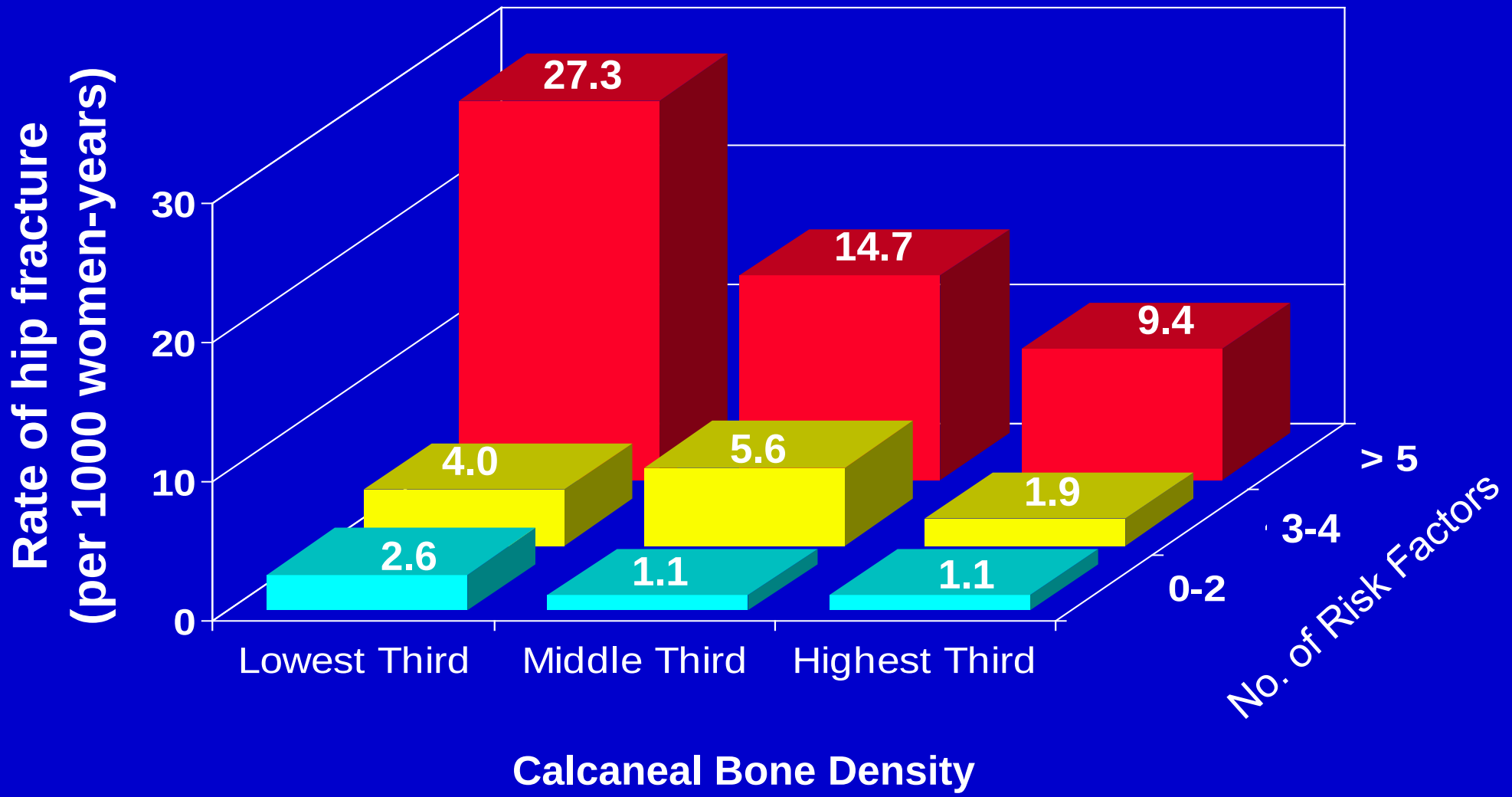
Falls cause fractures

Hospitalizations for osteoporosis fracture exceed MI, CVA and breast CA



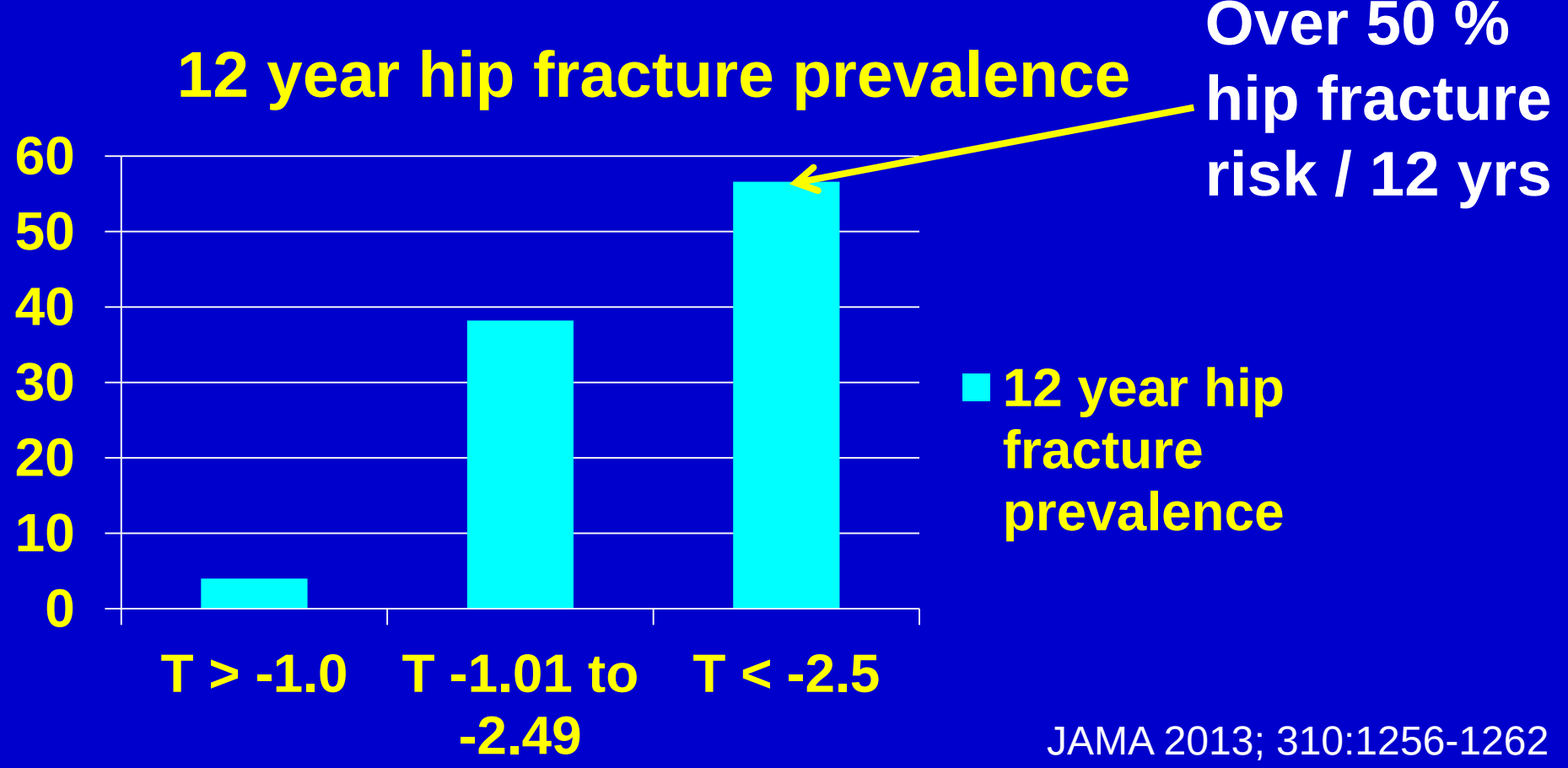
Mayo Clin Proc 2015; 90:53-62

Risk factors add up!



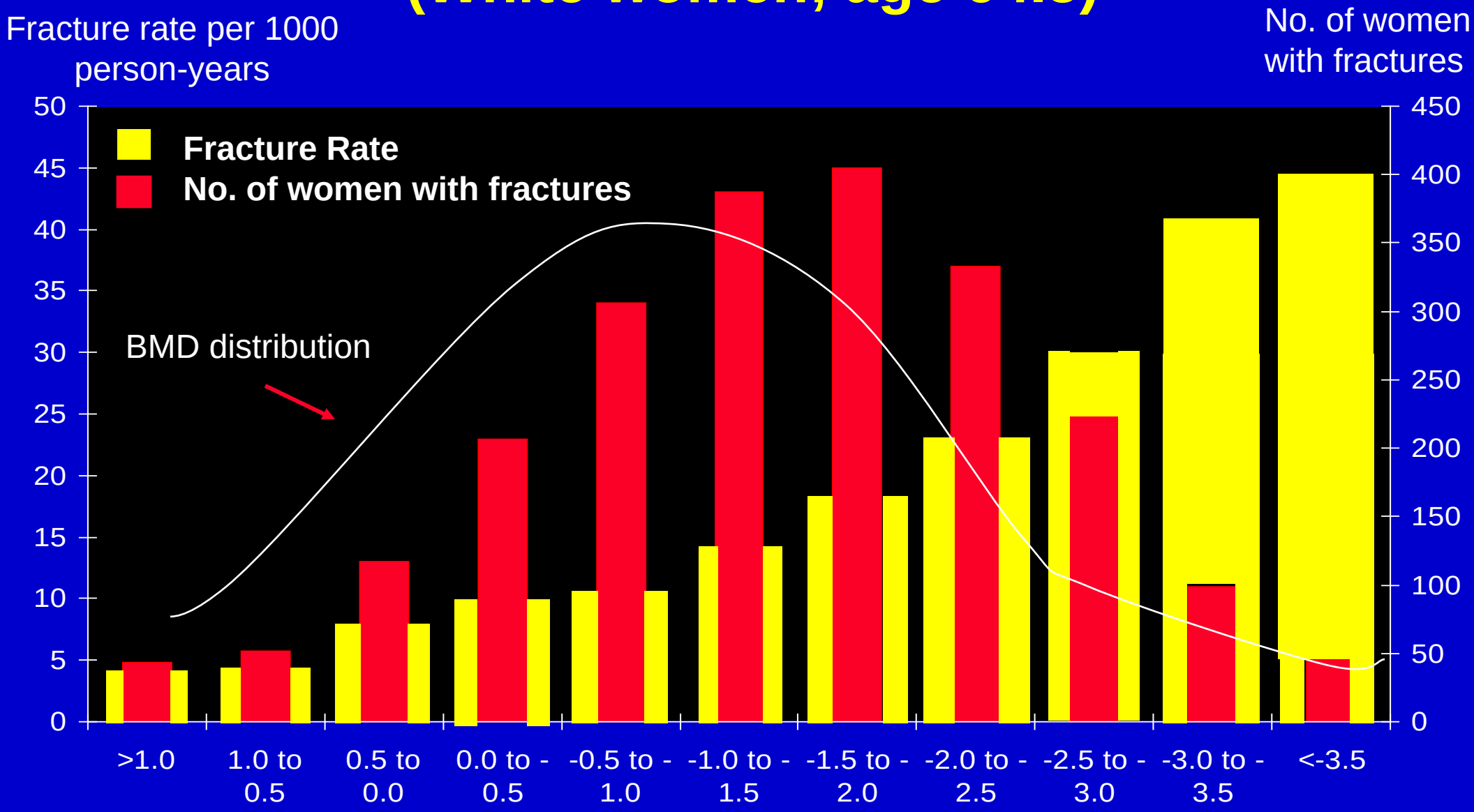
N Engl J Med 1995;332:770

Framingham cohort pre bisphosphones (1987-99), mean age 74.8 years, what about lifetime risks:



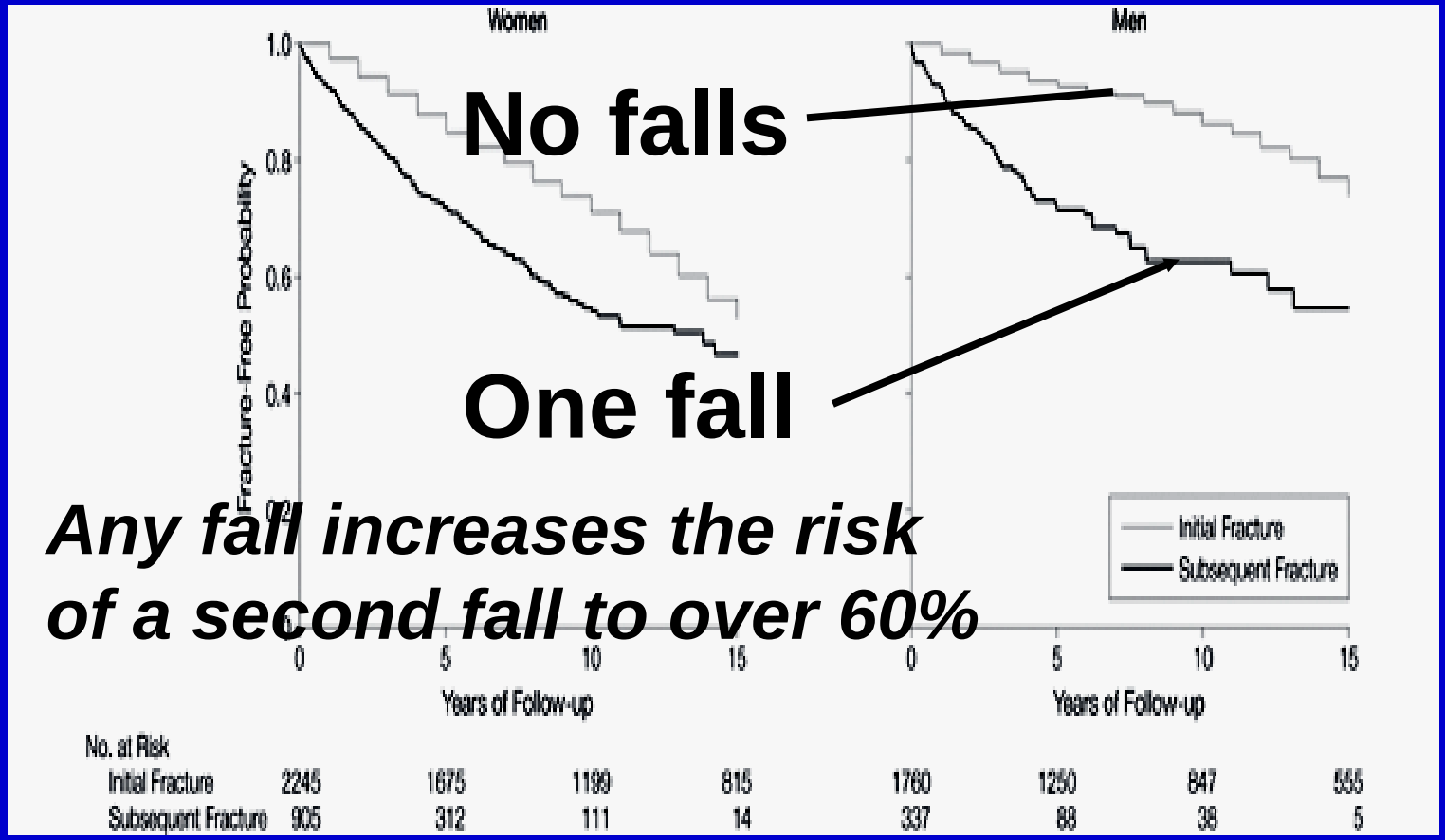
JAMA 2013; 310:1256-1262

NORA data: BMD and fracture risk (White women; age 64.5)



Falls predict risk for subsequent falls

Women Men



Fracture free over 5 yrs

20%

50%

5 years of follow-up

JAMA 2007;297:390

Medications associated with fall risk

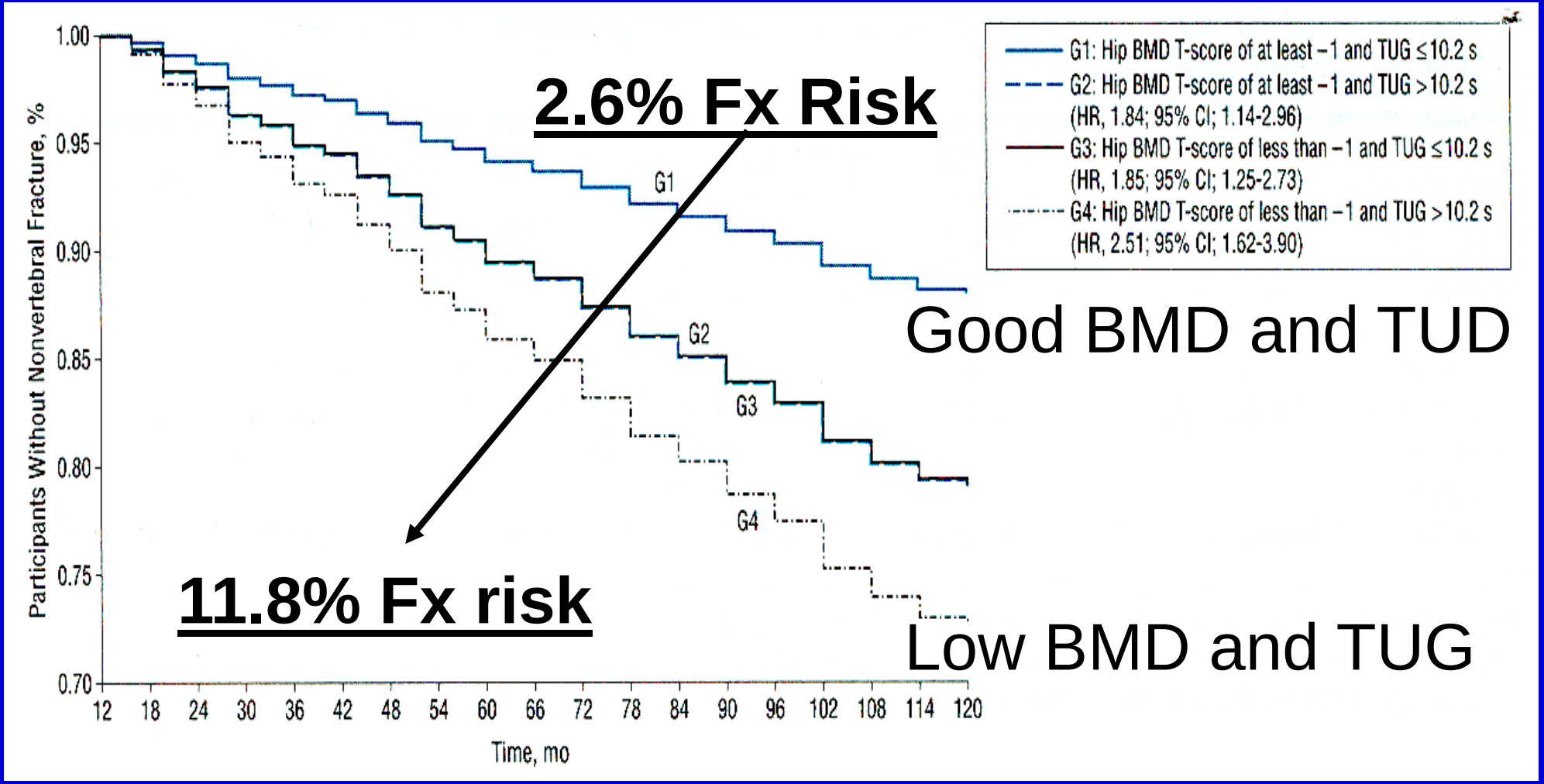
	Odds Rates (95% C.I.)
Sedative/hypnotics	1.31 (1.14-1.50)
Neuroleptics/antipsychotics	1.71 (1.44-2.04)
Antidepressants	1.72 (1.40-2.11)
Antihypertensives	1.26 (1.08-1.46)

Arch Intern Med 2009;169:1957

Trust your clinical judgment: "Timed Up and Go" (TUG) over 10 seconds predicts hip fracture risk

- Timed Up and Go (TUG): Time taken to get out of a chair, walk 10 feet (3 M) and return to the chair; normal ≤ 10 seconds
- Australian cohort of 1126 women, followed for 10 years
- Ten year risk for fracture 54% higher in highest risk group, low BMD and prolonged TUG

10 year hip fracture risk for frail patients with osteopenia is 12%



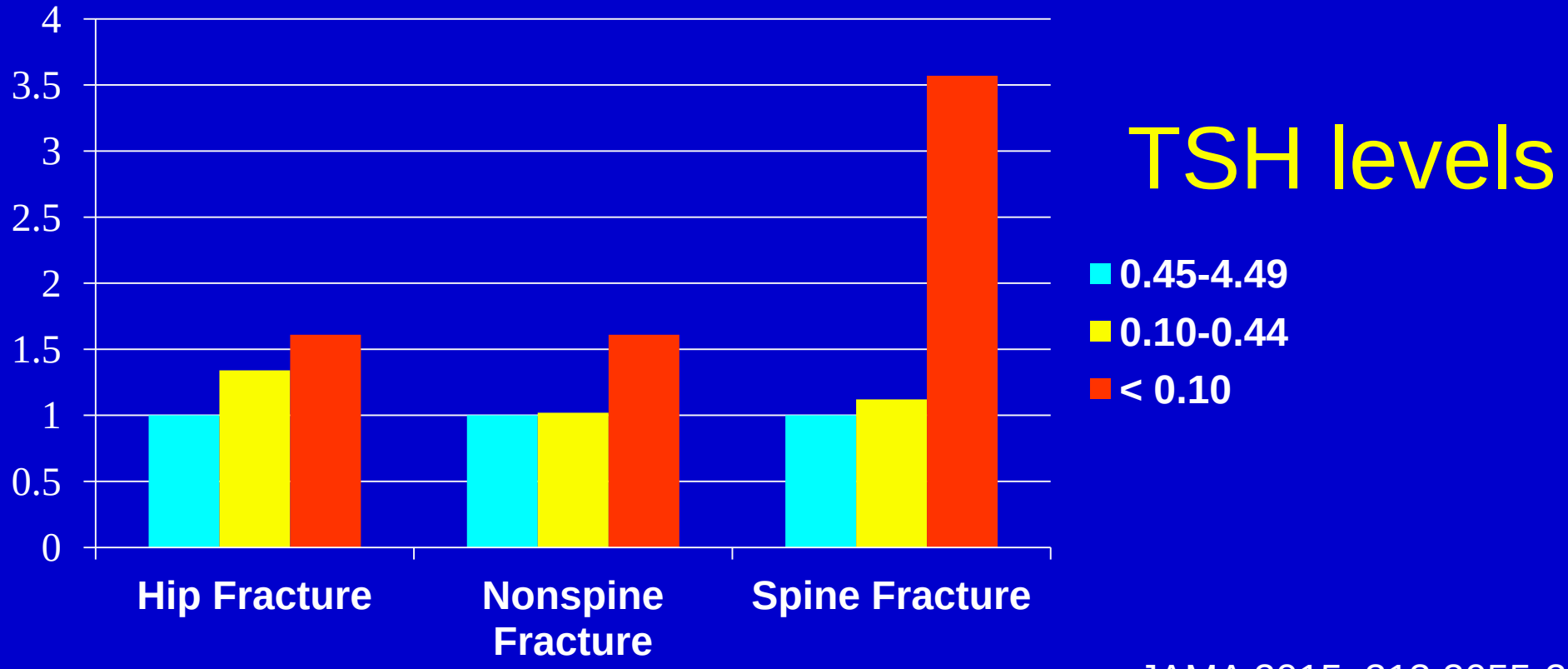
Arch Intern Med 2011; 171:1665-1661

Contributors to Osteoporosis

Calcium
Vitamin D
Estrogens
Age
Sex
Race
Smoking
Exercise
Alcohol
Exogenous steroids
Hyperthyroidism
Growth hormone
Diabetes mellitus
Anticoagulants
Excessive Vitamin A
Inflammatory bowel disease
Depression
Homocysteine elevation
Androgen deficiency
Breast cancer survivors
Pelvic irradiation
PPI usage
Thiazolidinediones
Cardiovascular disease

Subclinical hypothyroidism and hip fracture risk

Meta-analysis, N = 70 298, 13 RCTs



JAMA 2015; 313:2055-2065

Laboratory tests:

All patients:

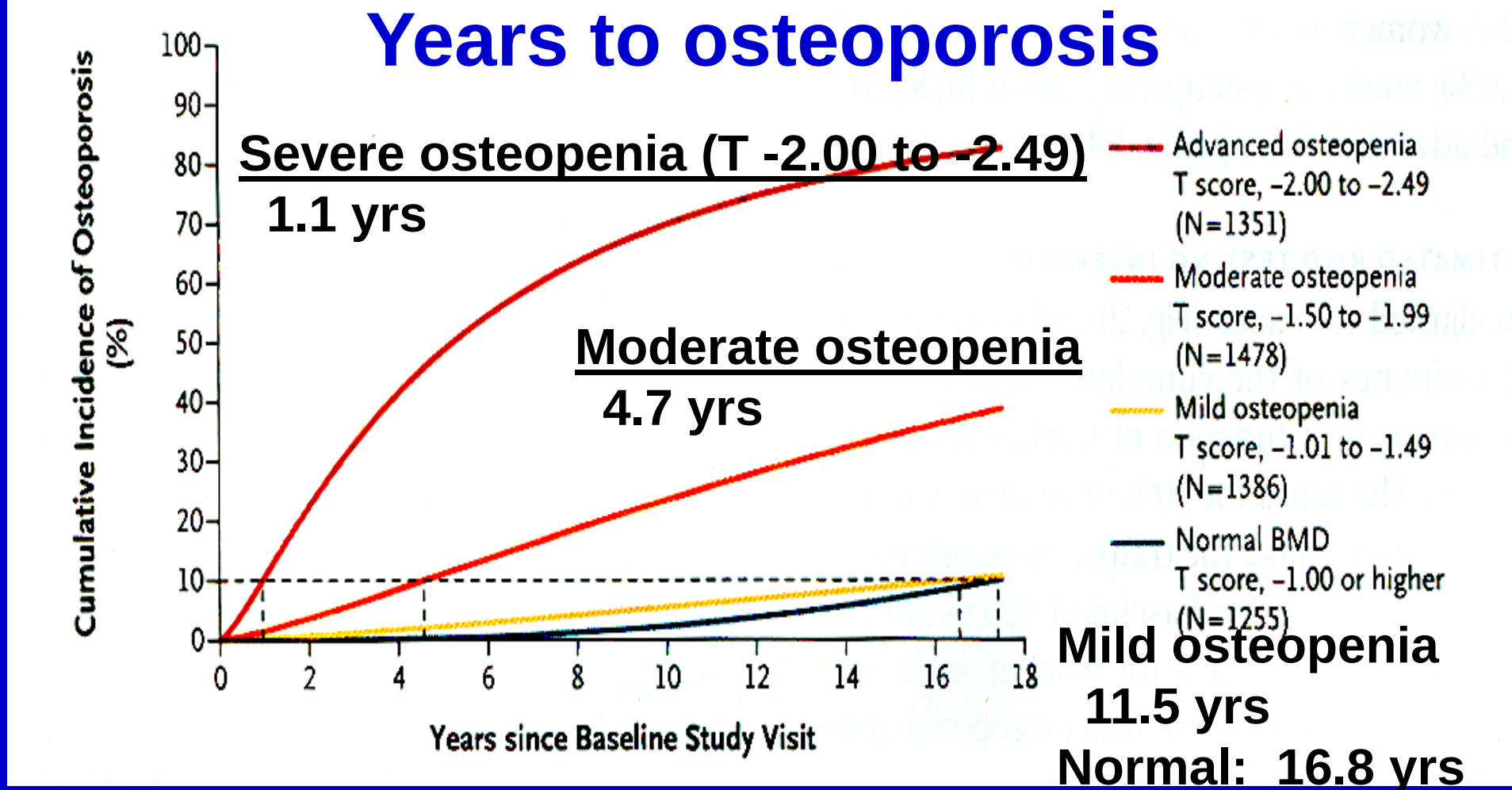
- CBC & ESR
- Ca^{++}
- $PO_4^{=}$
- TSH
- Vitamin D (25 OH)
- Bone densitometry
- ? PTH (for vitamin D deficiency and hyperparathyroidism)

When to order bone densitometry:

- Diagnosis and screening
- Screening for high risk:
  - history of steroid use
  - history of calcium loss (multipregnancy)
  - low Vitamin D level
  - unexpected non traumatic fracture
  - family history
  - estrogen deficiency (anorexia, anovulatory cycling, etc.)
- Monitoring therapy: every 2-3 years
- Assisted decision-making

Good early BMD predicts lower future risk for progression to osteoporosis

(9704 North Carolina white women followed 15 yrs)



Osteoporosis screening for men: Routine >80, high risk over 65 years

Age	No fracture ($ per QALY)	Previous clinical Fracture ($ per QALY)
> 65	129,665	47,537
> 70	92,769	35,037
> 75	66,071	23,260
> 80	45,587	15,477

JAMA 2007;298:629-637

Markers of bone turnover of little clinical value:

- Do not predict BMD
- Increased in women with high turnover postmenopausal osteoporosis
- Useful for monitoring response to therapy

What about online tools?

- FRAX has become the standard but…only 70% accurate
- No measure of frailty
- Based on country-specific date
- Little added value beyond the BMD and age

Ann Rheum Dis (online 8 Aug, 2015) 1-10

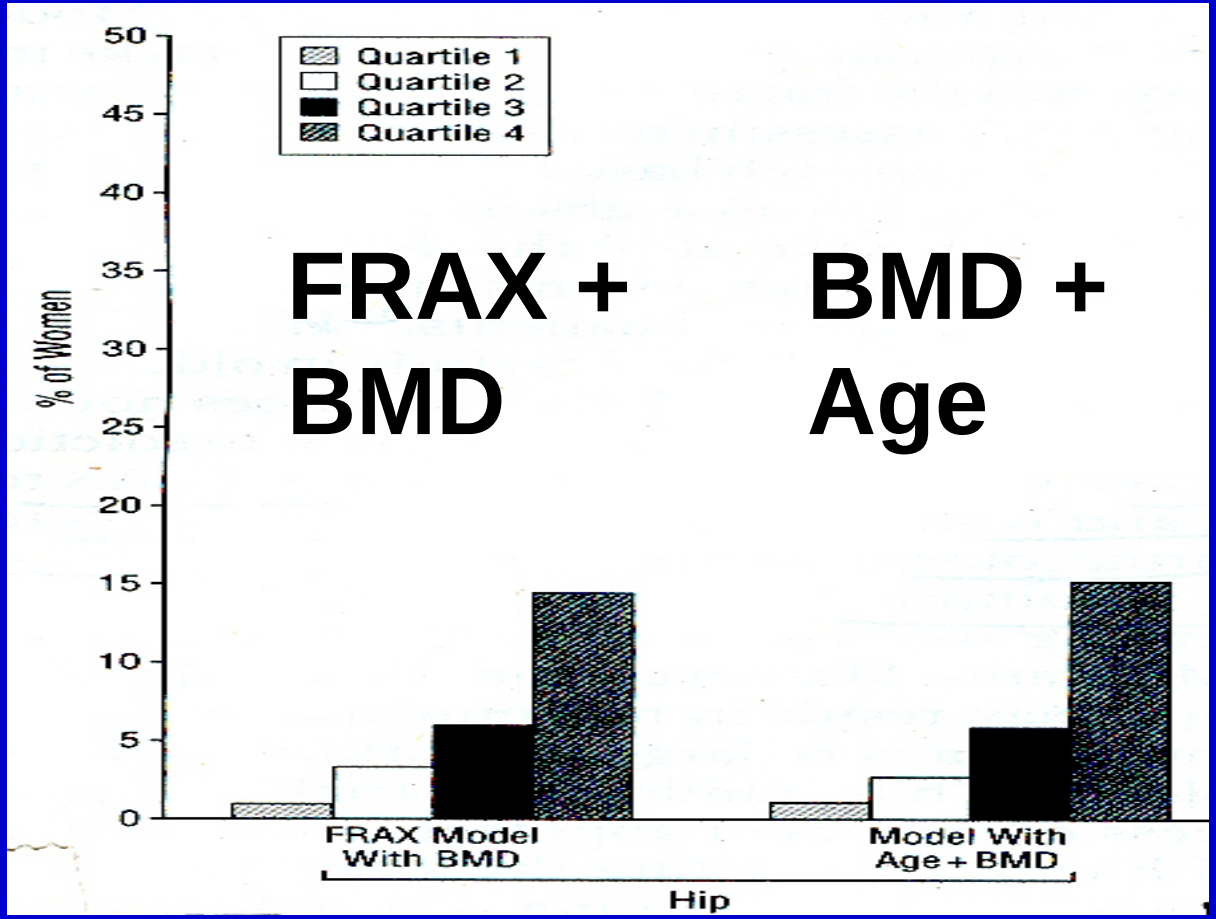
FRAX risk factors

Age
BMI
Sex
Personal fracture history
Steroid use
RA
Presence of DM, osteogenesis imperfecta,
untreated hyperthyroidism,
early menopause, malnutrition, liver disease
Parental hip fracture
Current smoking
Alcohol (≥ 3/d)

Osteoporosis Int 2007;19:285-397

FRAX with BMD no different then BMD alone in predicting hip fractures in women

Percent with fx



Arch Intern Med 2009;169:2091

Let’s talk about interventions

- “Non pharmacologic”
  - Exercise
  - Calcium
  - Vitamin D
- Antiresorptive
  - Estrogens
  - Bisphosphonates
- Anabolic
  - Teriparitide
  - Denosumab

What is the value of exercise and balance training?

Physical activity encourages bone growth along lines of stress.

- **The bone density in the dominant arm of a tennis player is 35% higher.**

Balance training reduces fall risk

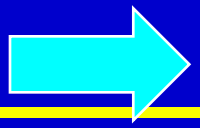
Balance training reduces fall risk in patients with Parkinson's Disease

	Tai Chi (N=65)	Resistance (N=65)	Stretching (N=65)
Total falls	62	133	186
Falls/group			
Any	19	31	26
1	3	8	4
2	4	7	2
≥3	12	16	20

N Engl J Med 2012; 366:511-9

Six month exercise intervention reduced fractures over the next 7 years

Fractures	Exercise	Control
Foot	2	0
Knee/tibia/fibula	3	5
Femur	0	5
Other	12	13
Total	**17**	**23**



Arch Intern Med 2010;170:1548-1556

What are benefits of an ambitious exercise intervention?

Finnish RCT, 2010-2013

N = 409, women age 70-80

Home dwelling

Four groups:

1. Exercise and placebo
2. Exercise and vitamin D
3. No exercise and vitamin D
4. No exericse and placebos

JAMA Intern Med Mar 23, 2015

Finnish exercise intervention

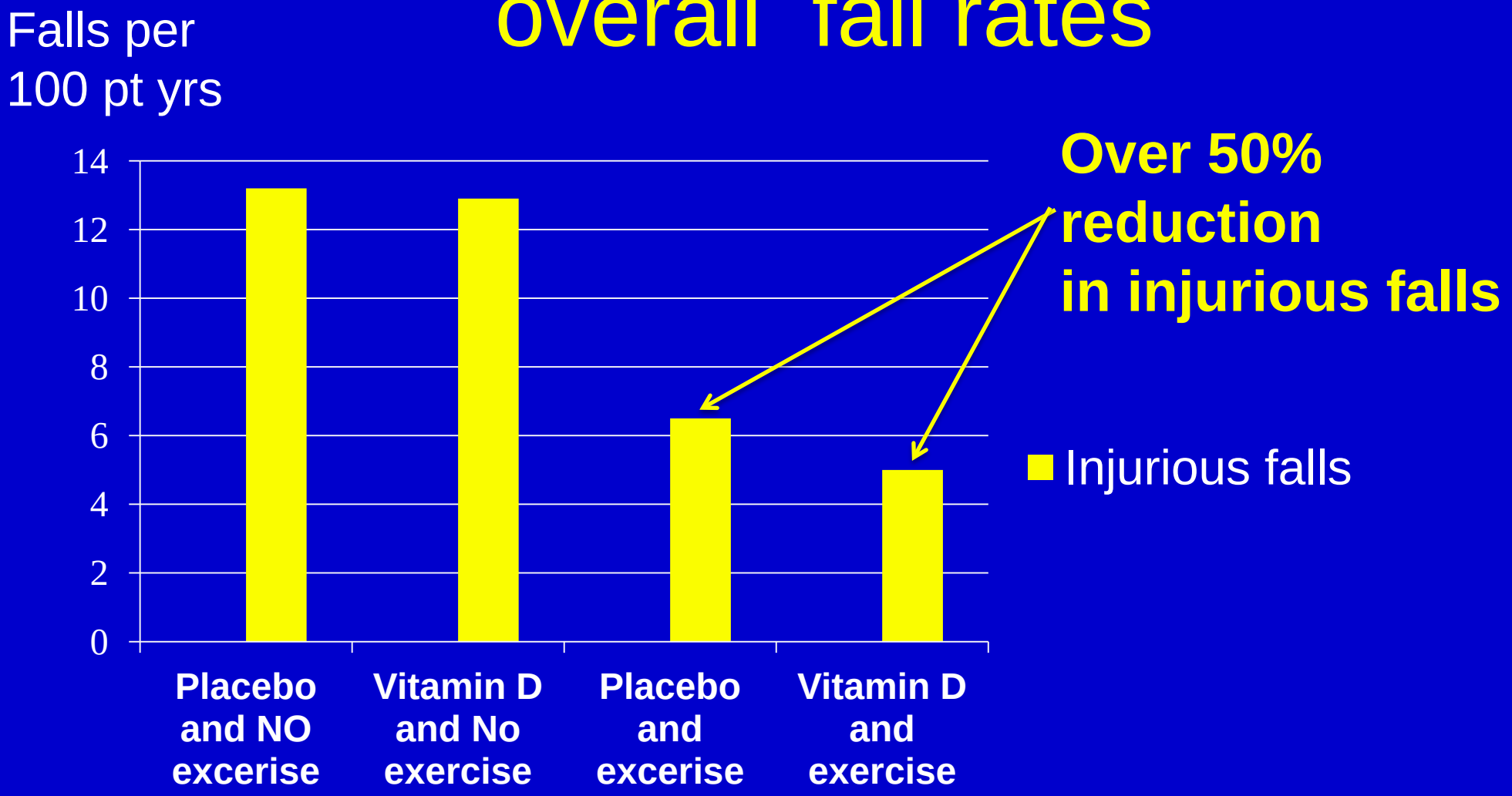
No exericse = Maintain pre-study levels
Exercise = Twice a week for 12 weeks

- Once a week thereafter for 2 years
- PT directed classes
- Balance, weight bearing, strength, agility, function
- Machines, free weights
- Home training all other days

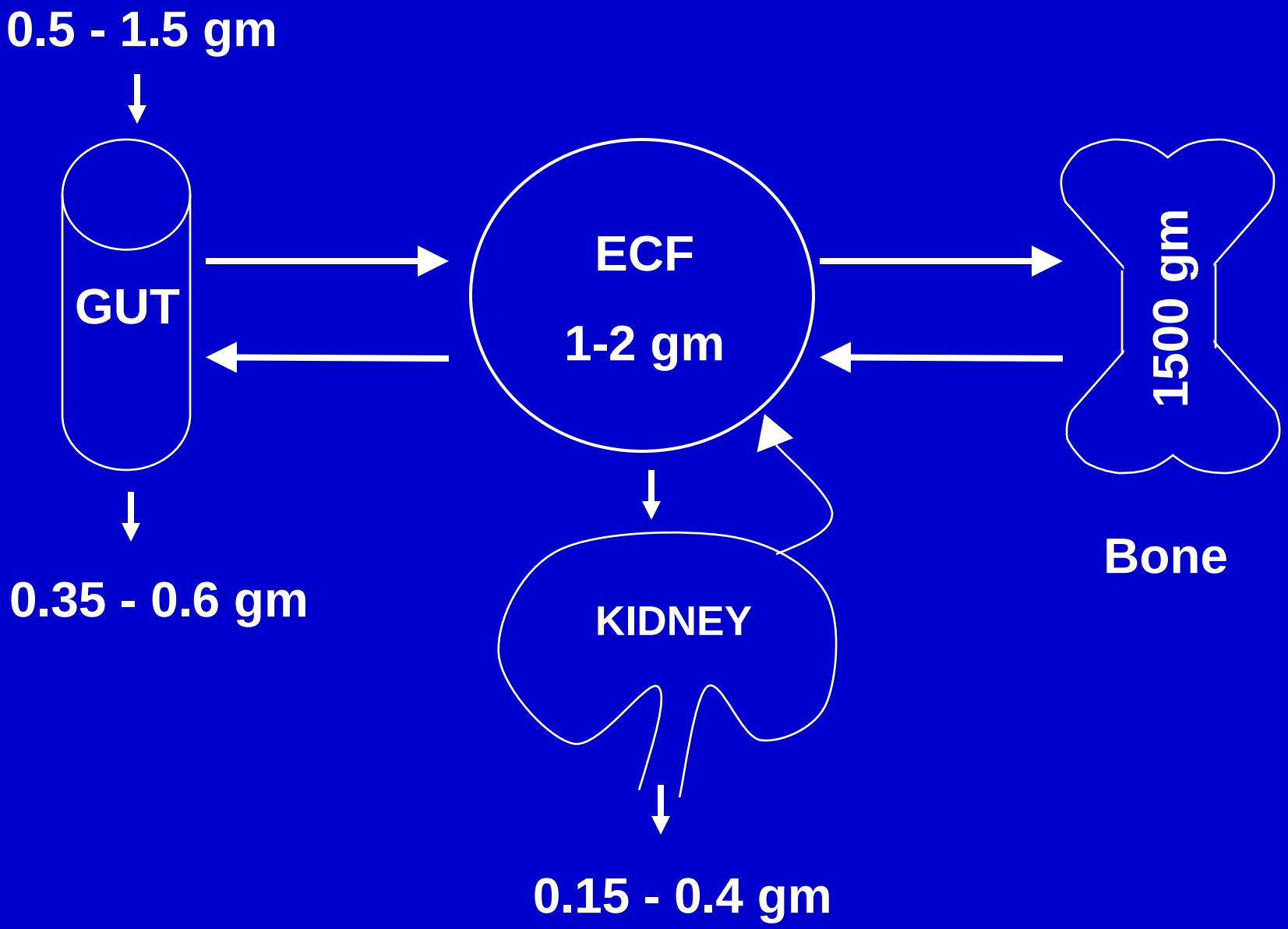
Finnish exercise participants

	Placebo and no exercise	Vitamin D and no exercise	Placebo and exercise	Vitamin D and exercise
Age	73.8	74.1	74.8	74.1
Weight	72	73	71	73
Vitamin D	27.1	26.4	27.8	26.2
HTN	42	52	36	53
DM, %	9	12	10	6
No meds	2.5	2.6	2.3	2.7
Sys BP	146	148	148	148

Two years of an aggressive exercise program reduced injurious falls but not overall fall rates



Calcium homeostasis



Meta-analysis (17 RCTs) show calcium reduces fracture risk

	Risk Reduction (95% C.I.)	NNT (95% C.I.)
Calcium+/-Vitamin D	12% (5-17)	63 (37-192)

Lancet 2007;370:657-666

WHI: Calcium reduces fracture rate (N=36282, 62 yrs of age, 7 yrs follow-up)

Hip fracture rate/year (%)	Calcium + D[+]	Placebo	Hazard Ratio (95% C.I.)
Intention to treat	0.14	0.16	0.88 (0.72-1.08)
Adherent patients [++]	0.10	0.14	0.71 (0.52-0.97)

[+] Calcium 1000 mg/d + Vitamin D 400 I.U./d

[++] Took 80% or more of medication

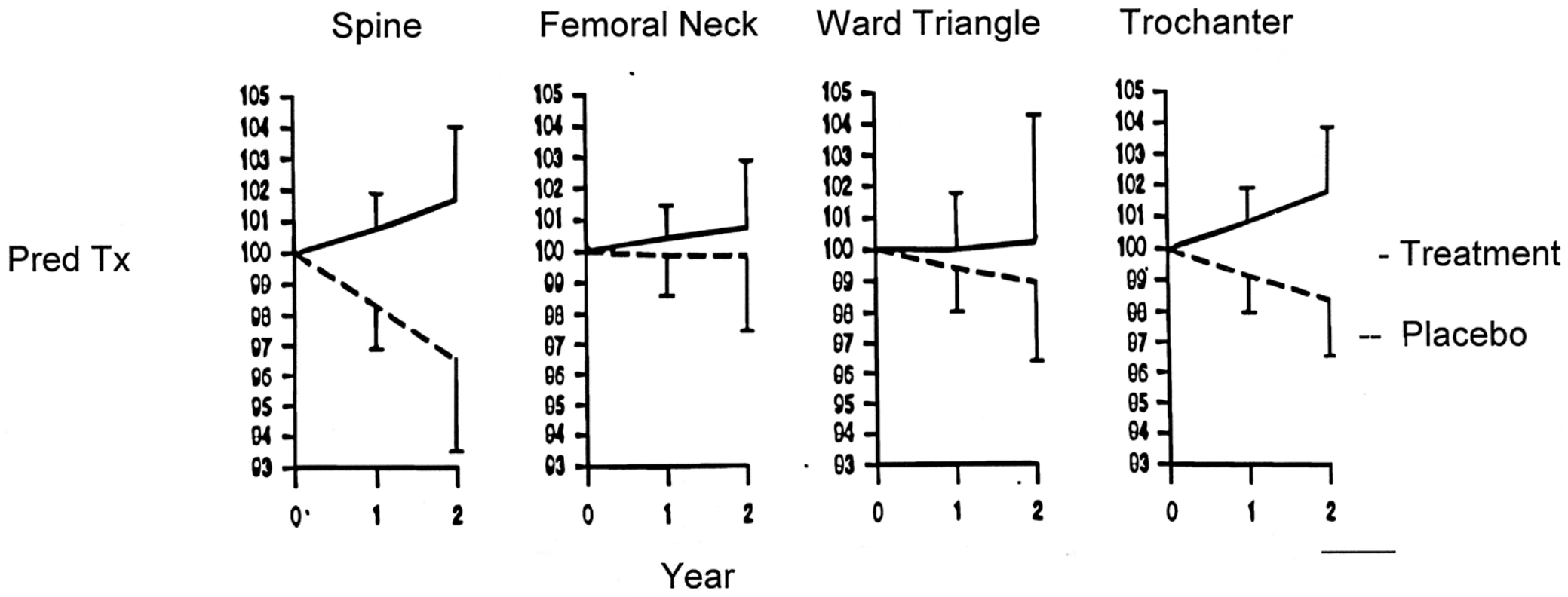
Calcium Content

Food	Calcium (mg)
General Mills Total (3/4 cup)	1,000*
Lactaid Calcium Enriched Milk (1 cup)	500*
Silk Almondmilk or soymilk (1 cup)	450*
Orange juice, with calcium (1 cup)	350*
Yogurt, plain, nonfat (6 oz.)	340
Milk (1 cup)	300
Yogurt, fruited, nonfat (6 oz.)	260
Sardines, canned (3 oz.)	250
Salmon, canned, with bones (3 oz.)	240
Mozzarella, Part skim (1 oz.)	220
Swiss cheese (1 oz.)	220
Frozen yogurt, premium (1/2 cup)	200
* Contains added calcium	

Calcium Content (cont'd)

Food	Calcium (mg)
Cheddar cheese (1 oz.)	190
Greek yogurt, plain, nonfat (6 oz.)	190
Cottage cheese, 2% (1/2 cup)	130
Spinach (1/2 cup cooked)	120
Frozen yogurt, regular (1/2 cup)	100
Almonds (23 nuts, 1 oz.)	80
Bok choy (1/2 cup cooked)	80
Kale (1/2 cup cooked)	60
Edamame, shelled (1/2 cup cooked)	50
Cream cheese, tub (2 Tbs.)	40
Broccoli, shopped (1/2 cup cooked)	30
* Contains added calcium	

Calcium (1000 mg/day) and Vitamin D reduce steroid effect on bone density



Calcium and risk for MI

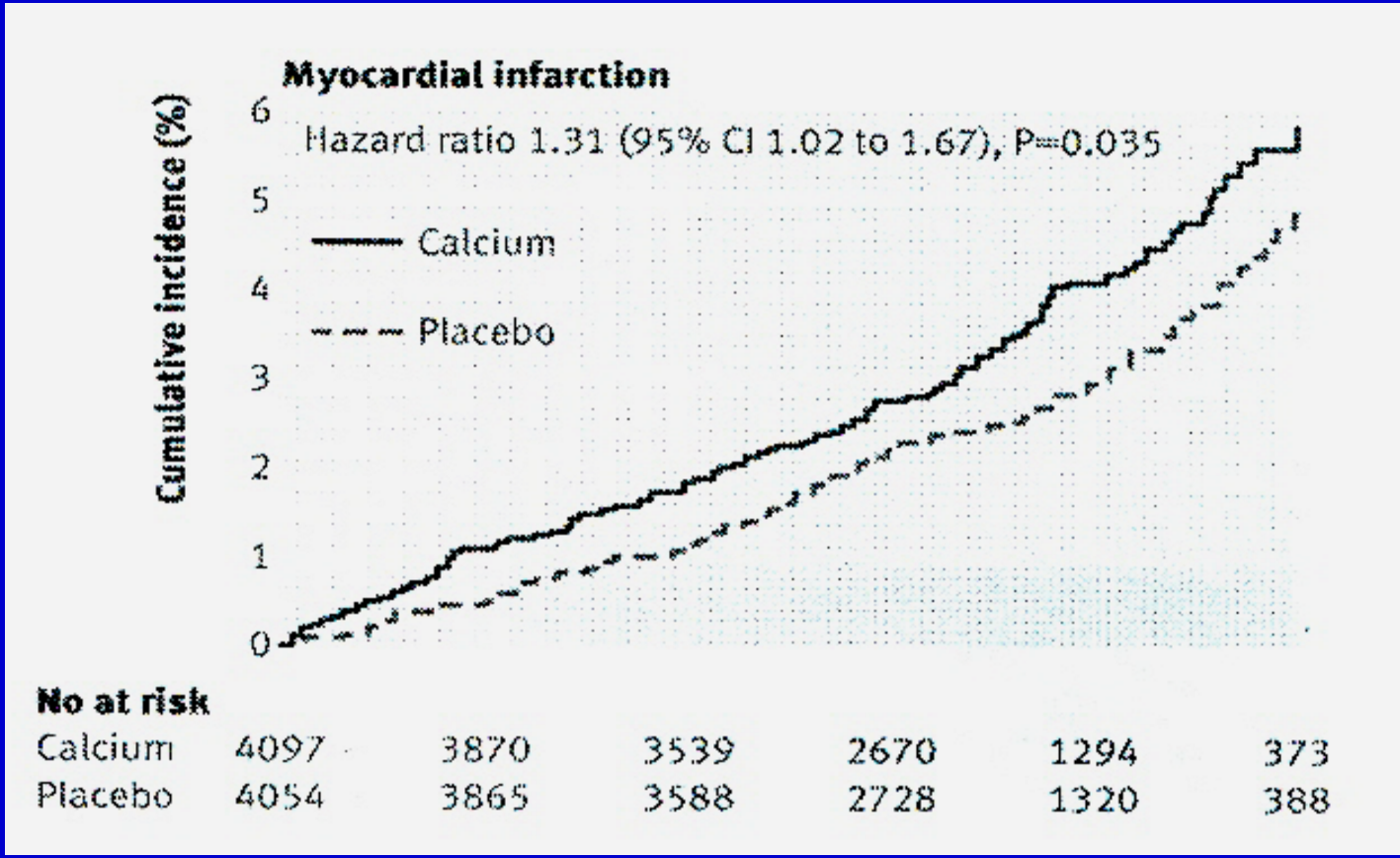
Study design:

- 190 studies in the published literature, 1966-2010 but 162 excluded (111 too small, 30 too short, 21 poor design).
- 15 studies included
  - 5 with “patient level” CV outcome data
  - 6 with partial CV outcome data
  - 4 with no CV outcome data
- Patient level data available on 63% (8151/11921)

BMJ 2010;341:c3691

Calcium and risk for MI

Patient outcomes



The CI for MI is very wide and barely significant

NS for CVA and mortality

How much Vitamin D should you recommend?

- Vitamin D is a hormone (i.e. a mediator)!!
  - Calcium absorption
  - Immune response
  - Inflammatory response
  - Soft tissue
- Do you need to “treat to a level?”
  - 2011 IOM target 50 nmol/L for “efficacy”

Vitamin D deficiency is common

Patient population	Location	Mean Age	Vitamin D deficiency, %
Osteoporosis center	Italy	68	76
Chronic shoulder pain	MN	10-65	93
Women with hip fx	UK	81	70
Women with OA	Boston	66	22
Osteoporosis patients	Spain	69	67
Osteoporosis patients on active therapy	N. Am	71	52
Osteoporosis patients	S. Calif.	--	53
Hospital fx patients	MN	> 50	97

Mayo Clin Prac 2006;81(3):353-373

Is it time to stop worrying about vitamin D? USPSTF says yes!

	Risk Ratio (95% C. I.)
Mortality overall	0.83 (0.70-0.99)
Mortality, institutional	0.72 (0.56-0.94)
Mortality, non institutional	0.93 (0.73-1.18) NS
Hip fracture	0.96 (0.72-1.29) NS
Any fracture	0.98 (0.82-1.16) NS
Any fall	0.84 (0.69-1.02) NS

Ann Inter Med 2015; 162:109-122, 133-140

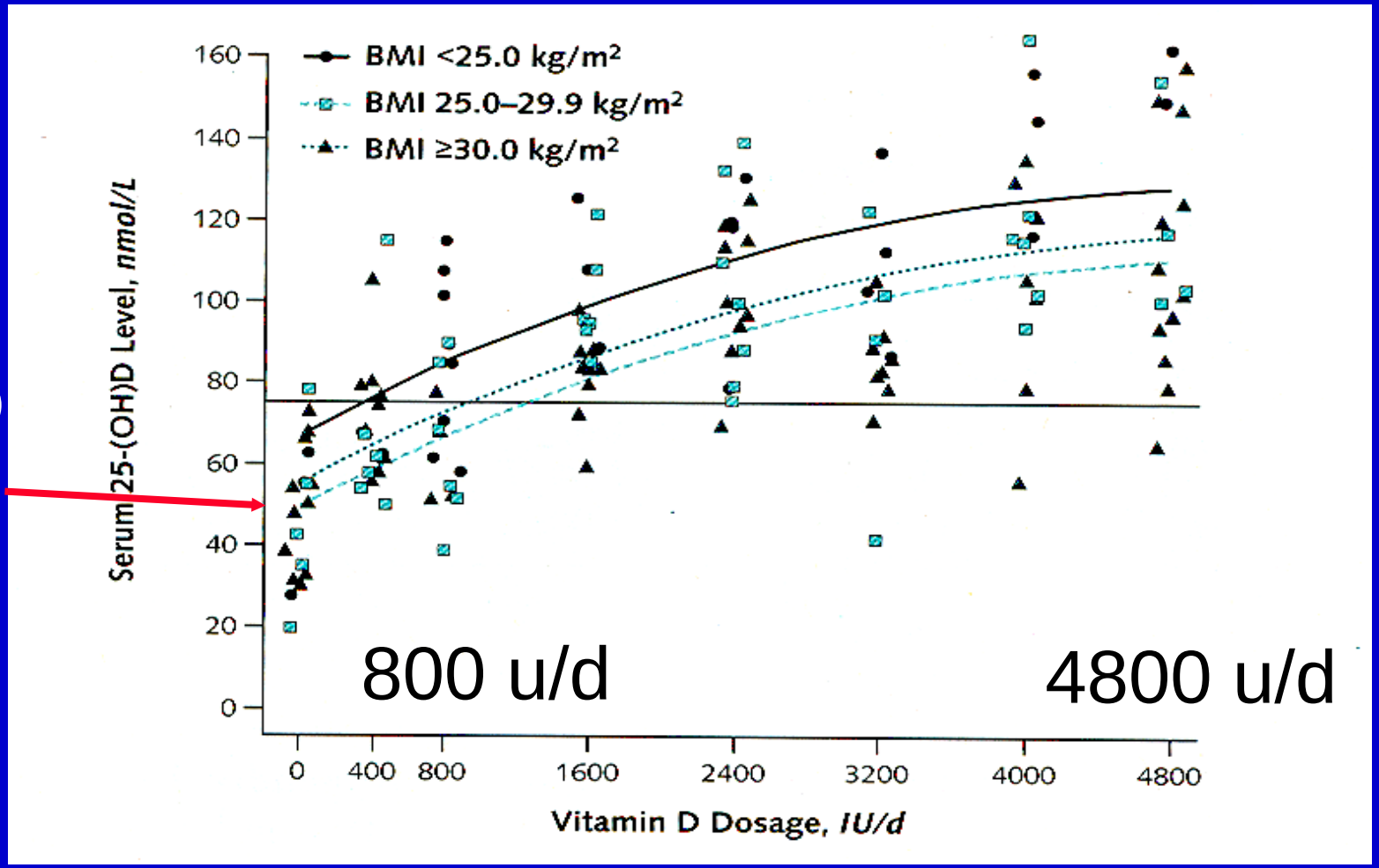
Current “target” levels for Vitamin D

Deficiency	<20 ng/mL
Probably normal	20-30 ng/mL
Optimal	30-50 ng/mL
Possibly toxic	> 50 ng/mL
Clearly toxic	>499 ng/mL

Ann Inter Med 2015; 162:109-122

Vitamin D supplement of 6-800 units/d is adequate to maintain levels

Vit D 50



Vitamin D supplement levels

Annals Intern Med 2012; 156:425-437

Vitamin D treatment strategies

Recommended daily

Age 19-50 years	600 units/d
Age > 50 years	600-800 units/d

Deficiency treatment

50,000 units/week for 8 weeks

or

6000 units/d

Then…

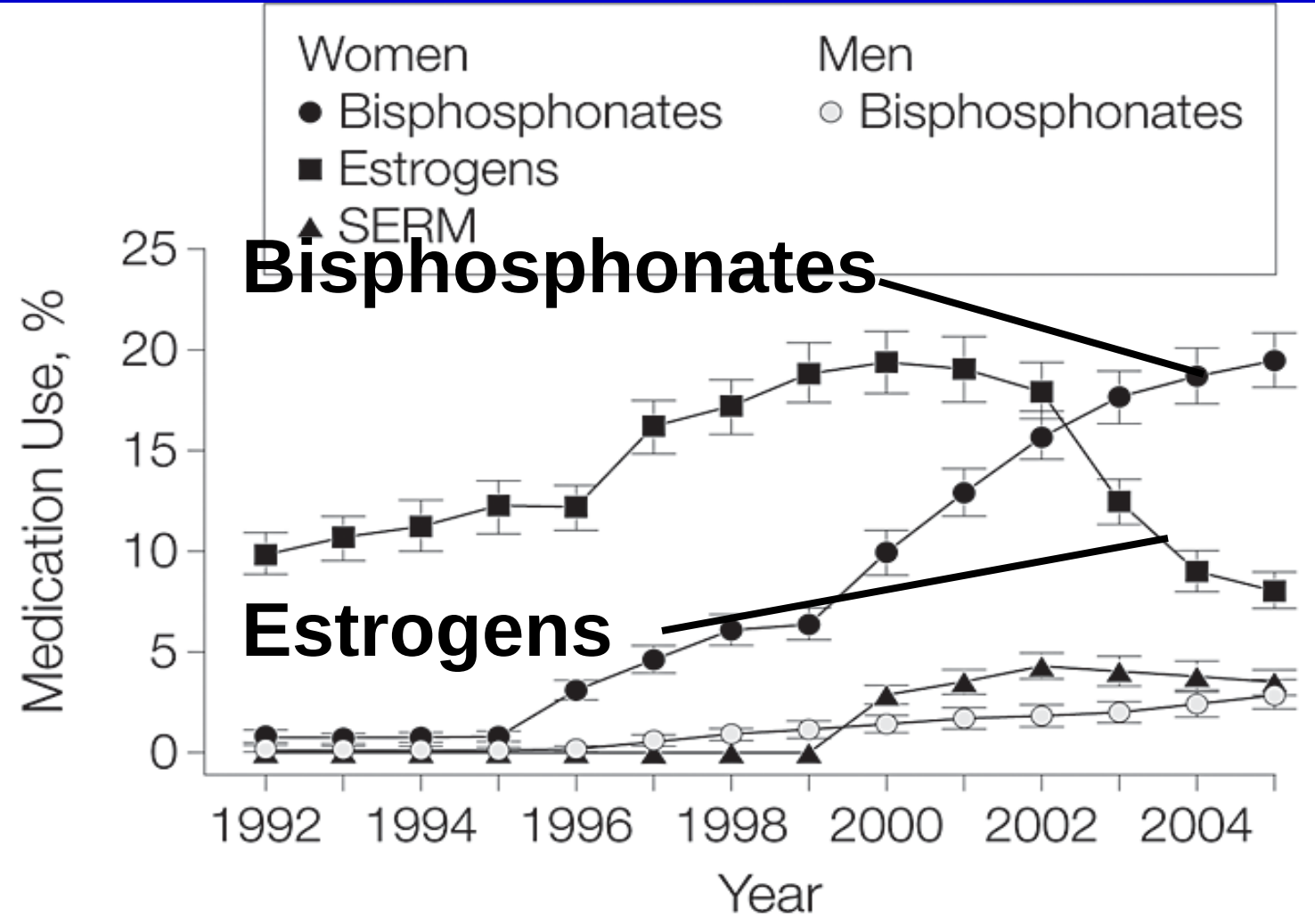
1500-2000 units/d for maintenance

J Clin Endocrine Metab 2011;97:1-20

Bisphosphonates

- Inhibits bone resorption
- Renal clearance (avoid when GFR under 30-35)
- Long “terminal” half life for alendronate (i.e. is stored in the bone and recycled for 10-20 years)
- Work in all age groups

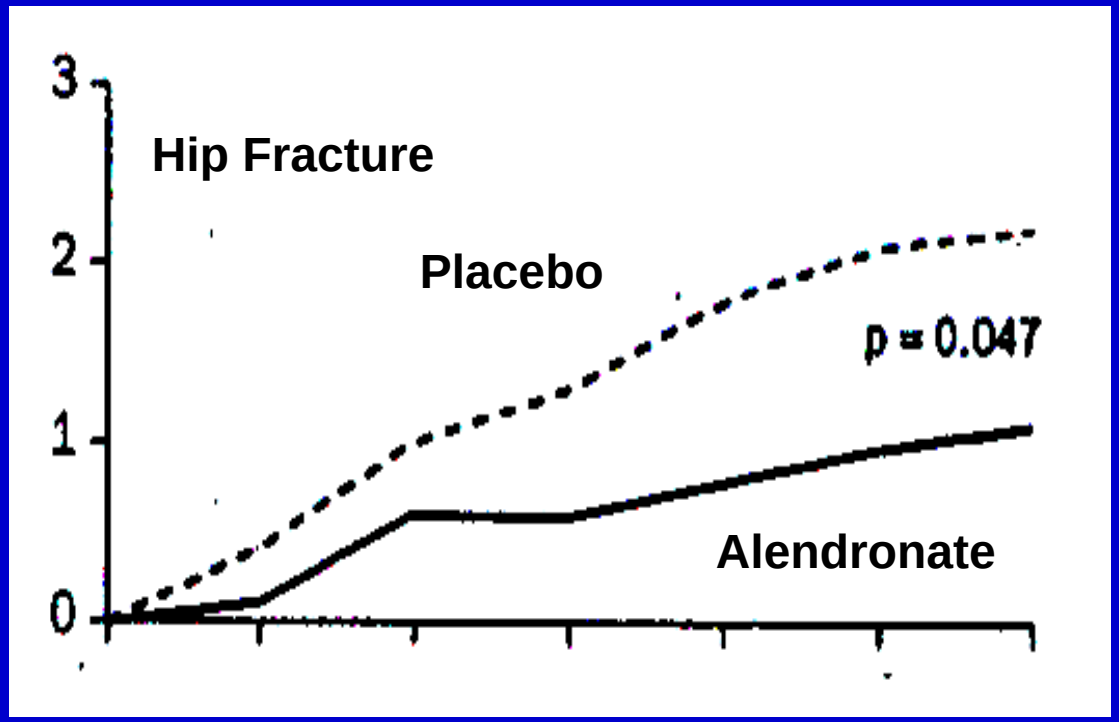
Bisphosphonates are your preferred treatment



JAMA 2009;302:1573-1579

US: Alendronate reduces fracture rate in severe osteoporosis

(T< -2.1 and fracture history, 1996)



2.2% / 3 years

51% lower hip fx

1.1% / 3 years

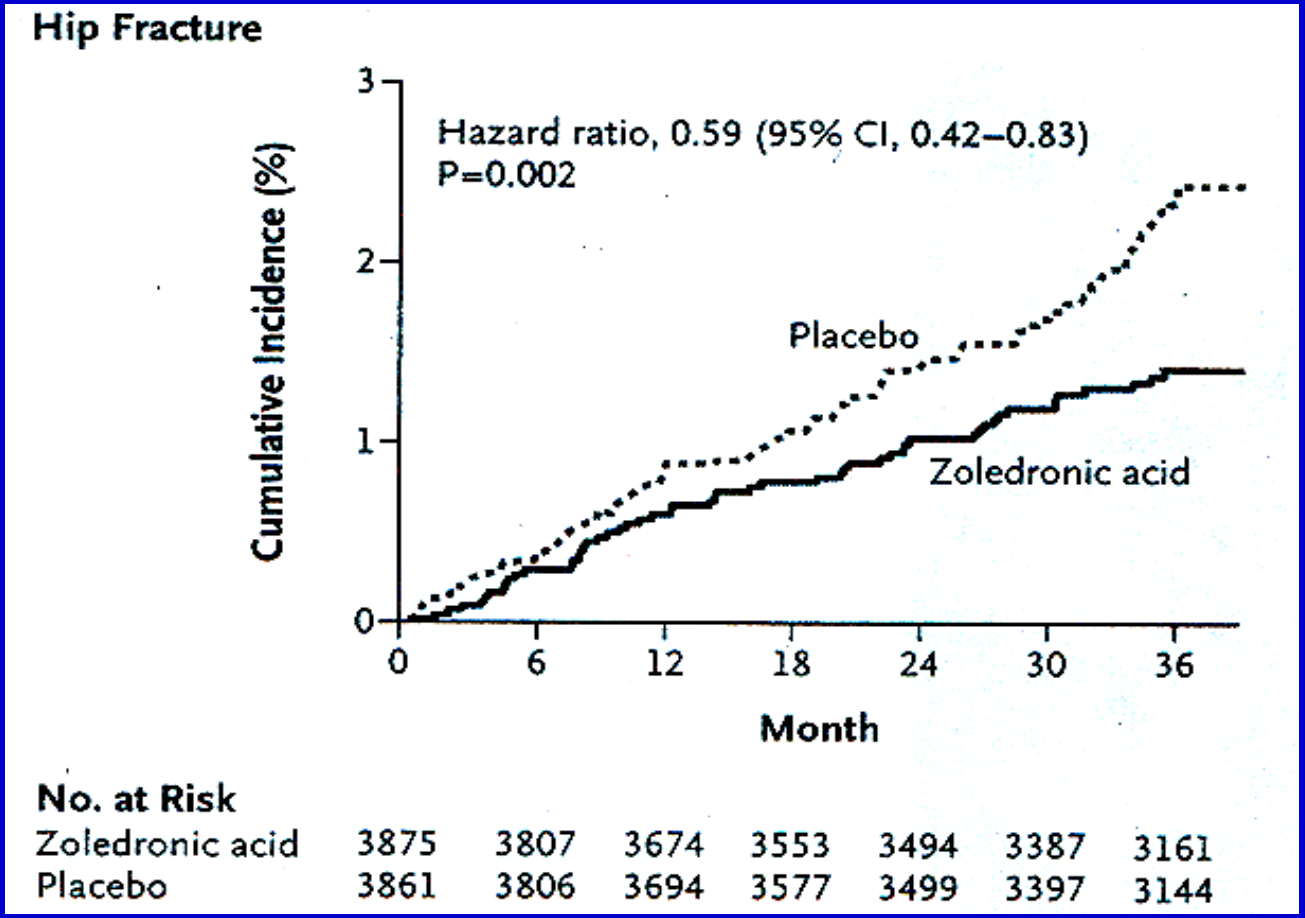
Lancet 1996;348:1538

1998 US study: Alendronate DID NOT reduce fracture rate in patients with osteopenia (T<-1.6)

Type of FX	Placebo (N=2218)	Alendronate (N=2214)	Relative risk
Hip	***1.1%***	***0.9%***	***0.79 (0.43-1.44)***
Wrist	3.2%	3.7%	1.19 (0.87-1.64)

N Engl J Med 1998;348:1539

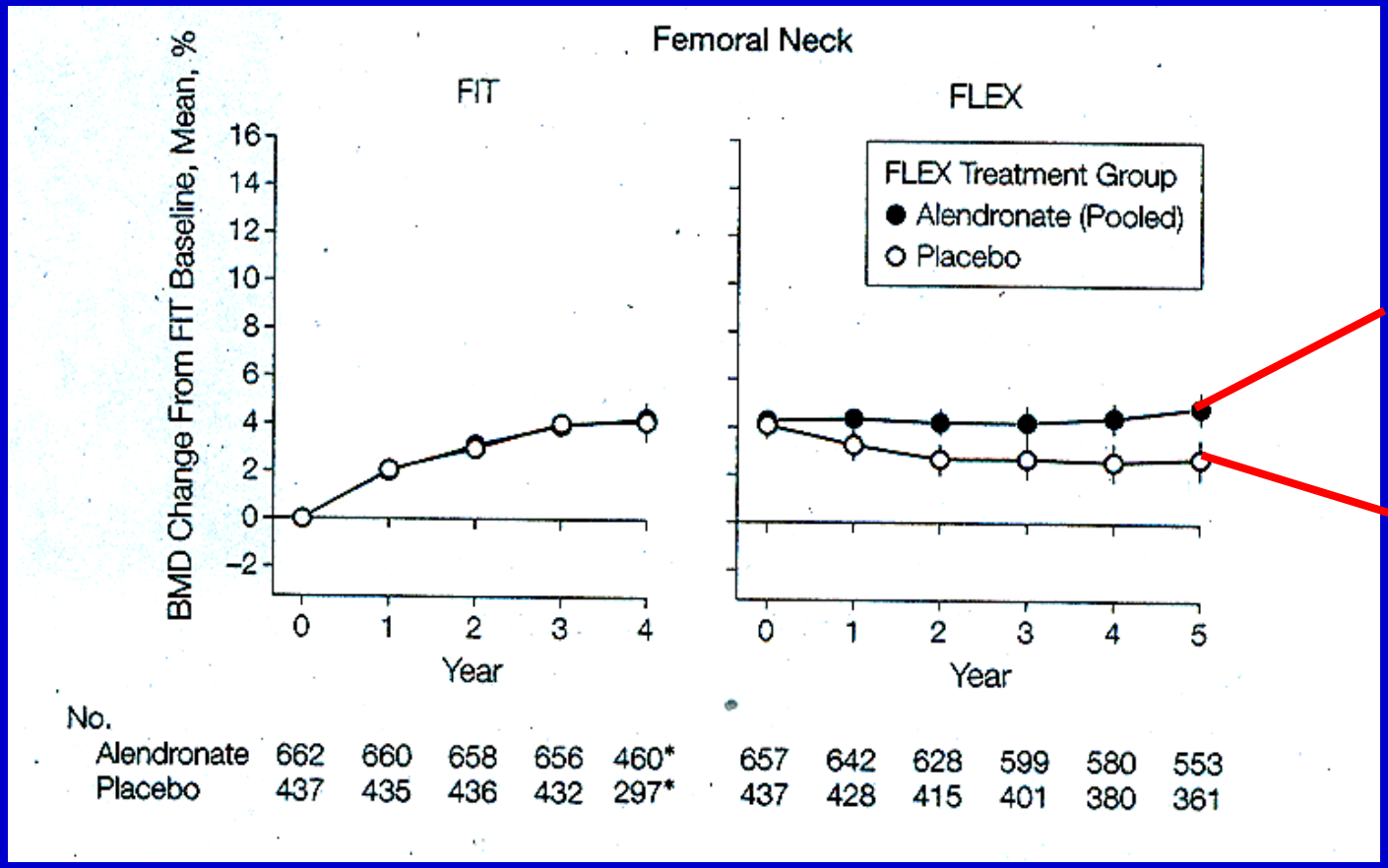
Annual Zoledronate infusions reduce hip fracture rates



41% lower hip fracture rate

N Eng J Med 2007;350:1817

Hip BMD declines slightly after 5 years among patients on alendronate but fracture rate did not



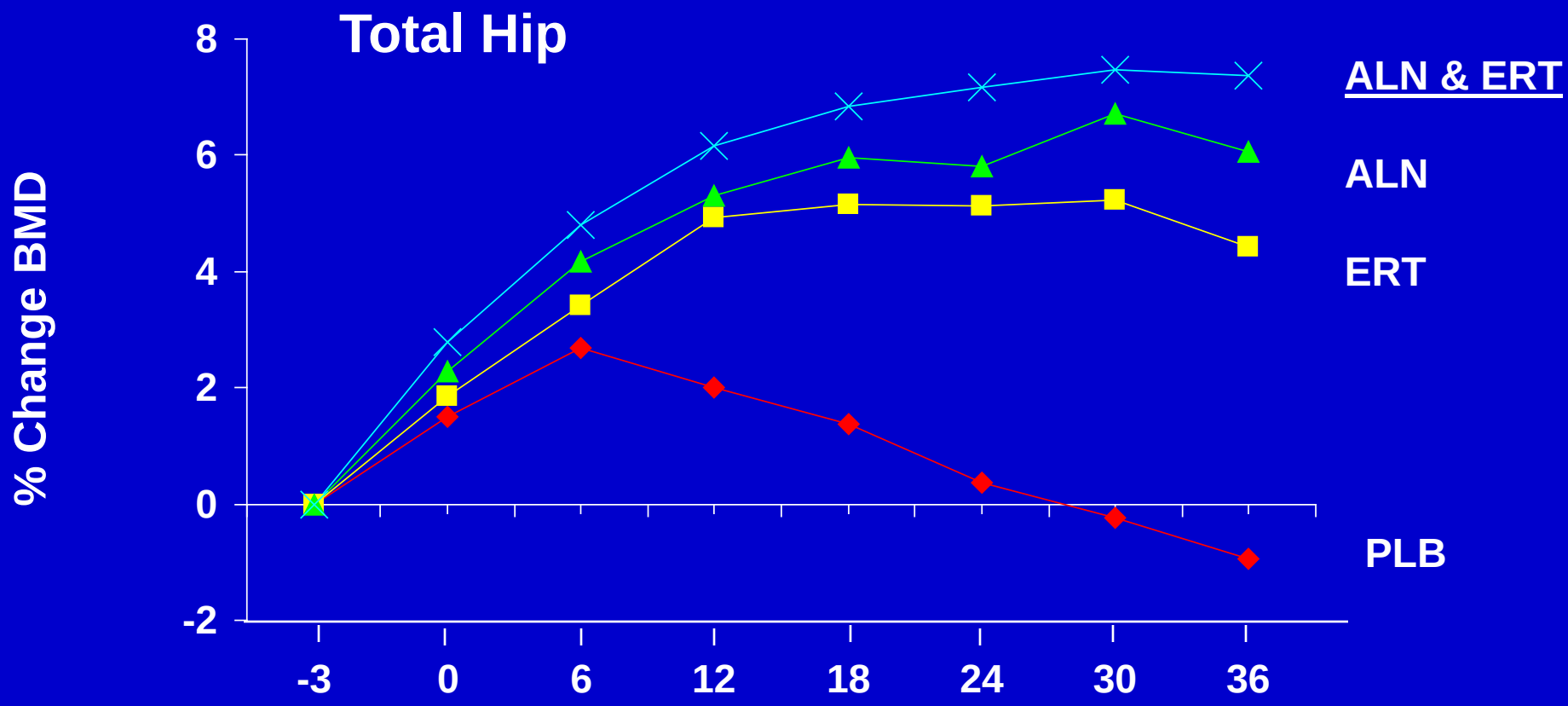
NS change in fx rate

Alendronate continued

Alendronate stopped

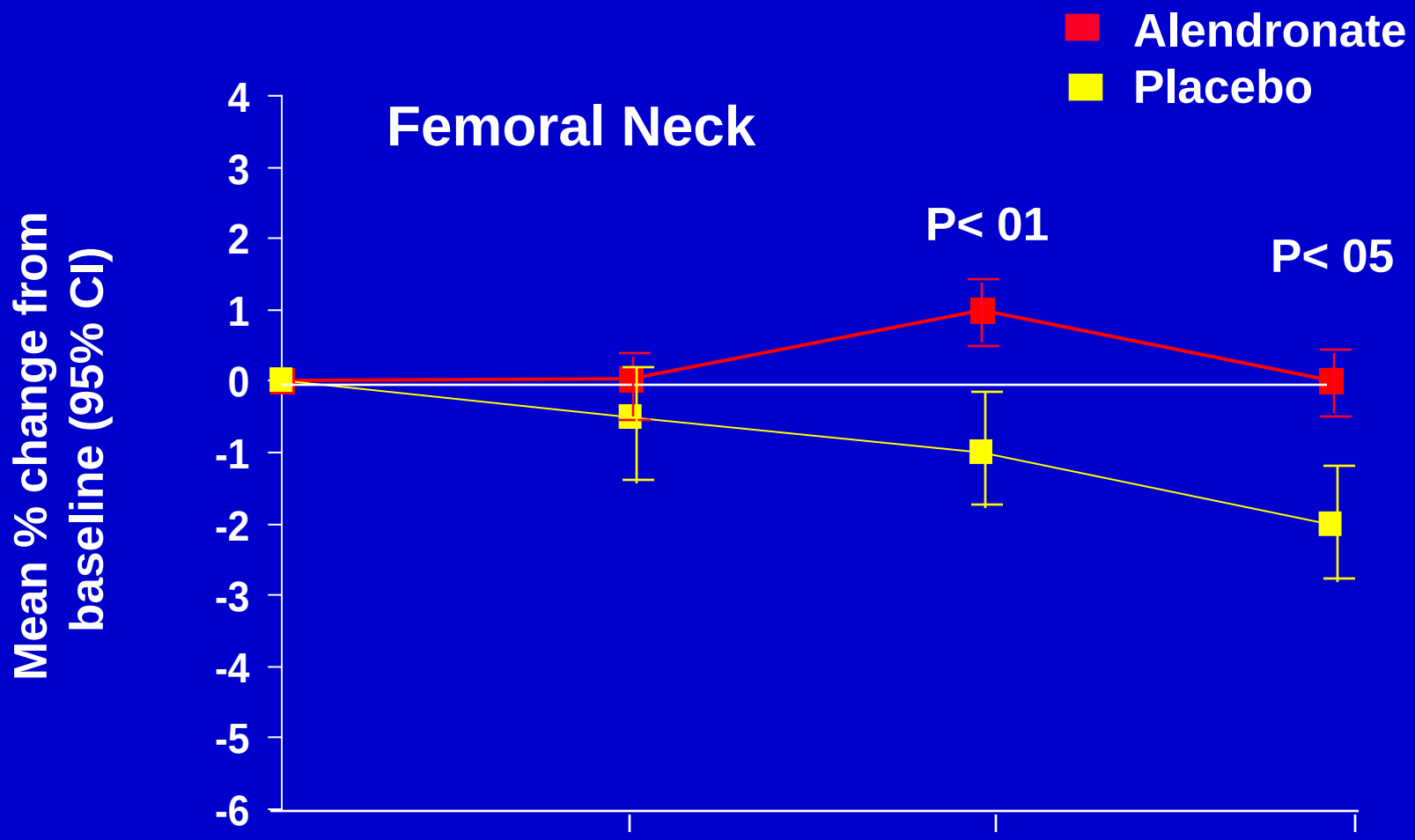
JAMA 2006;296:2932

Alendronate and ERT substantially improve BMD at three years



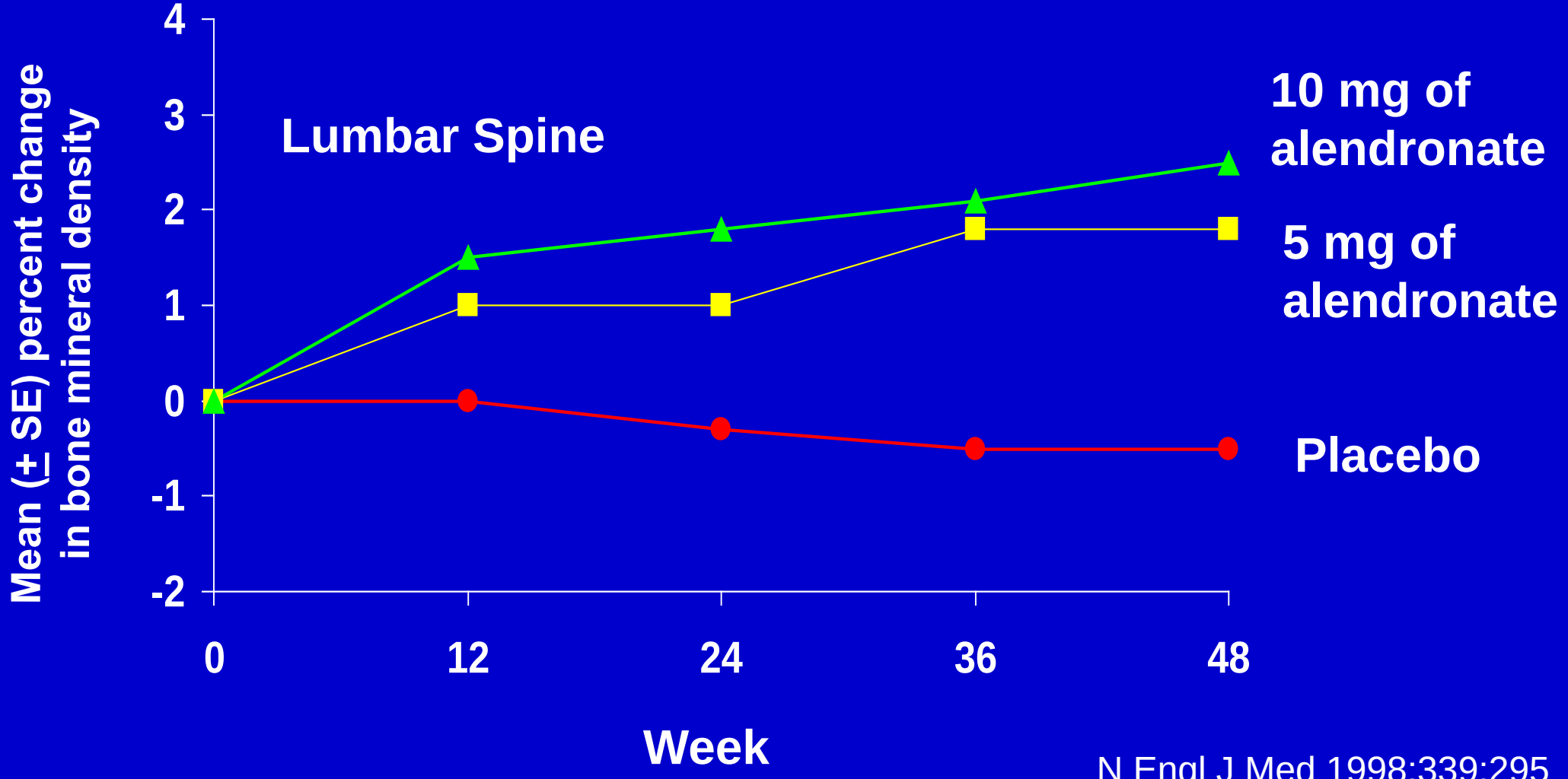
JAMA 2003;289:2529

Alendronate stabilizes BMD after discontinuation of ERT



Arch Intern Med 2003;163:789-794

Alendronate at HALF DOSE reduces steroid effect on bone density



N Engl J Med 1998;339:295

Bisphosphonates now challenged

September 2011. FDA report on bisphosphonates:

"**The safety of long-term bisphosphonate therapy continues to be unclear as study results are conflicting as to whether or not ONJ, atypical femoral fractures or esophageal cancer are associated with use of bisphosphonates for the prevention and treatment of osteoporosis… findings with increased duration of exposure to oral bisphosphonates, with the highest prevalence observed at 4 or more years of use.**"

Bisphosphonates: The dark side

- Jaw osteonecrosis
- Myopathy
- “Chalk stick” fractures
- Acute MI
- AF

Black box warning: Jaw osteonecrosis

2004 report of unexpected cluster in patients with malignancies on iv bisphosphonates. Also seen in patients with osteoporosis on oral agents (7/63).

Jaw osteonecrosis

Bisphosphonates and jaw osteonecrosis (N=368, 2006 literature review)

Diagnoses

Multiple myeloma	46.5%
Metastatic breast CA	38.8%
Metastatic prostate CA	6.2%

Therapies

Zoledronate/Pamidronate	94%
Oral Alendronate	4.2%

Myopathy

In 2008 the FDA issued a warning about the “possibility” of “severe and sometimes incapacitating bone, joint, and/or muscle pain in patients taking bisphosphonates.”

Femoral shaft fractures

In 2008, Neviaser et al reported a case series of 20 patients with low energy transverse or shot oblique femoral fractures, 19 taking alendronate.
RR calculated at 139 (95% C.I. 19-939)

Femoral shaft fractures

Meta-analysis of bisphosphonate trials: Risk for fracture by type for 3 years of treatment

Type of fracture	NNT
Hip prevented:	90
Subtrochanteric induced:[+]	
High risk from bisphosphonate	725
Low risk from bisphosphonate	2899

[+] Hypothetical risk limits, literature suggests average risk is 2.3.

N Engl J Med 2010;362:1769

Subtrochantic fracture risk highest after five years of bisphosphonate use

	Transient	< 3 years	3-5 years	≥ 5 years
Odds ratio	1.0	0.9 (NS)	1.59 (NS)	**2.74**

JAMA: 2011;305:783-789

Bisphosphonate use increased risk for subtrochantic fractures but risk disappeared within 2 years of stopping

Bisphosphonate use	Adjusted Relative Risk	Adjusted Absolute Risk Per Patient Year
Ever	47.3	1/2000
< 1 yr off	42.9	1/2000
1-2 yrs off	3.5	< 1/10,000
> 2 yrs off	3.2	< 1/10,000

N Engl J Med 2011;364:1728-1737

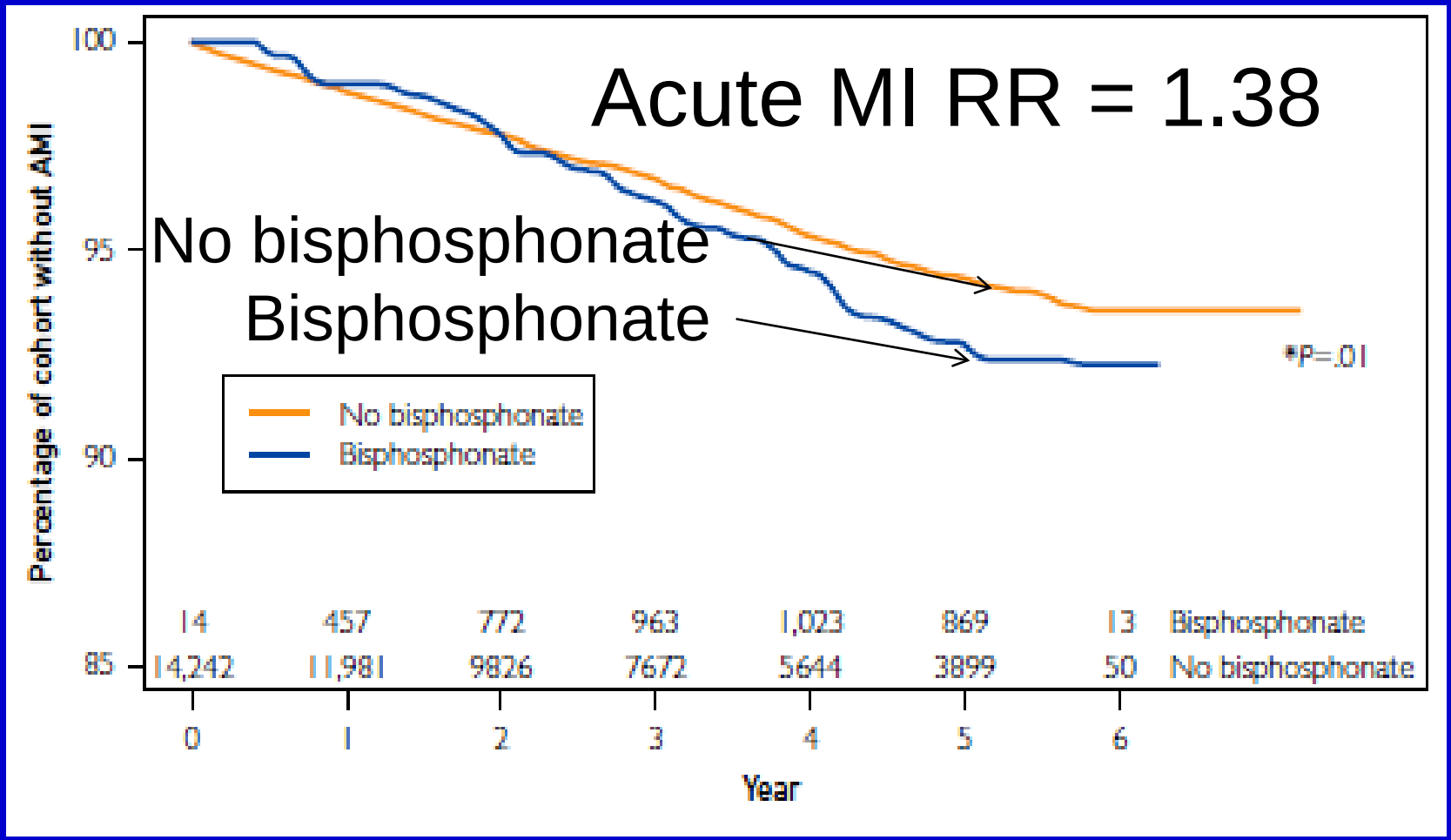
Acute myocardial infarction (2014)

In the VAMC cohort of 14,256 followed after femoral or vertebral fractures, 1998, bisphosphonate use was associated with increased risk for an acute MI

Mayo Clin Proc 2014:89:43-51

Bisphosphonate use and increased risk for AMI

% no AMI



Mayo Clin Proc 2014;89:43-51

Atrial fibrillation (2014)

A meta-analysis of RCT and cohort data from 135,347 patients showed an increased risk for AF

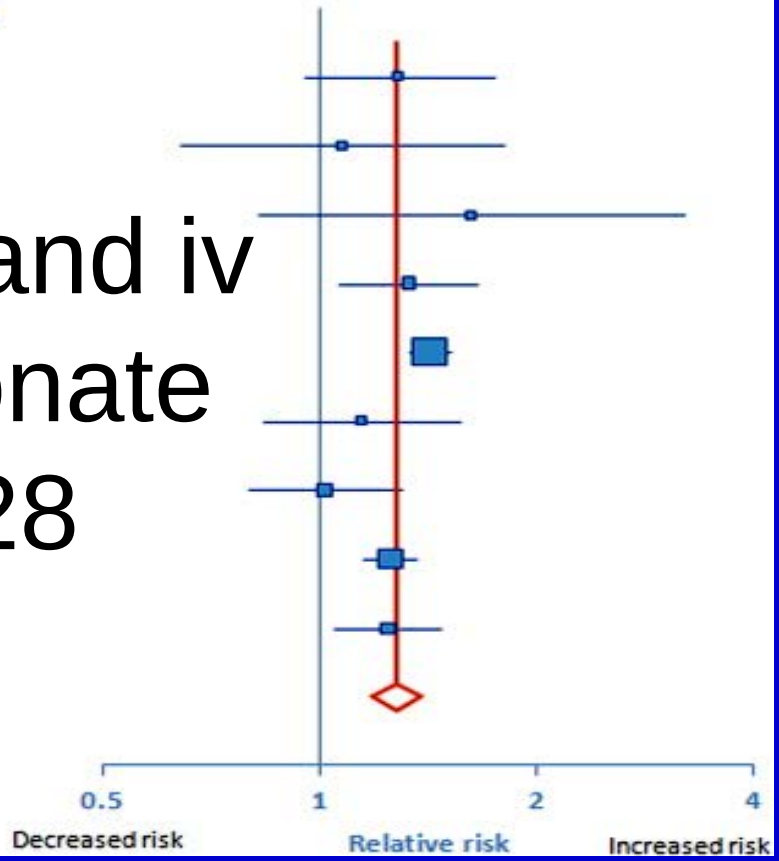
Am J of Cardiology 2014:133: 1815 - 1821

Bisphosphonate use and increased risk for atrial fibrillation

Author	Bisphosphonates Events (total)	Comparator Events (total)	Relative Risk (CI)	Weight %	P value
Black (2007)	94 (3862)	73 (3852)	1.28 (0.95; 1.74)	5.53%	0.1
Lyles	29 (1065)	27 (1062)	1.07 (0.64; 1.8)	2.09%	0.79
Black (2012)	21 (616)	13 (617)	1.62 (0.82; 3.2)	1.23%	0.17
Erichsn	128 (3981)	192 (7906)	1.32 (1.06; 1.64)	9.26%	0.01
Wilkinson	1234 (6857)	1742 (13714)	1.42 (1.33; 1.51)	29.78%	0
Cummings	81 (3236)	71 (3223)	1.14 (0.83; 1.56)	5.16%	0.43
Karam	189 (10018)	94 (5048)	1.01 (0.79; 1.29)	7.83%	0.92
Abrahamsen	797 (14302)	1280 (28731)	1.25 (1.15; 1.36)	25.93%	0
Huang	663 (21037)	158 (6220)	1.24 (1.05; 1.47)	13.22%	0.01
Synthesis	3236 (64974)	3650 (70373)	1.28 (1.18; 1.38)	100%	0

Test for Heterogeneity: Q statistic = 12.6 (p=0.125), I^2 = 37%

Pooled po and iv bisphosphonate AF RR= 1.28



Am J of Cardiology 2014:133: 1815 - 1821

Bisphosphonates side by side

	Dose	"Retention" half-life	Cost
Alendronate	70 mg/wk	> 10 yrs	$4/mo
Risedronate	35 mg/wk	9.5 days	$40/mo
	150 mg/wk		$40/mo
Zolendronate	5mg/yr IV	7 days	$1300/yr

Do not treat osteopenia with bisphosphonates

	Femoral neck T-score		
	-1.5	-2.0	-2.4
Age 55	$255,823	$94,386	$74,200
Age 65	**$283,933**	$92,409	$70,732
Age 75	**$322,250**	$108,714	$86,465

2005: Cost benefit analysis

Patients who take their bisphosphonates do better!

(N=35,537, national cohort)

	Persistent (%)	Non-persistent (%)	RR (p value)
Bisphos use	≥80%	<80%	
Vertebral fracture	1.7	2.6	0.643 (p<0.001)
Hip fracture	1.3	2.1	0.612 (p<0.001)

Mayo Clin Prac 2006;81:1013-1022

When should your patients take a bisphosphonate holiday?

5 years for alendronate

- Follow BMD and resume if decline

-Follow BMD and switch to alternative if decline

There MAY be patients who should continue on bisphosphonates, those with persistent severe osteoporosis

FLEX Extension (beyond 5 yrs of alendronate)

BMD, start of extension	Vert fx rate Placebo	Alend	NNT
T < -2.5	9.3%	4.5%	21
T -2.5 to -2.0	5.8%	2.8%	33
T > -2.0	2.3%	1.2%	81

N Engl J Med 2012; 366:2051-3

Bisphosphonates should be used with circumspection

- When are bisphosphonates appropriate?
  - T $\leq$-2.5 at the hip
  - “Advancing” osteopenia
- How long should they be used?
  - Five years
- What do you need to know about the side effects?
  - More than you thought

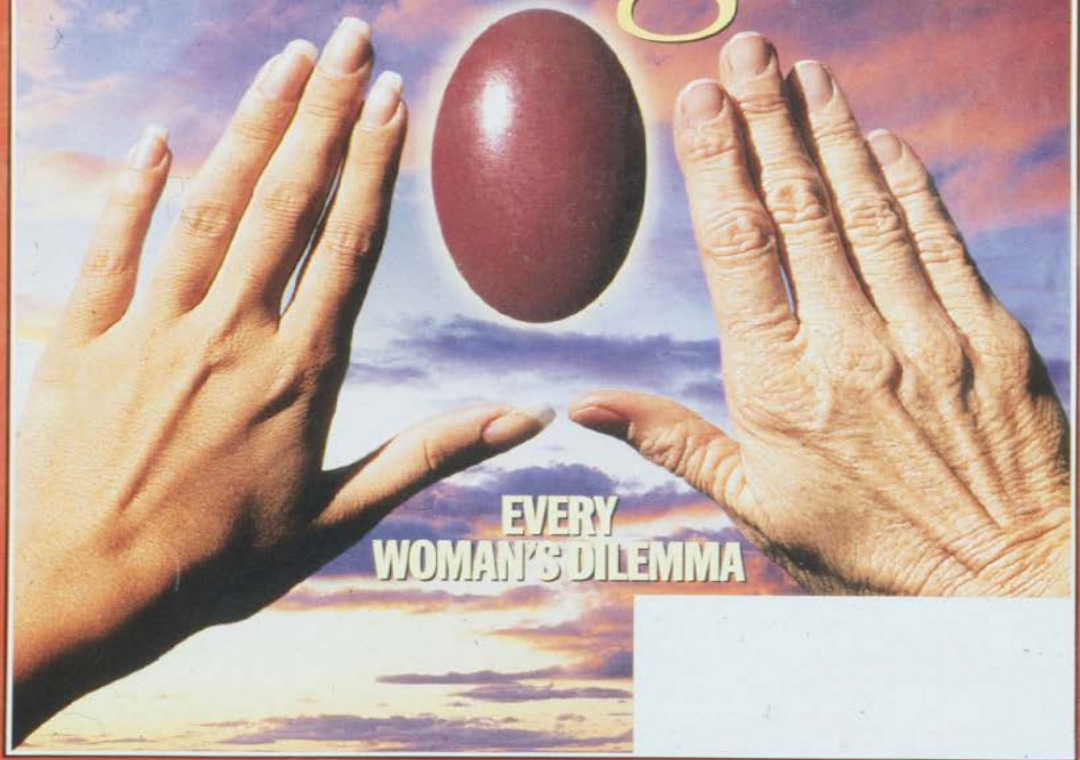
JUNE 26, 1995

Scott O'Grady, Part 2: The Big Spin

$2.95

TIME

Estrogen



EVERY WOMAN'S DILEMMA

Mechanism:

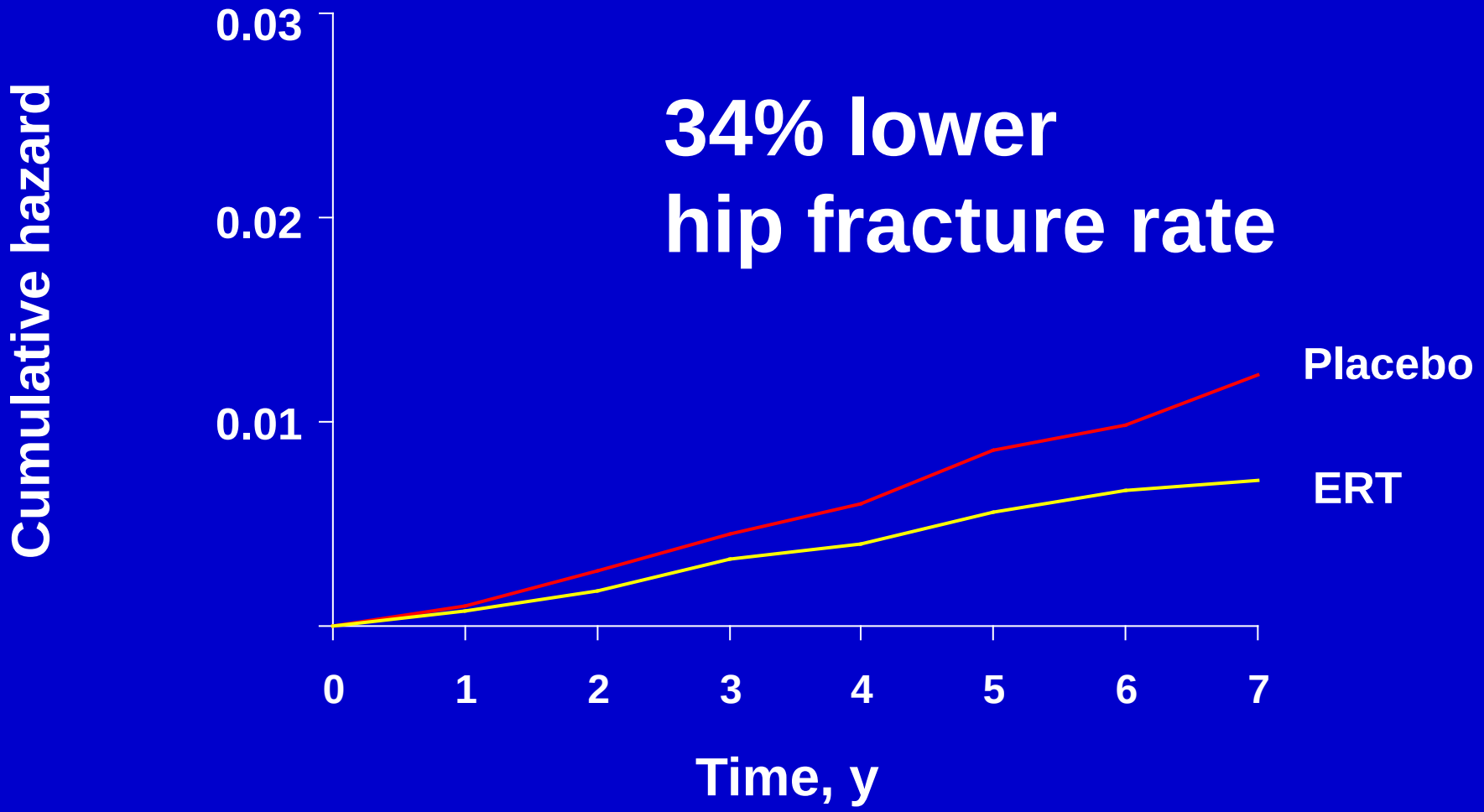
Estrogens inhibit osteoclastic activity.

The response is based on the dose, higher doses increase bone density more.

Estrogens can improve bone density at any age after menopause.

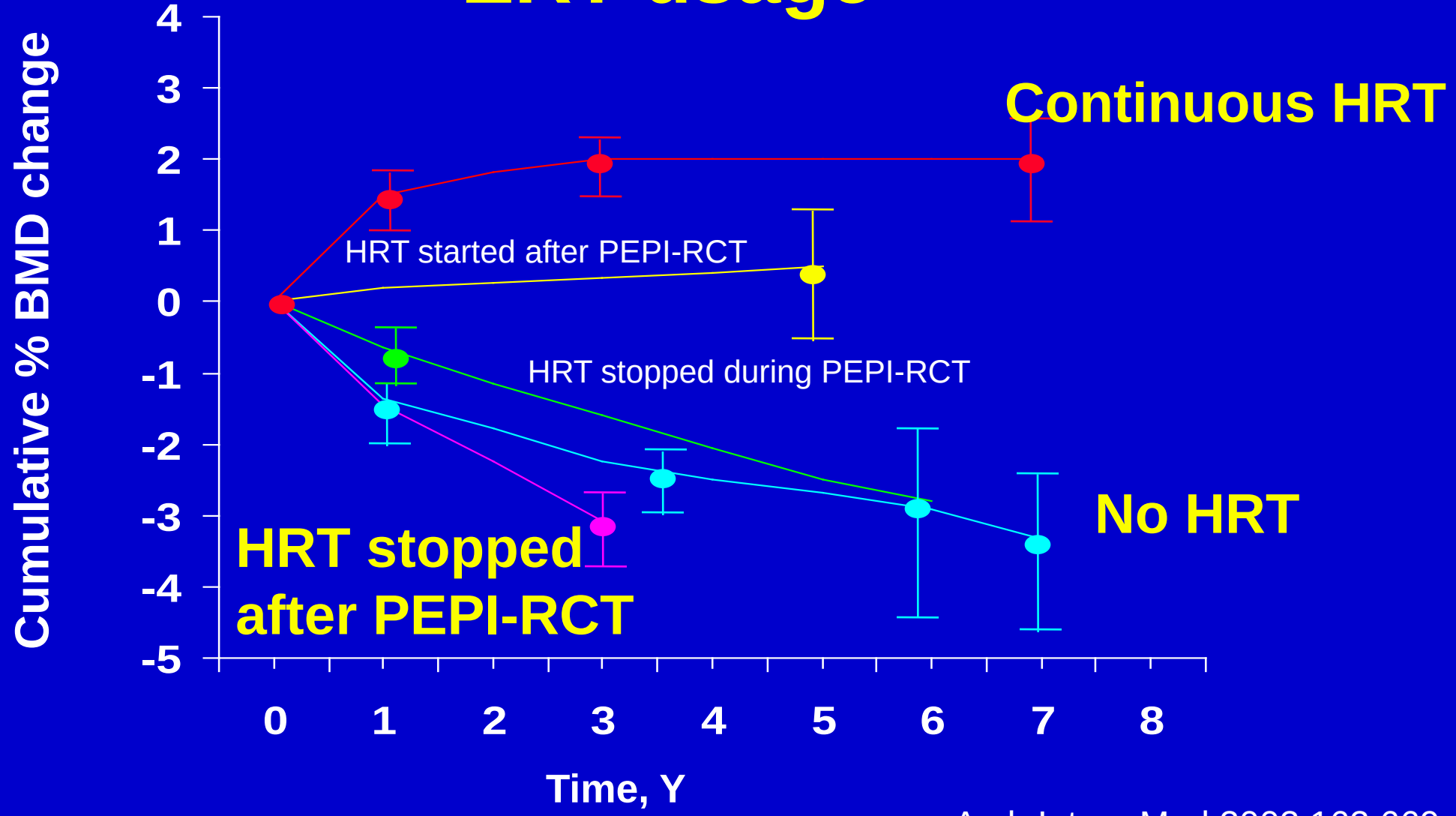
The improvement of bone density is lost within 1-2 years after cessation.

WHI: Combination ERT vs. placebo, hip fracture risk



JAMA 2002;288:328

PEPI: Bone density change and ERT usage



Arch Intern Med 2002;162:669

WHI: Patient outcomes Combination estrogen/progestin vs. placebo

Absolute excess events per 10,000 patient years

CAD events	7
CVAs	8
PEs	8
Invasive breast cancer	8
Total	31[+]

[+] Approximate three events for 200 women treated for five years

What about raloxifene?

- Not equal to estrogen
- Data is not substantial

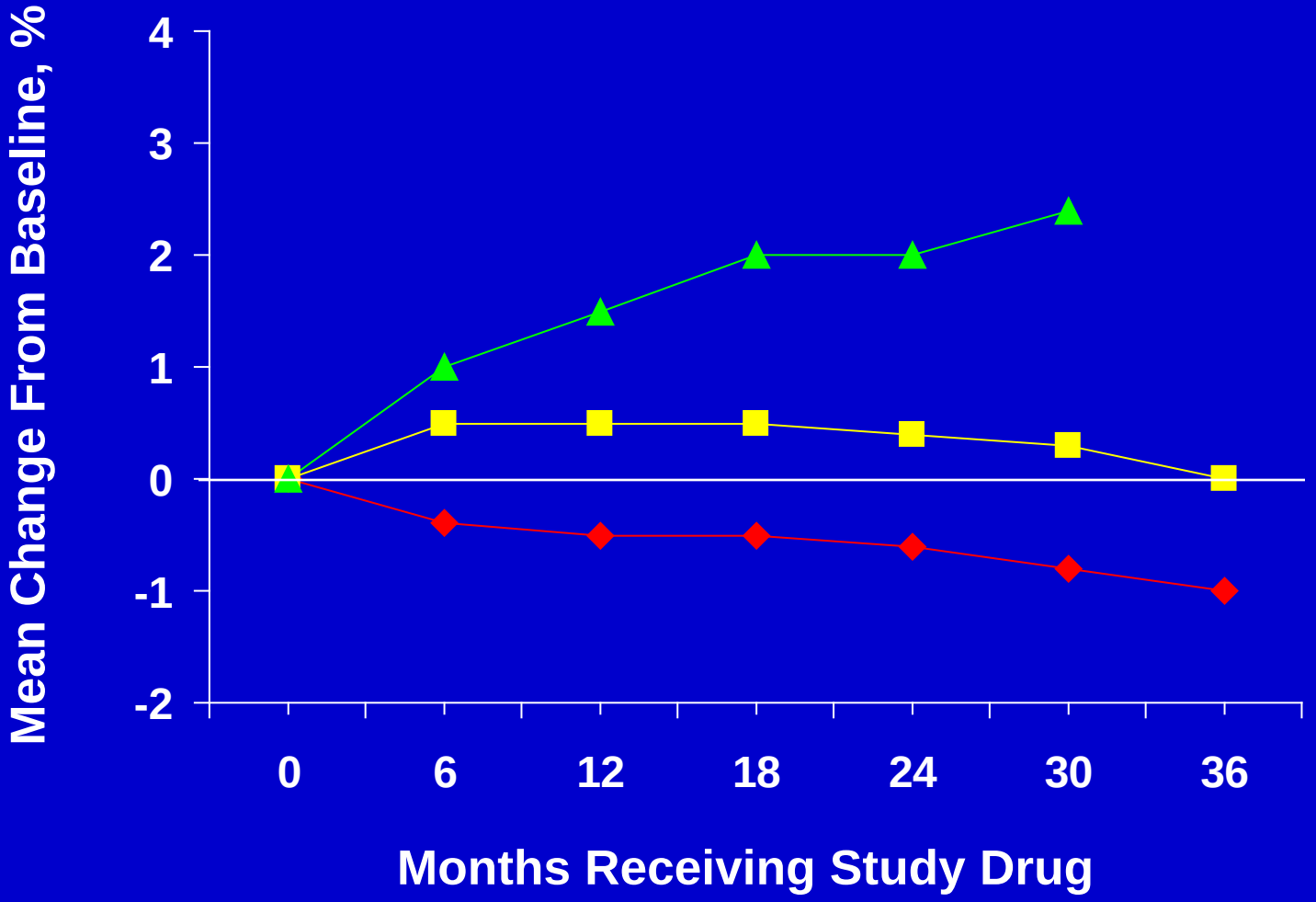
Raloxifene does not reduce hip fractures (N=10,101; 5.6 year follow up; age 67.5)

	(Hazard ratio, 95% C.I.)
Coronary events	NS
Invasive breast cancer	0.56 (0.38-0.83)
Fatal stroke	1.49 (1.0-2.24)
Venous thrombosis	1.44 (1.06-1.95)
Vertebral fracture	0.65 (0.47-0.89)
Non vertebral fracture	**NS**

Raloxifene increases vascular event rates (N=10,101; 5.6 year follow up; Age 67.5)

Reduction of invasive breast cancer	1.2/1000 patient yrs
Reduction in vertebral fractures	1.2/1000 patient yrs
Increase in fatal stroke	0.7/1000 patient yrs
Increase in venous thromboembolic events	1.2/1000 patient yrs

Raloxifene does not match estrogens (RCT, N=619 women with TAHs)



Arch Intern Med 2004; 164:875

What are the options for your patients who need more…enter the anabolics

- Hormonal
  - Teriparatide
- Biologics
  - Denosumab
  - Romosozumab
- Combination therapies
  - Estrogens and bisphosphonates
  - Teriparatide and denosumab

Teriparatide mechanism:

Intermittent PTH fraction administration has an ***anabolic*** effect. Trabecular bone density and strength increase. Cortical bone strength increases by improving the bone thickness with little change in bone density. NOT used with bisphosphonates.

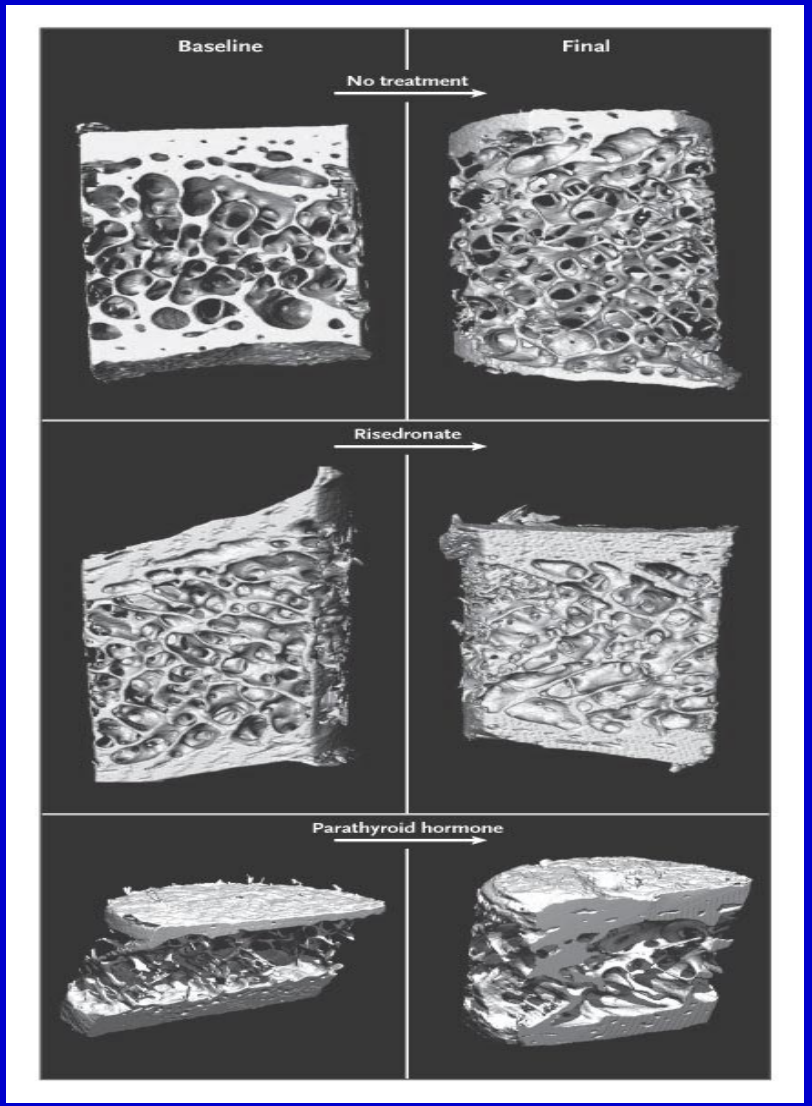
Dosage:

20-40 mg subcutaneously

Side effects:

Myalgia

PTH thickens internal bone trabeculation and cortex with less impact on BMD



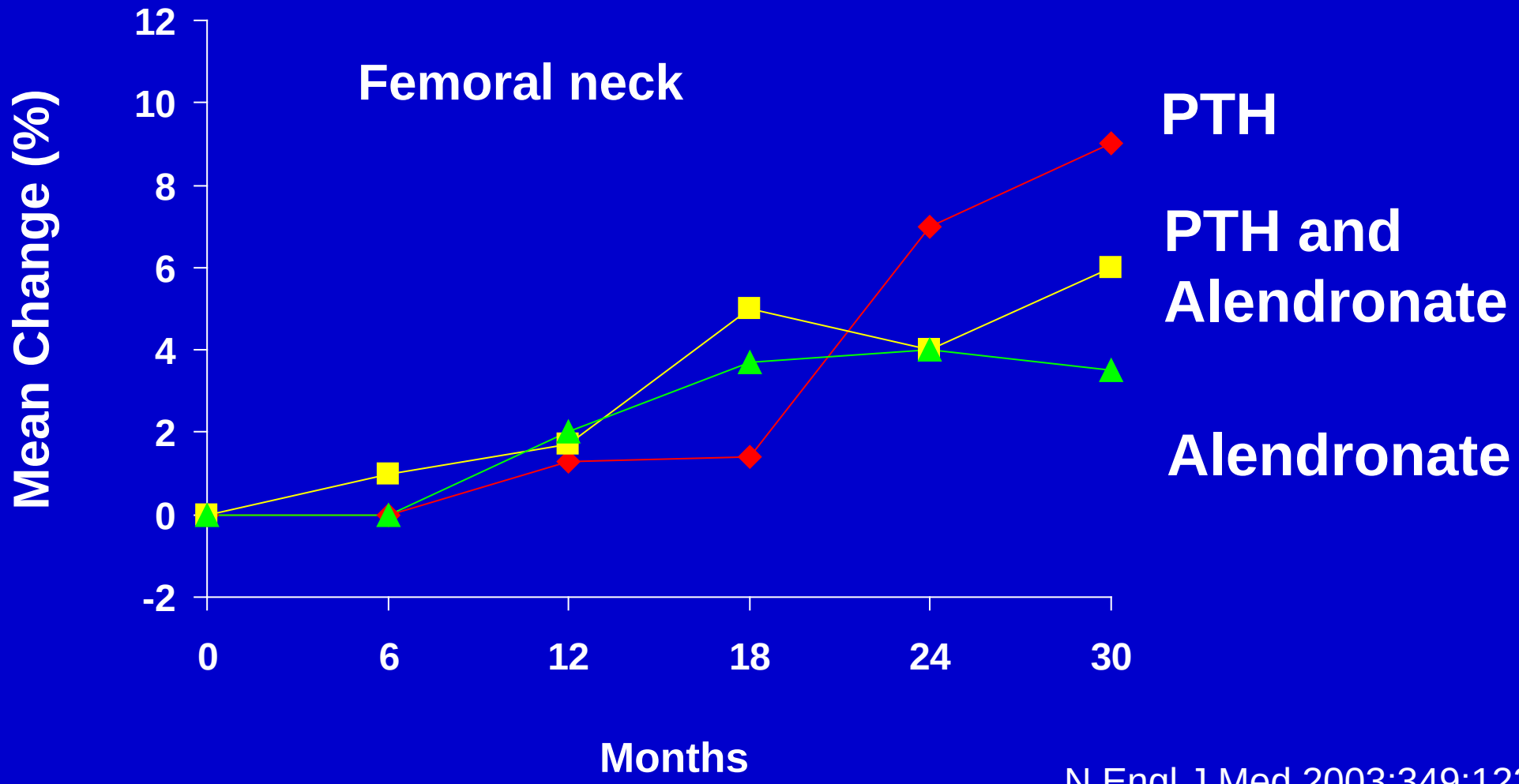
No treatment

Risedronate

PTH

N Engl J Med 2006;354:2258

PTH alone improves bone density more than combination or Alendronate alone



N Engl J Med 2003;349:1221

Teriparatide works, especially at LS spine

2013 Meta-analysis:

8 RCTs, 2388 patients with osteoporosis

	Spine	Hip
BMD increase	8.14%	2.48%
Fracture reduction	70.0 %	38.0%

Int J Clin Pract 2012; 66: 199-209

Denosumab mechanism:

Monoclonal antibody directed against the receptor ligand (RANKL). Binding the ligand reduces osteoclastic activity.

This is a “biologic” that interacts with other receptors, hence the dermatologic SE

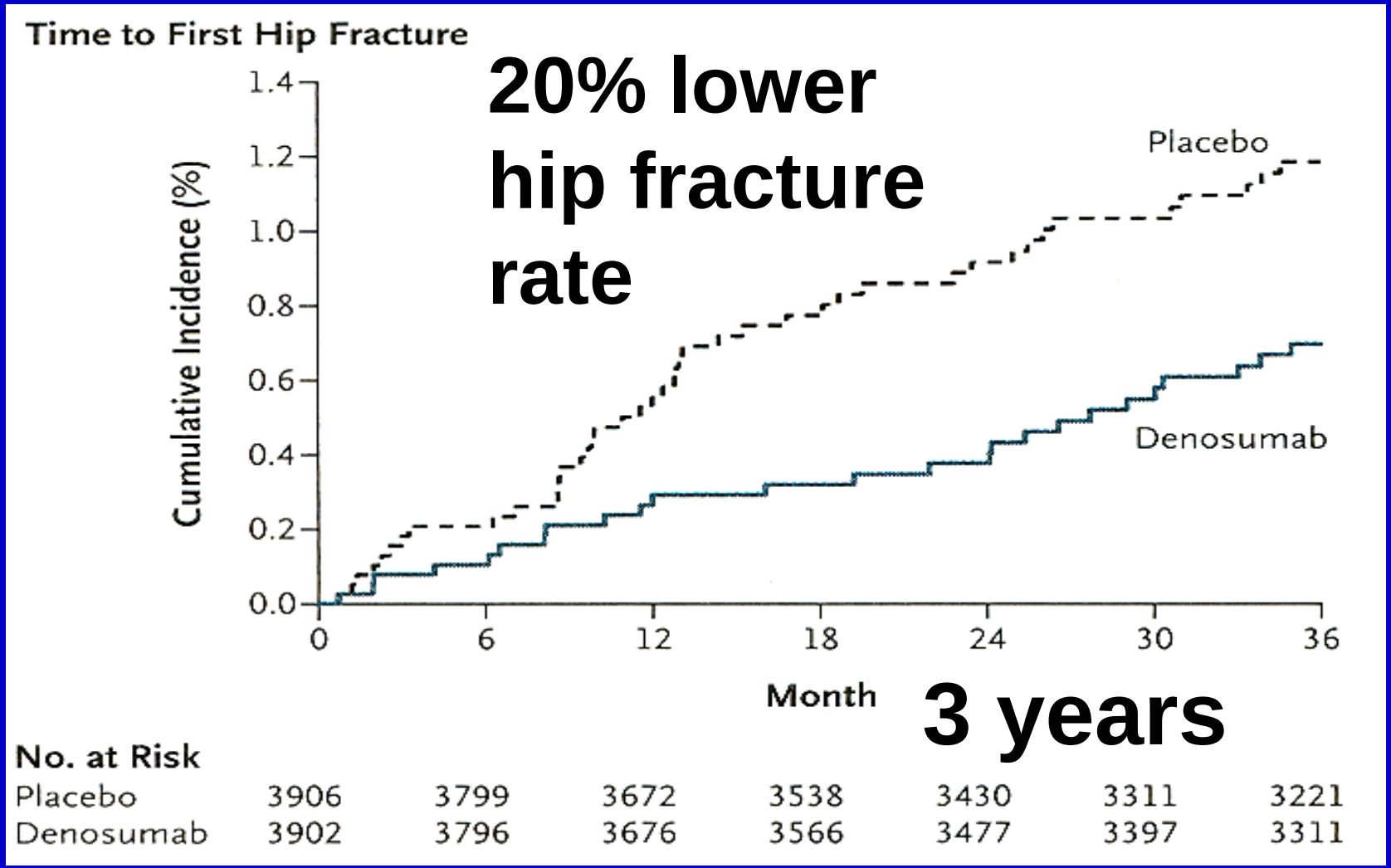
Dosage:

60 mg subcutaneously every 6 months

Side effects:

Eczema, cellulites

Denosumab reduces hip fractures



N Engl J Med 2009;361:756-765

More biologic anabolics are coming

ORIGINAL ARTICLE

Romosozumab in Postmenopausal Women with Low Bone Mineral Density

Michael R. McClung, M.D., Andreas Grauer, M.D., Steven Boonen, M.D., Ph.D.,*
Michael A. Bolognese, M.D., Jacques P. Brown, M.D., Adolfo Diez-Perez, M.D., Ph.D.,
Bente L. Langdahl, Ph.D., D.M.Sc., Jean-Yves Reginster, M.D., Ph.D.,
Jose R. Zanchetta, M.D., Scott M. Wasserman, M.D., Leonid Katz, M.D.,
Judy Maddox, D.O., Yu-Ching Yang, Ph.D., Cesar Libanati, M.D.,

N Engl J Med Online Jan 1, 2014

Romosozumab mechanism:

Monoclonal antibody that binds sclerostin, an osteocyte-derived inhibitor of osteoblast activity, and increases bone formation.

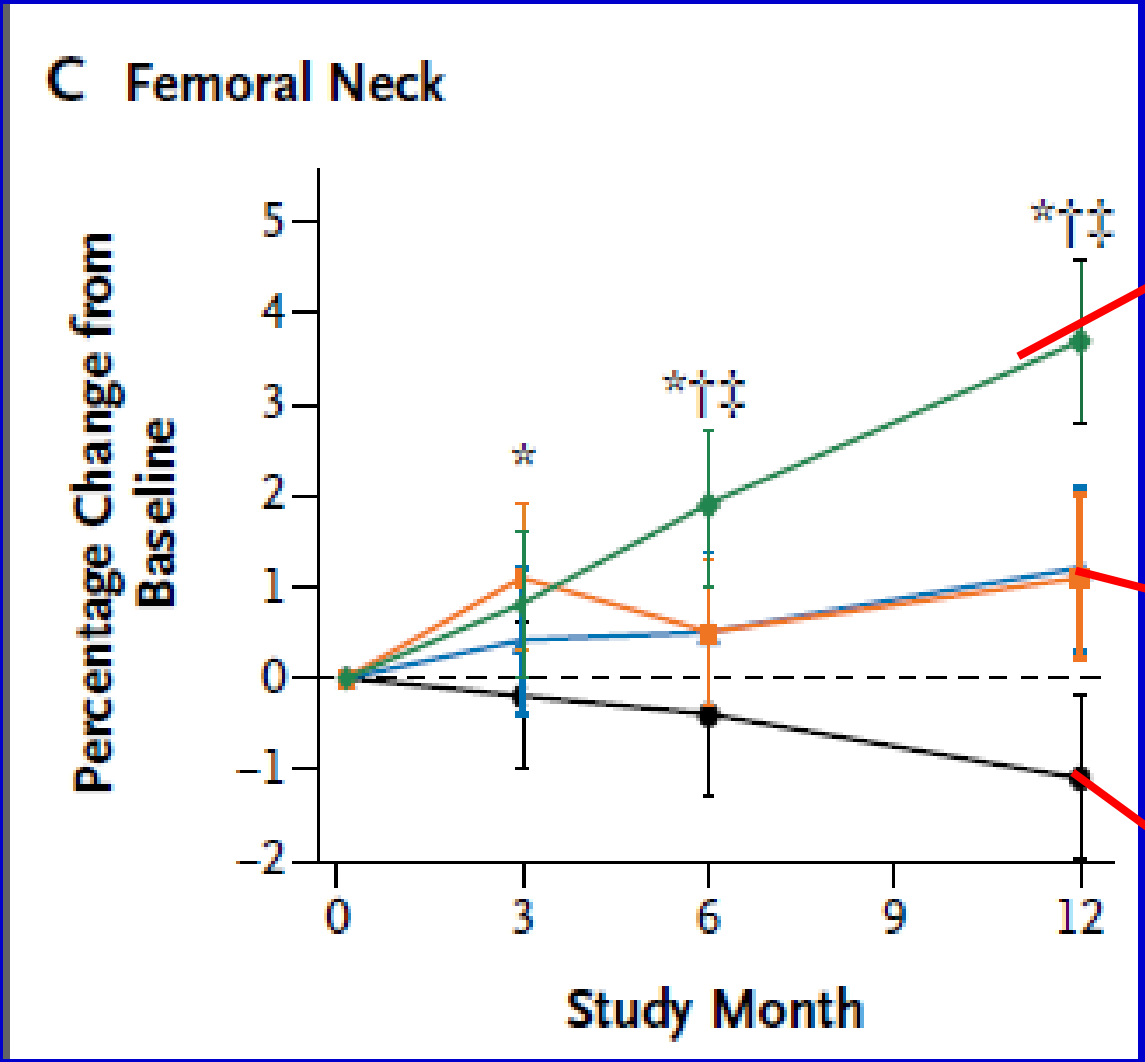
Dosage:

Subcutaneously monthly (at a dose of 70 mg, 140 mg, or 210 mg) or every 3 months (140 mg or 210 mg)

Side effects:

Mild local reactions

Romosozumab out performs other anabolic agents….in osteopenia



3.7% increase in BMD at 12 months with Romosozumab

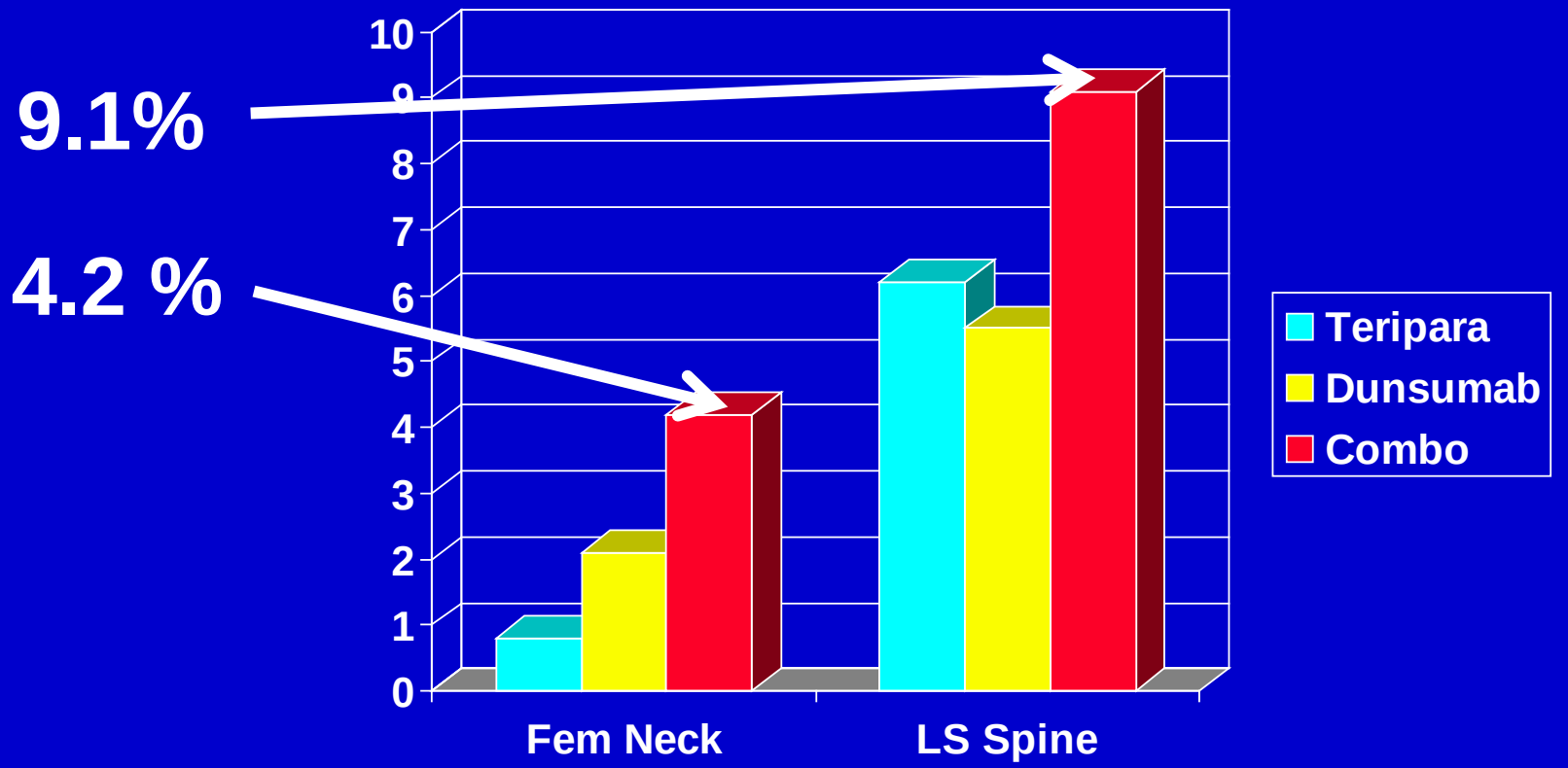
< 1% increase in BMD with both alendronate and teriparaitide

Placebo

N Engl J Med Online Jan 1,2014

Teriparatide and denosumab combination therapy

RCT, 1 year, 94 women with osteoporosis
Outcome: % BMD increase



Lancet Online, May 15., 2013

Costs of teriparatide and denosumab

	Dose	Cost
Teriparatide	20 mcg/d SC	$8000/yr
Denosumab	60 mg/6 mo SC	$2000/yr

Is there an optimal pharmacologic approach?

- Choose therapies that have been shown to work
  - Estrogens
  - Bisphosphonates
- Innovative therapies are in development
  - Use cautiously
  - Severe osteoporosis

Comparative benefits: NNT to prevent one fracture over 3 years

	Vertebral	Hip
Bisphosphonates		
Alendronate	60-89	50-60
Zolendronic Acid		30

Ann Intern Med 2014;161:711-756

In summary: Fracture prevention 101

- Assess risk
  - Level of frailty
  - Medications (are you contributing to risk?)
  - Hazards at home
- Emphasize the basics, intervene when needed
  - Exercise/balance (be creative!)
  - Calcium (500 - 1000 mg/day)
  - Vitamin D (800-1000 U/day)

Patient messages:

It is not thin bones that break, it is people who fall and break thin bones!

You walk to exercise because you need to be able to walk, practice, practice

Beware of the hazards at home

Use all the options available, especially the “stick”

Thank you

- Questions?

Recommendations

Major risk factors for osteoporosis:

- Parental history of hip fracture
- Current or past cigarette smoking
- Current or past alcoholism
- Body weight (BMI<23)
- Steroid use
- Hyperthyroid
- Early menopause, anovulatory cycles

Major risk factors for osteoporosis:

Always look at the medications

- Benzodiazepines
- Sedatives (Including OTCs like Tylenol PM)
- Antihypertensives
- Medications for neuropathies
  - Tricyclics

Your clinical assessment:

"Timed Up and Go (TUG) " = Chair-to 10 foot walk-to chair in ≤ 10 sec.

Balance/proprioception

Judgment/decision-making

Focus/attention/affect

Strength

"Social history"

Life style risks, e.g. alcohol

Risk taking activities

Recommendations:

- ***Bone density***

  Diagnosis
  Patient education and motivation
  To assess high risk situations
  To monitor therapy every 2-3 years
  Men over 80 (or over 65 if fracture history or risk factors).

Recommendations (cont):

- **FRAX** online assessment may be useful for determining whether to initiate therapy for men and women with osteopenia. The model may significantly overestimate risk.

- ***Markers of bone turnover***

  To follow patients for response

Recommendations (cont'd)

- ***Calcium***
  - 1000 -1500 mg/day

- ***Vitamin D***
  - 800 -1000 IU/day, treat to level of over 25 ng/mL

Recommendations (cont'd)

- ***Estrogens***

  Conjugated estrogen 0.3 - 0.625 mg/day

  Progestin if uterus intact but with high breast cancer risk

  Mammograms and clinical breast exams annually

  Can combine with bisphosphonates

Recommendations (cont'd)

- ***Bisphosphonates***
  - ***-Alendronate or residronate***
    - 70 mg./wk. for alendronate
    - 35 mg./wk. for residronate
    - severe osteoporosis
    - osteoporosis
    - men and women on short-term corticosteroids, half dose
    - "advancing" osteopenia

Recommendations (cont'd):

-*Zoledronate*

- infusion therapy, every 12 months
- men on leuprolide
- alternative to alendronate and residronate

Recommendations (cont'd)

- ***Tamoxifen/Raloxifene***
  - limited value, vascular risk
- ***Teriparatide***
  - expensive, two years followed by bisphosphonate
- ***Calcitonin***
  - ? painful stress fractures

Recommendations (cont'd)

- ***Denosumab***
  - 60 mg subcutaneously every 6 months
- ***Combination therapy***
  - estrogens and bisphosphonates
  - teriparatide and denosumab