BAD TO THE BONE

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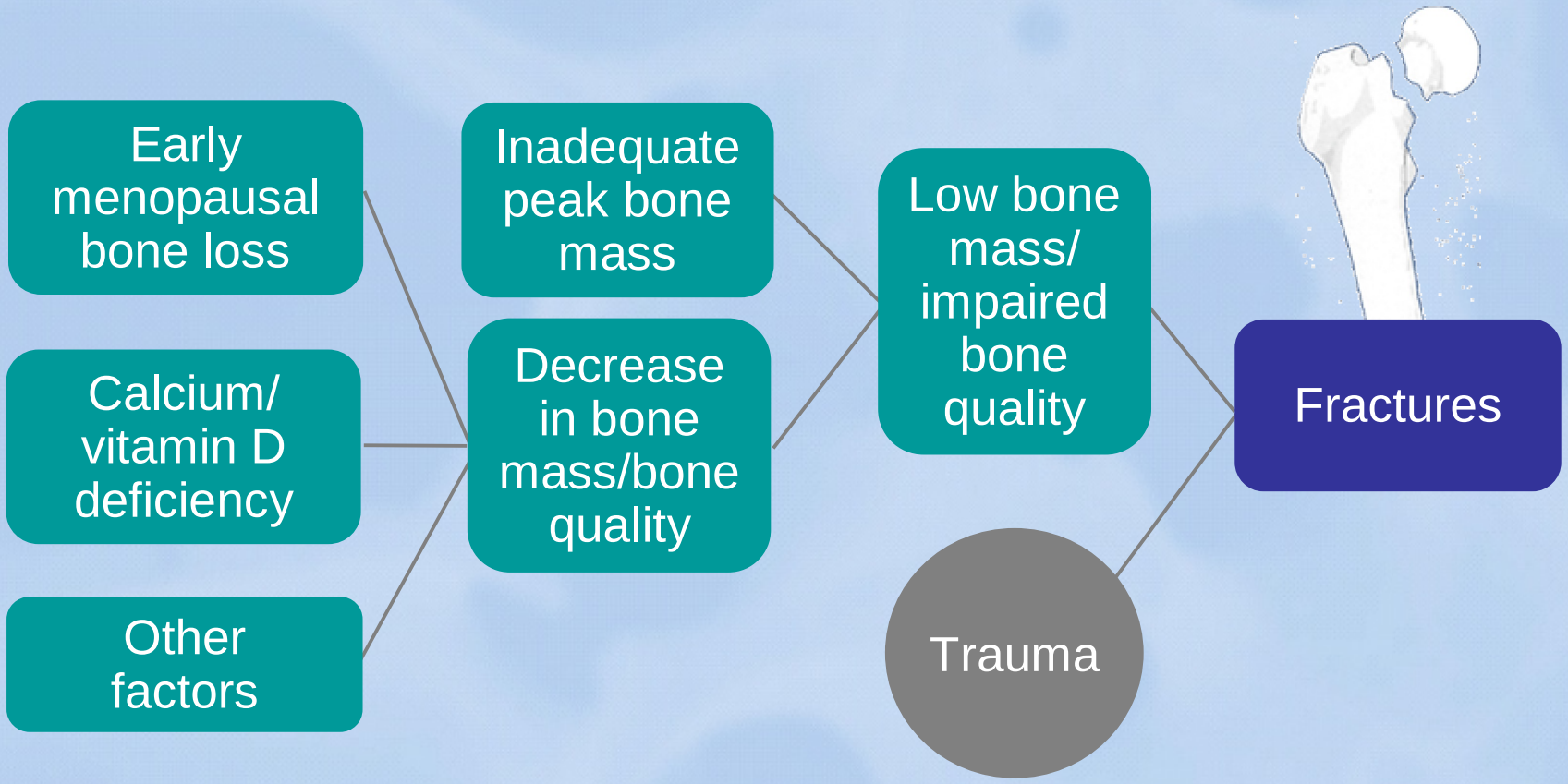
GP CME Conference

Rotorua, June 2008

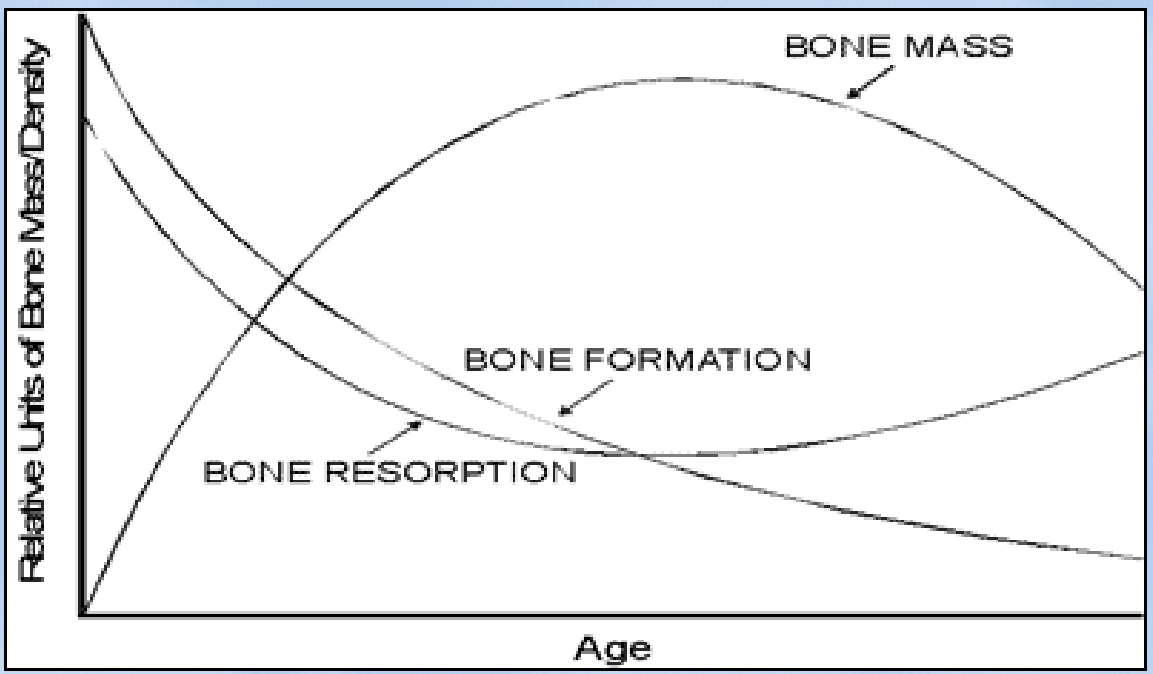
Agenda

- Osteoporosis in Men
- Vitamin D and Calcium
- Long-term treatment with Bisphosphonates

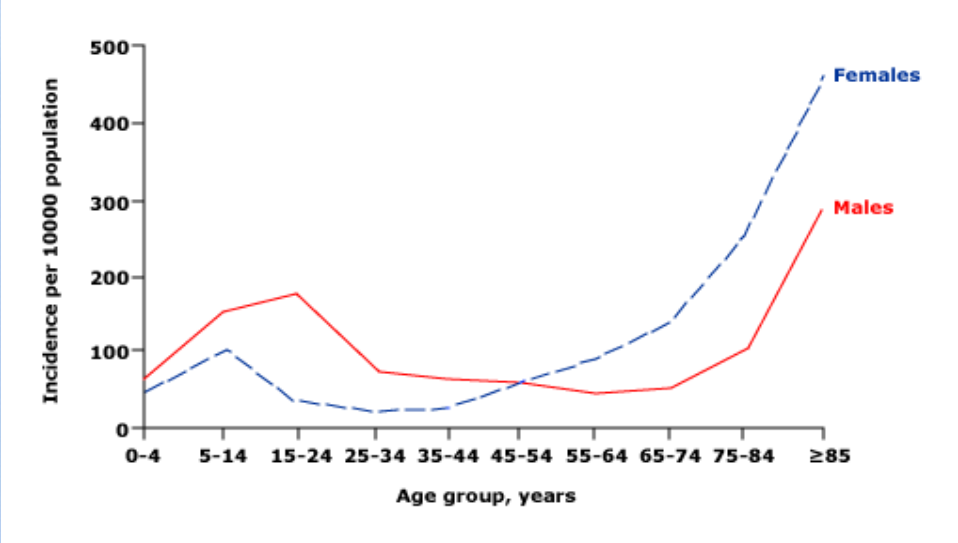
Pathophysiology of Osteoporosis



Bone Homeostasis



Fractures are Common in Men



- At 60, lifetime risk of osteoporotic fracture is 25%
- One third of hip fractures occur in men
  - Hip or vertebra 6% vs 18%
  - Colles' 2.5% vs 16%

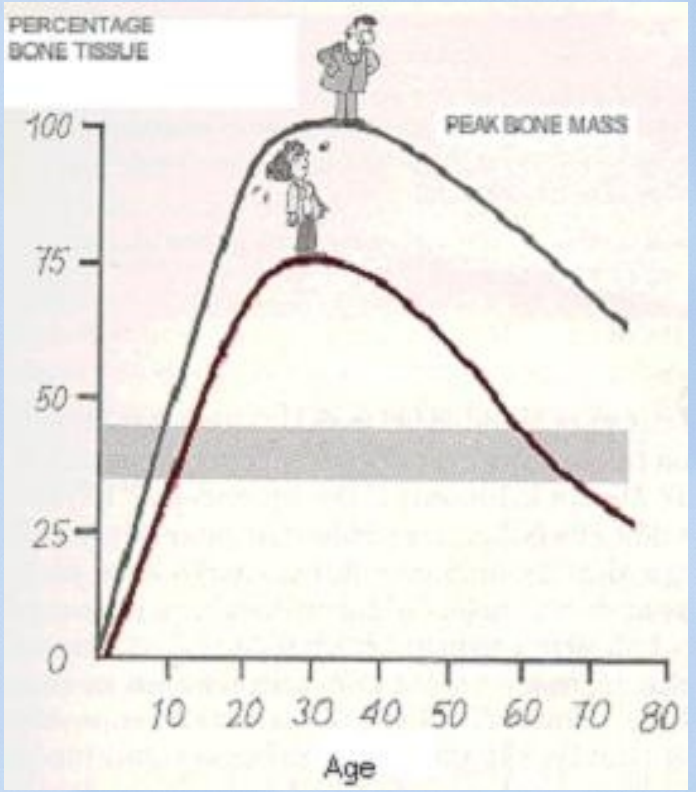
Remaining Lifetime Risk of Fragility Fractures in the Swedish Population

	Lifetime risk at age 50 (%)	
Type of fracture	Women	Men
Hip	22.9	10.7
Distal forearm	20.8	4.6
Vertebrae (clinical)	15.1	8.3
Proximal humerus	12.9	4.1
Any of the above	46.4	22.4

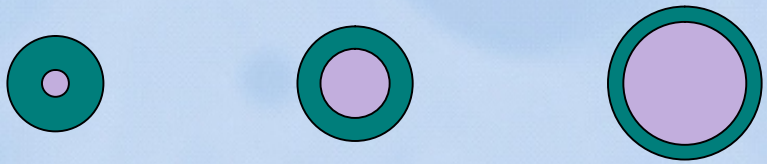
Kanis, J. A., et al. Osteoporos Int. 2002 11:669-74, with permission from Springer-Verlag.

It’s Good to be a Man

- Peak Bone Mass is Higher
  - Pubertal growth regulated by sex steroids
  - Higher ratio of cortical to cancellous bone
  - Greater BMD than women partly due to larger bone size



Effect of Bone Geometry on Bone Strength



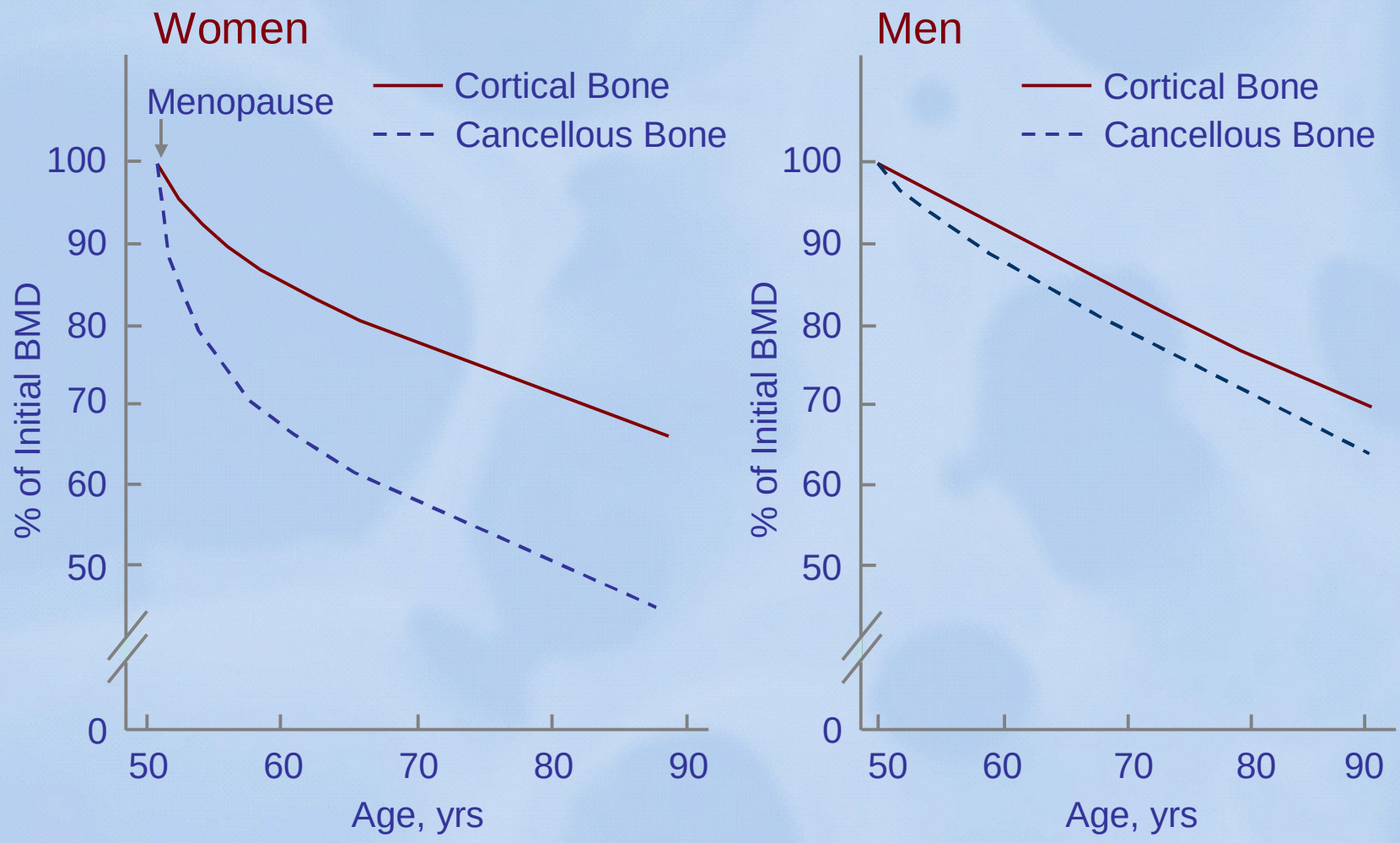
Cross-sectional area	1.0	1.0	1.0
Bending Strength	1.0	4.0	8.0
Axial Strength	1.0	1.7	2.3

These three cylinders have identical cross-sectional areas. Their bending strength is determined by the distance of their material from the axis. A larger bone (e.g. in a man) is much stronger than a smaller bone with the same mineral content.

Men Are Different From Women

- Bone loss is less and later
  - No postmenopausal rapid decline in estrogen
  - No preferential cancellous bone loss
  - Different fracture patterns (forearm fractures rare)
- Fracture rates approximate women but 10 years later
- Fractures in Men indicate a much poorer health state

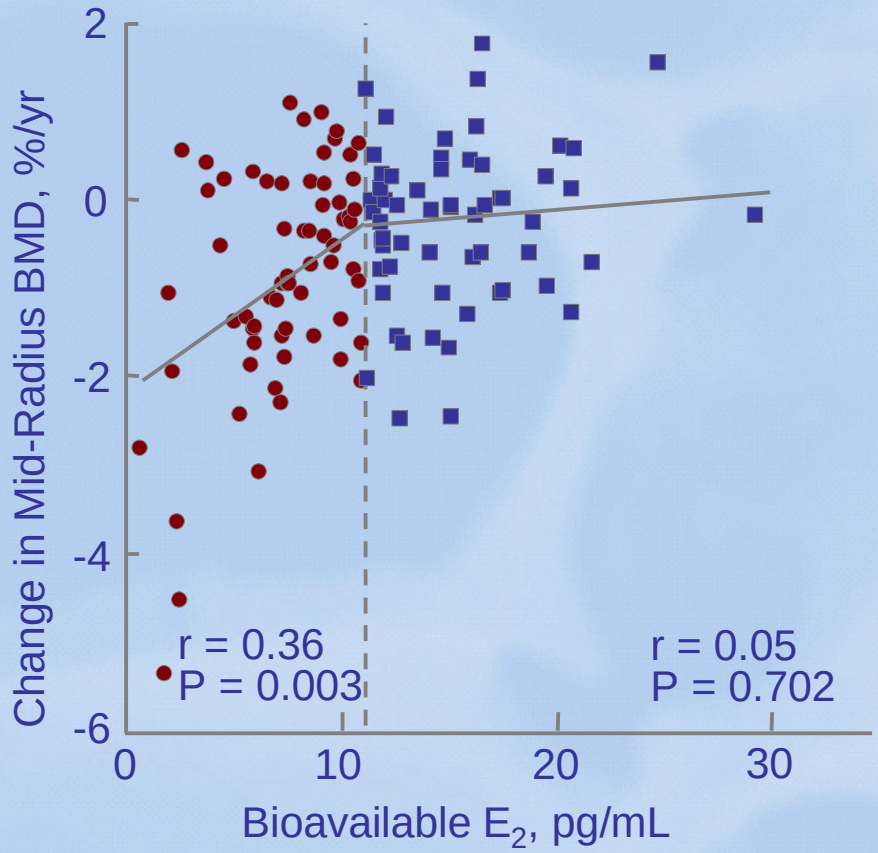
Patterns of Bone Loss in Men and in Women



Causes of Low Bone Mass in Men

- Low PBM
  - Constitutional delayed puberty
  - Primary hypogonadism
  - Androgen insensitivity
- Causes of increased bone loss
  - Alcohol
  - Prostate cancer
  - Androgen deprivation (orchidectomy, GnRH inhibitors)
  - Oestrogen deficiency (aromatase inhibitors)

Bone Loss Due to Sex Steroid Deficiency in Men



- Bioavailable T and E_2 decline with normal aging
- Bone loss in men is best correlated with bioavailable E_2
- Bioavailable E_2 is a determinant of bone mass in men, as in women

Khosla, S., et al. J Clin Endocrinol Metab. 2001 86:3555-61, with permission, Copyright 2001, The Endocrine Society.

Bone Loss in Men

- Bone loss accelerates after 70
- Mostly due to decreased formation
  - In women – due to loss of trabeculae
- 40-60% of osteoporotic men have secondary osteoporosis (Vs 5-10% of women)
  - Investigation has a higher yield of pathology
  - Mortality following hip fracture is higher (indicates frailty, poor health)
- Fractures can be predicted by
  - Fractures, especially radius
  - Low levels of physical activity in elderly men
  - Family history

‘Causes’ of Low BMD and Fractures in Men

- Idiopathic 40-60%
- Glucocorticoids
- Smoking
- Alcohol
- Hypogonadism
- Hypercalciuria
- Weight loss
- Low calcium intake
- Low levels of physical activity (especially in elderly)

Treatment of Osteoporosis in Men

- Resistance training (increases BMD but no fracture data)
- Testosterone replacement
  - Works best for hypogonadal adolescents
  - Increases in BMD of 9% over 3 years in hypogonadal men >65
  - Increase in trabecular connectivity by MRI
  - Little evidence of benefit in eugonadal men
    - but significant harms
  - IM treatment more effective than transdermal in observational studies
- No role for androgen therapy

Ebeling, NEJM 2008; 358:1474-1482

Fracture Risk Reduction in Osteoporosis

Risk Factors	Therapies
• Bone loss/low BMD Calcium/D deficiency Estrogen deficiency	• Preserve/increase BMD Calcium/D supplementation Drug therapy
• Tendency to fall Muscle weakness Poor balance	• Fall prevention Strengthening exercises, vit D Balance exercise

Calcium and Vitamin D

NICE guidelines: Secondary Prevention of Osteoporosis

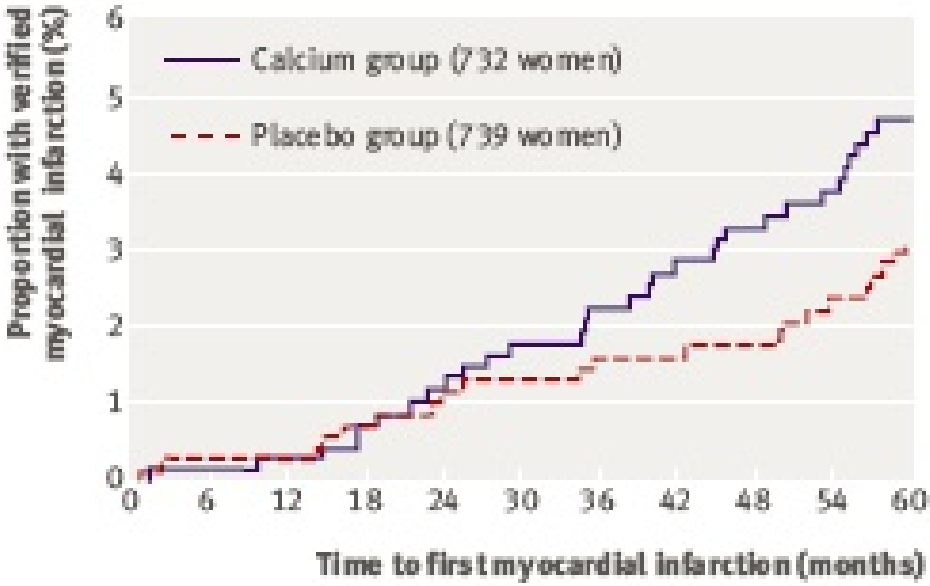
- Bisphosphonates are recommended as first-line treatment options for the secondary prevention of fragility fractures
- Adequate levels of calcium and vitamin D required to ensure optimum effects of treatments for osteoporosis
- Calcium and/or vitamin D supplementation should be provided unless clinicians are confident that women who receive treatment have an adequate calcium intake and are vitamin D replete

Adapted from National Institute for Clinical Excellence. January 2005.
Bisphosphonates, selective oestrogen receptor modulators and parathyroid hormone for the secondary prevention of osteoporotic fragility fractures in postmenopausal women.

Vascular Events in Healthy Older Women Receiving Calcium Supplementation (Bollard et al BMJ 2008:336:262-266)

- Primary prevention study over 5 years, 1471 postmenopausal women, mean age 74
- Randomised to placebo or 1000mg/d Ca as citrate
- Outcomes
  - Fractures
  - Deaths, sudden deaths, MI, angina, stroke, TIA
  - Composite endpoint: MI, stroke, sudden death
- Rationale
  - Ca supplements increase HDL:LDL ratio
  - Some evidence that Ca reduces cardiac events

Calcium and Heart Disease



Kaplan-Meier survival plot showing proportion of healthy postmenopausal women assigned to calcium supplementation or to placebo that had a verified myocardial infarction during the study. Included are events self reported by participants and those from the national database of hospital admissions and review of death certificates (P=0.14 when compared by log rank test)

Calcium and Heart Disease

Table 3 | Verified vascular events self reported by healthy postmenopausal women assigned to calcium supplementation or to placebo or reported by family members. Values are numbers of women (numbers of events) unless stated otherwise

Vascular event	Calcium group (n=732)	Placebo group (n=739)	P value*	Relative risk (95% CI)
Myocardial infarction	21 (24)	10 (10)	0.047	2.12 (1.01 to 4.47)
Stroke	31 (34)	22 (23)	0.21	1.42 (0.83 to 2.43)
Sudden death	3	3	1.0	1.01 (0.20 to 4.99)
Myocardial infarction, stroke, or sudden death	51 (61)	35 (36)	0.076	1.47 (0.97 to 2.23)

*Differences between groups in numbers of women with reported events, based on Fisher's exact test.

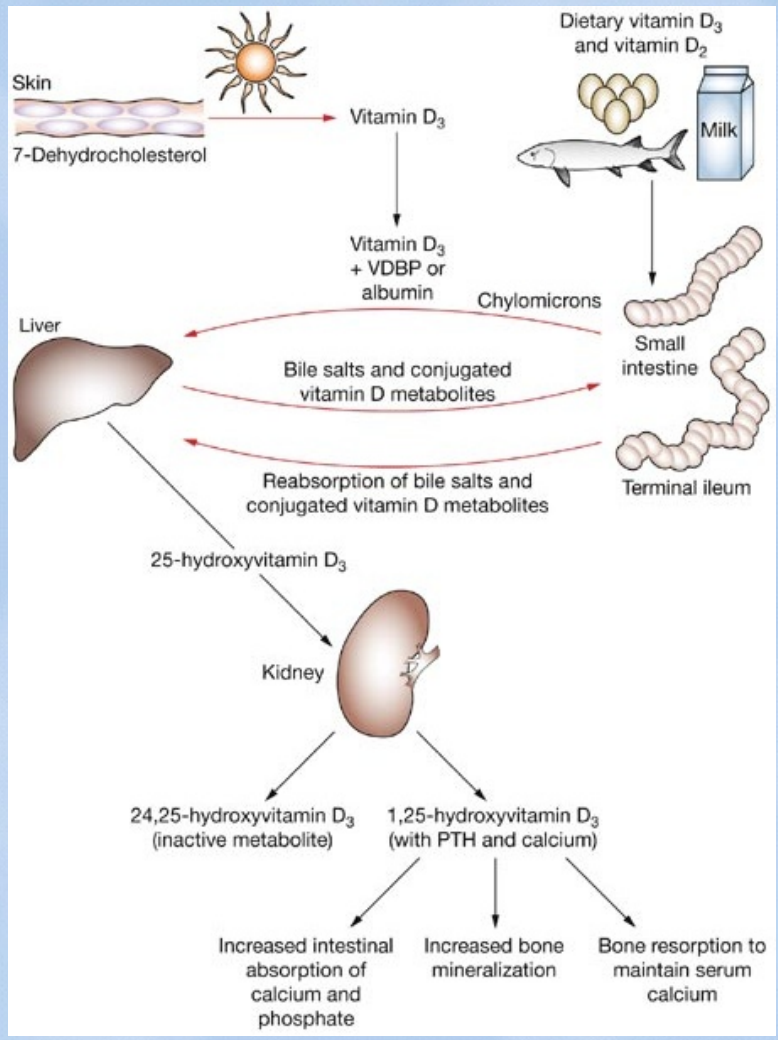
"the present study does not unequivocally show an adverse cardiovascular effect of calcium … this matter needs to be considered carefully"

What to Advise Patients About Calcium

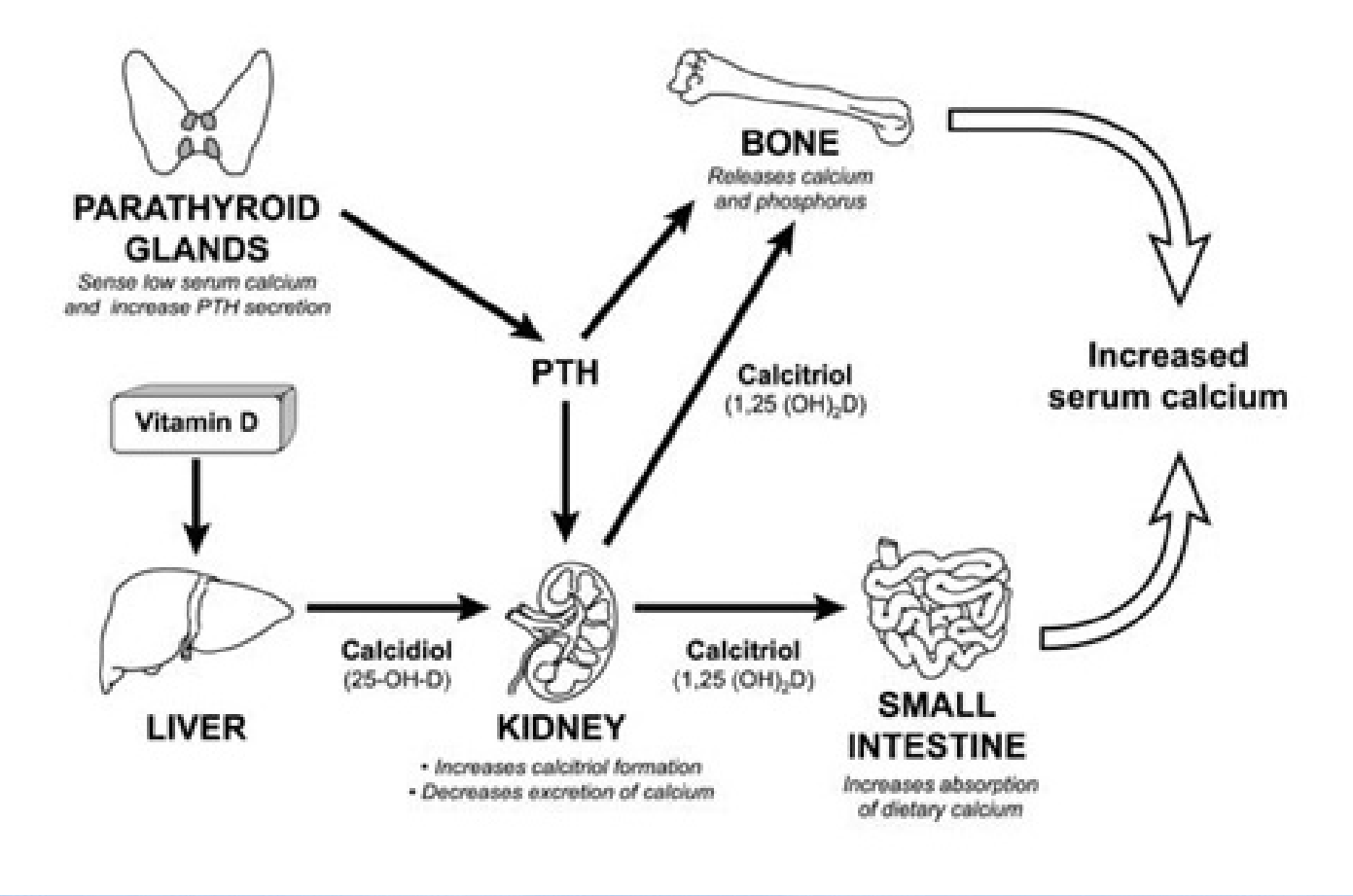
- You need some calcium to maintain bone health
  - If you have osteoporosis the need is greater
  - All drug trials of osteoporosis supplement calcium
- Aim for 1000mg – 1200mg from all sources
  - Supplement if necessary 500-1000mg/day
- High doses of calcium may be harmful if you have a high cardiovascular risk
  - High doses were used in the study
  - Elderly patients were enrolled
- Vitamin D can compensate for low calcium intake

Vitamin D: The Sunshine Vitamin

Vitamin D Metabolism



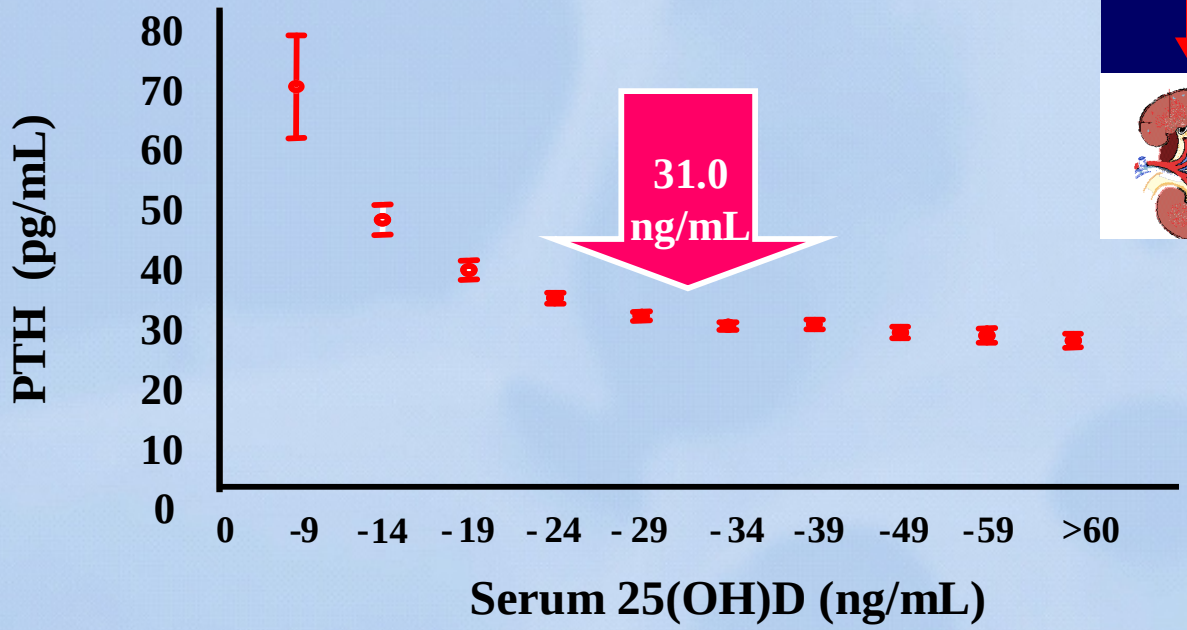
Actions of Vitamin D

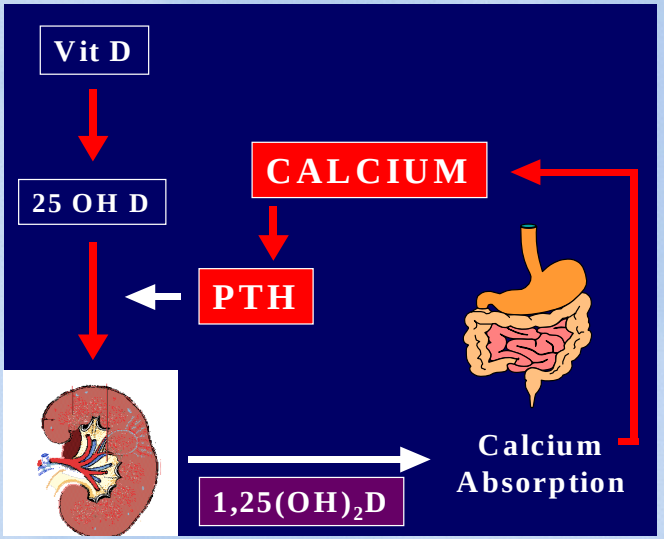


Vitamin D: How Much is Enough?

PTH reaches a plateau at 25(OH)D >31.0 ng/mL

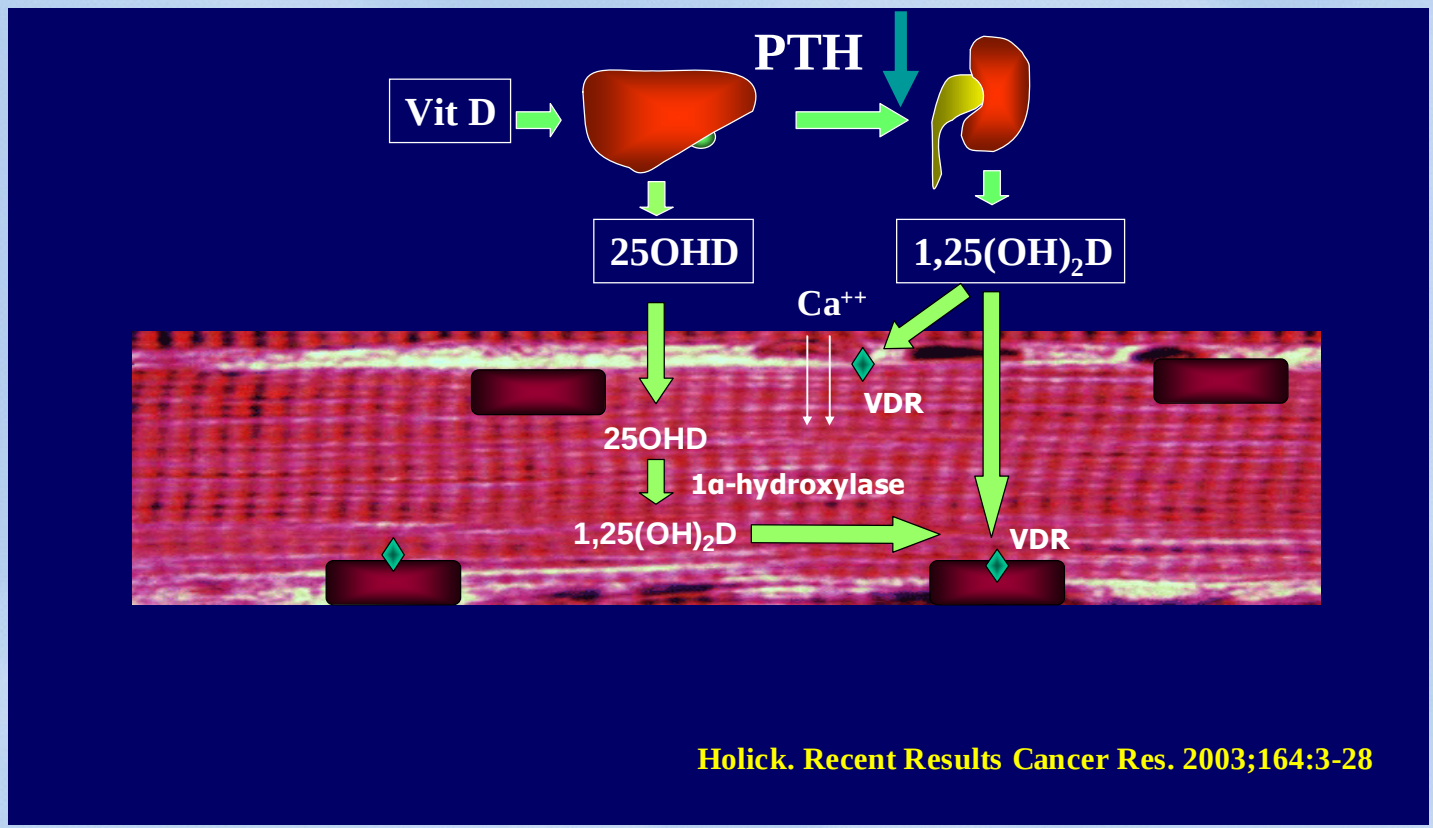
Inverse correlation between PTH and 25(OH)D; r = -0.290, p <0.001





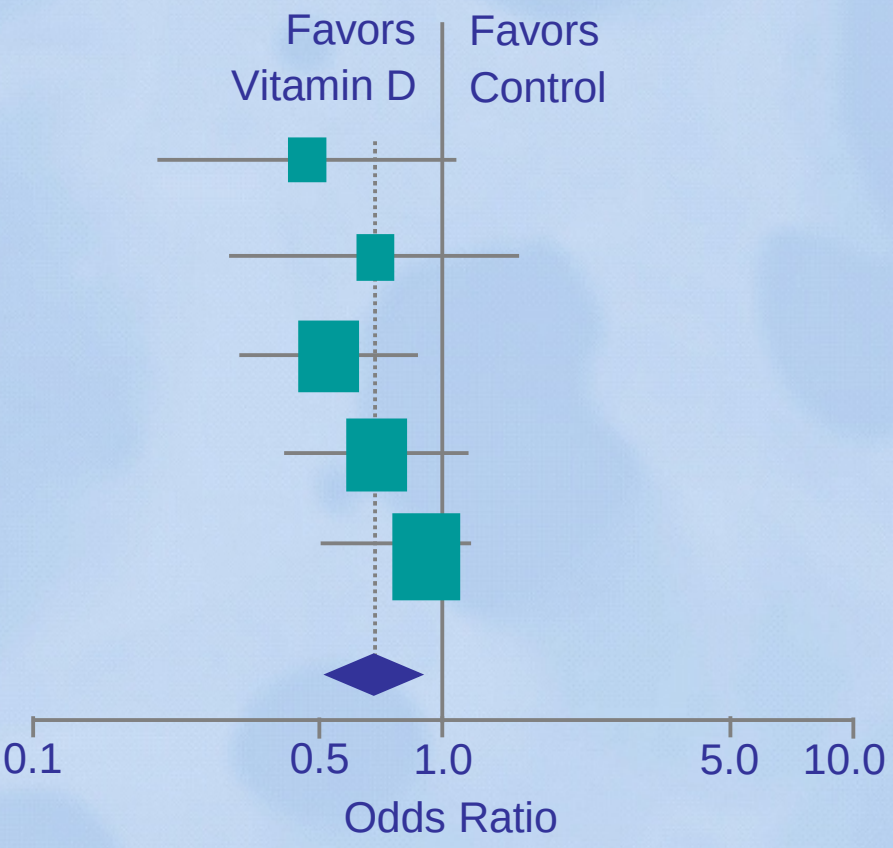
Lips, et al. J Intern Med 2006;260:245-254

Vitamin D and Muscle Function



Vitamin D Prevents Falls: Meta-analysis

Source	Odds Ratio (95% CI)
Pfeifer et al, 2000	0.47 (0.20-1.10)
Bischoff et al, 2003	0.68 (0.30-1.54)
Gallagher et at, 2001	0.53 (0.32-0.88)
Dukas et al, 2004	0.69 (0.41-1.16)
Graafmans et al, 1996	0.91 (0.59-1.40)
Pooled (Uncorrected)	0.69 (0.53-0.88)



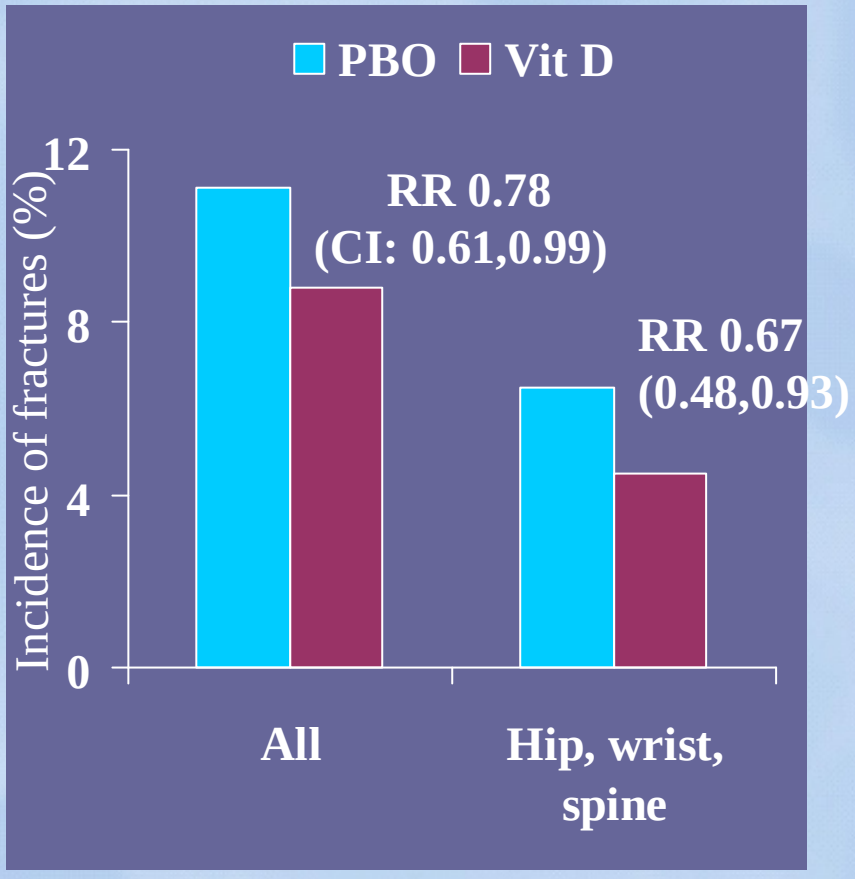
Redrawn from Bischoff-Ferrari H et al JAMA. 2004 Apr 28;291(16):1999-2006, with permission,

Vitamin D Supplements and Fracture Risk

- Five-year randomized, double-blind, controlled trial
- n = 2686 Age 65–85
- Vitamin D = 100,000 IU once every four months (equivalent to 800 IU/day)
- Men (75.8%) and women living in the community

Post Rx Vitamin D status

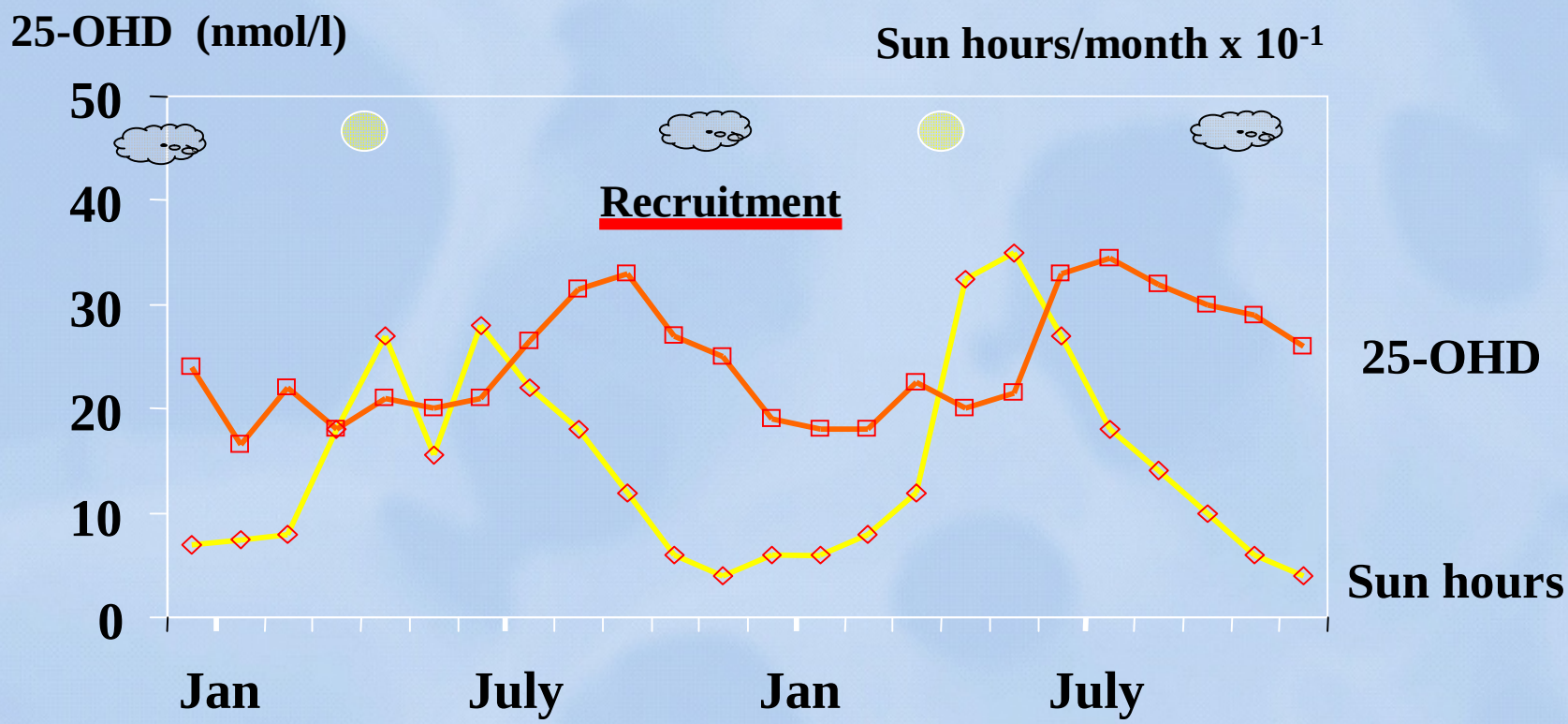
	n (%)	25 OH D
PBO	**114 (4.4)**	**23.5 ng/ml**
Vit D	**124 (4.6)**	**39.7 ng/ml**



Trivedi, et al. BMJ 2003;326:469-472

Alendronate + D: Efficacy Study Design

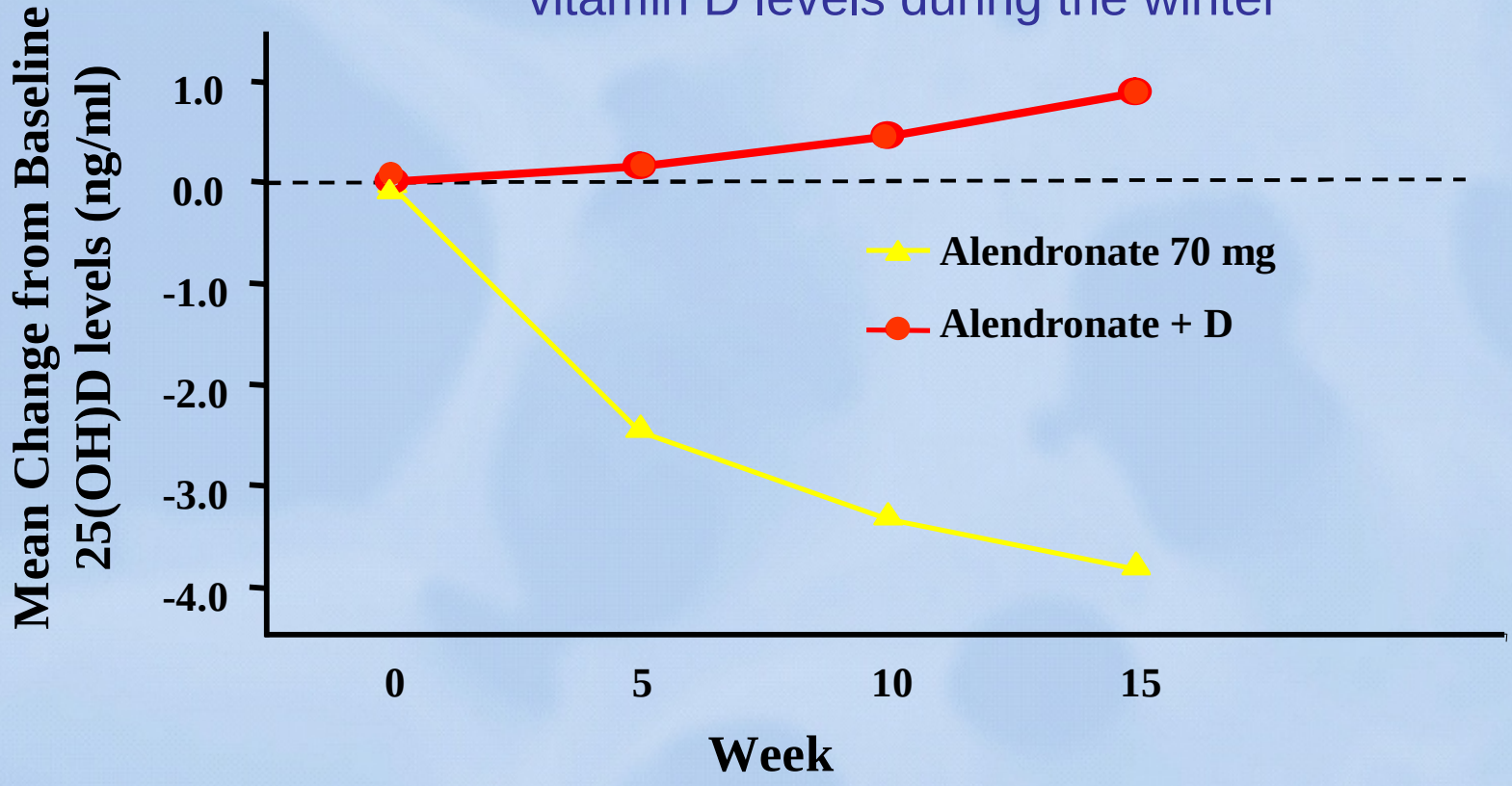
Winter, No vitamin D supplements or unprotected sunlight exposure



Mosekilde. 2005

Alendronate + D and Vitamin D Status

Patients treated with Alendronate + D maintained vitamin D levels during the winter

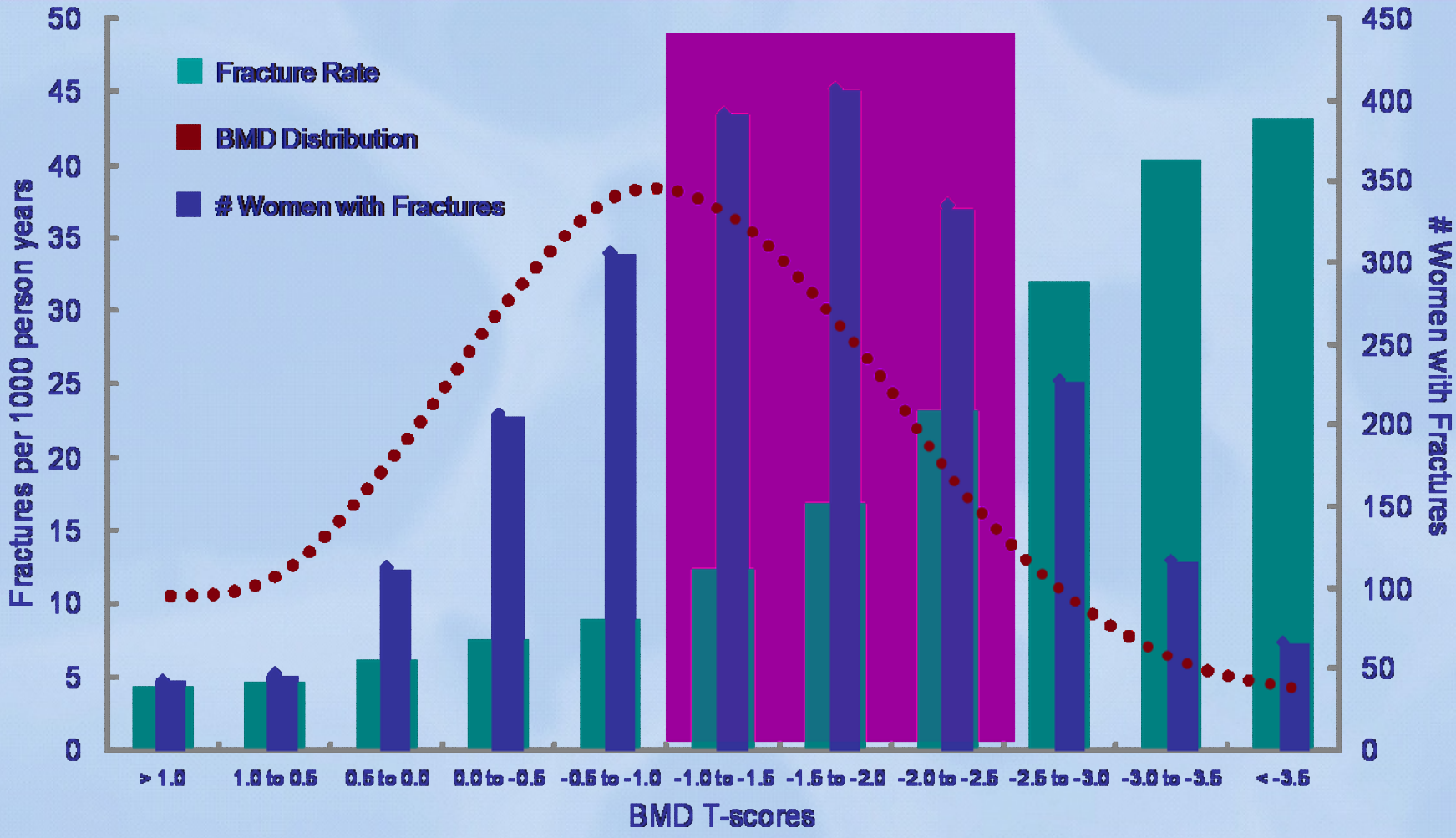


Recker, et al. Curr Med Res Opin 2006;22:1745-1755

Long-Term Treatment With Bisphosphonates

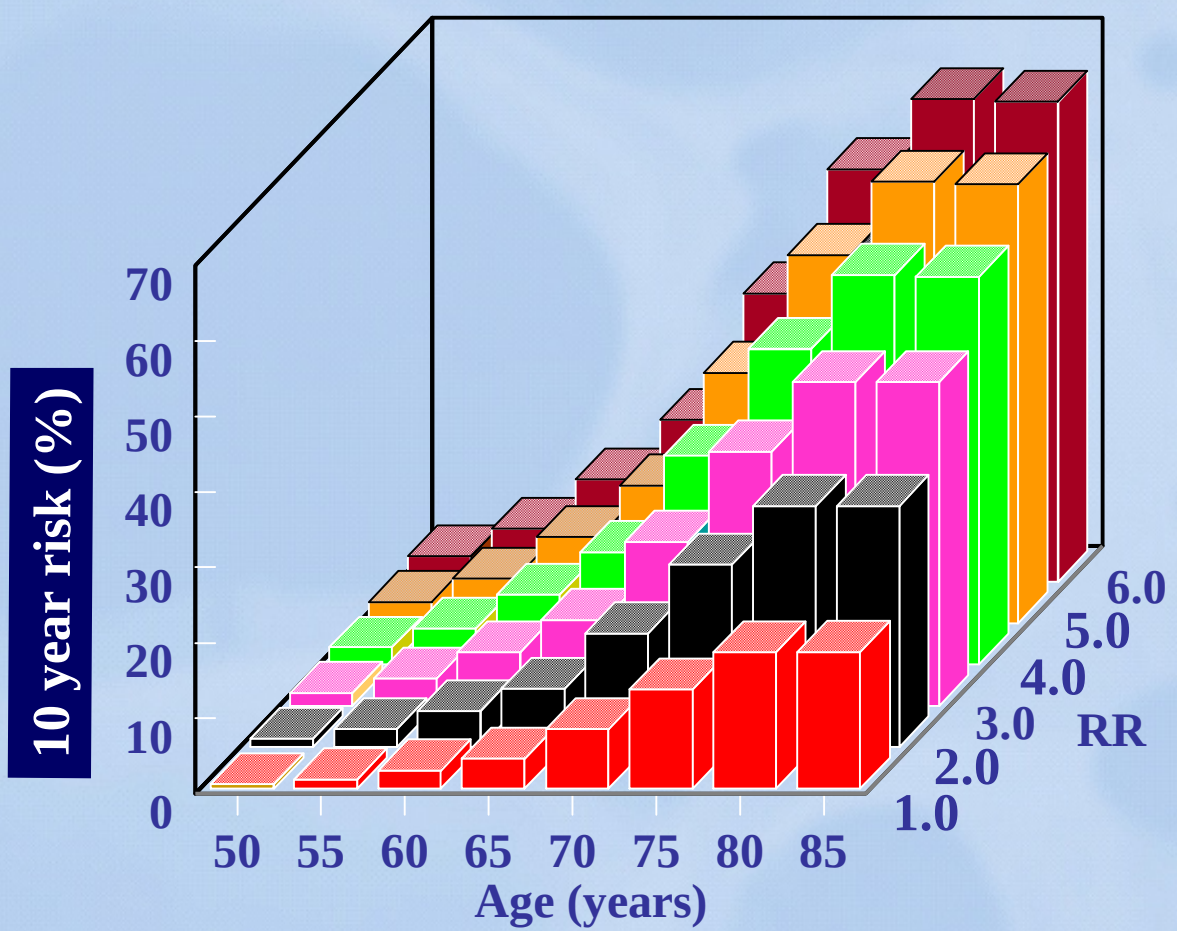
- Who To Treat?
- How Effective?
- What happens when you stop?

Fracture Rates, Population BMD Distribution and Number of Fractures in NORA



Siris, E. S., et al. Arch Intern Med 2004 164:1108-12, with permission. Copyright © 2004 American Medical Association

Ten year risk of hip fracture - Swedish women



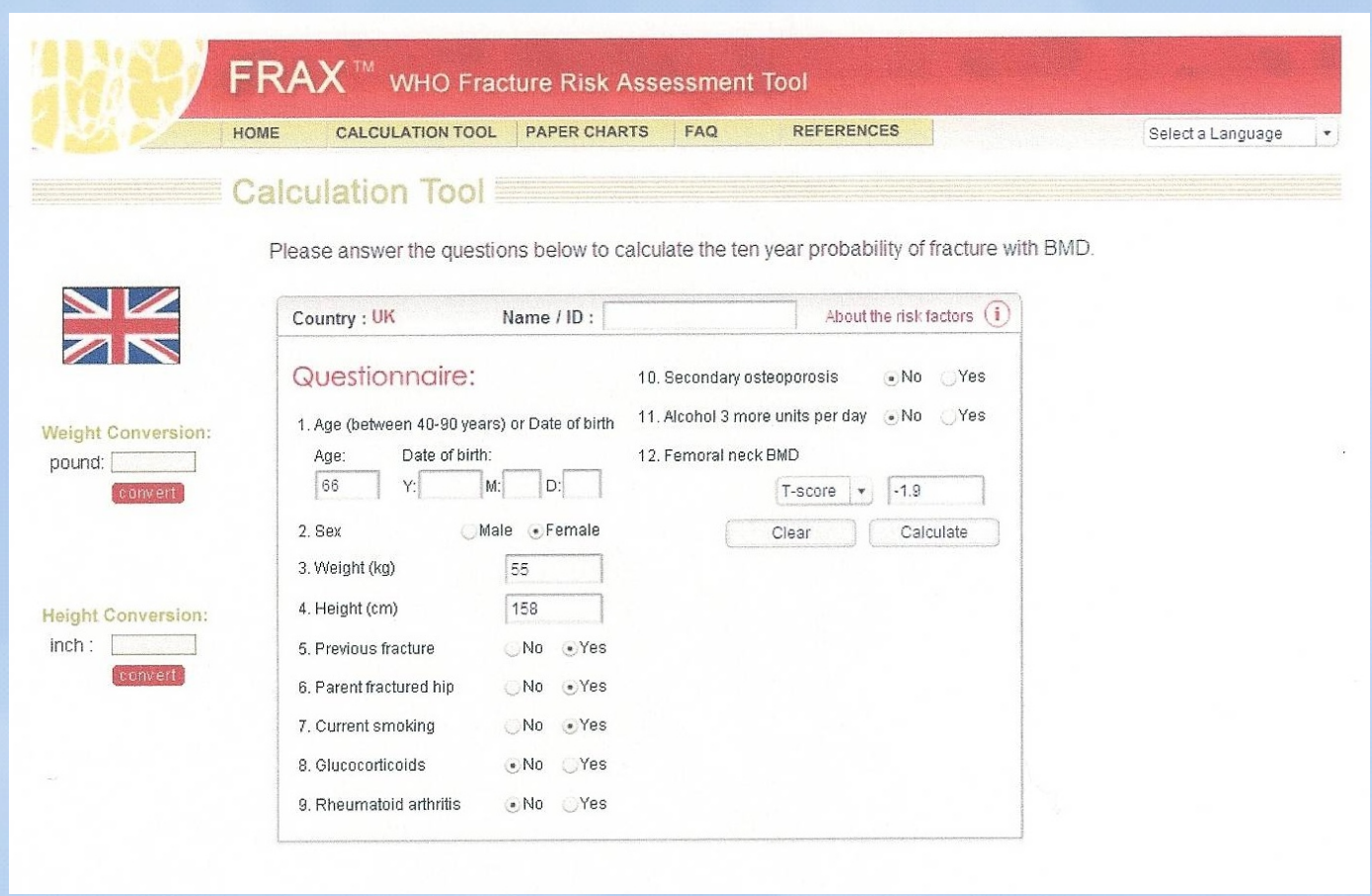
- Low BMD
- Age
- High bone turnover
- Falls
- Poor visual acuity
- Previous fragility Fx
- Glucocorticoids
- FH of hip fracture
- Low BMI
- Cigarette smoking
- Excess alcohol

Kanis et al. Bone 2002;30: 251-258

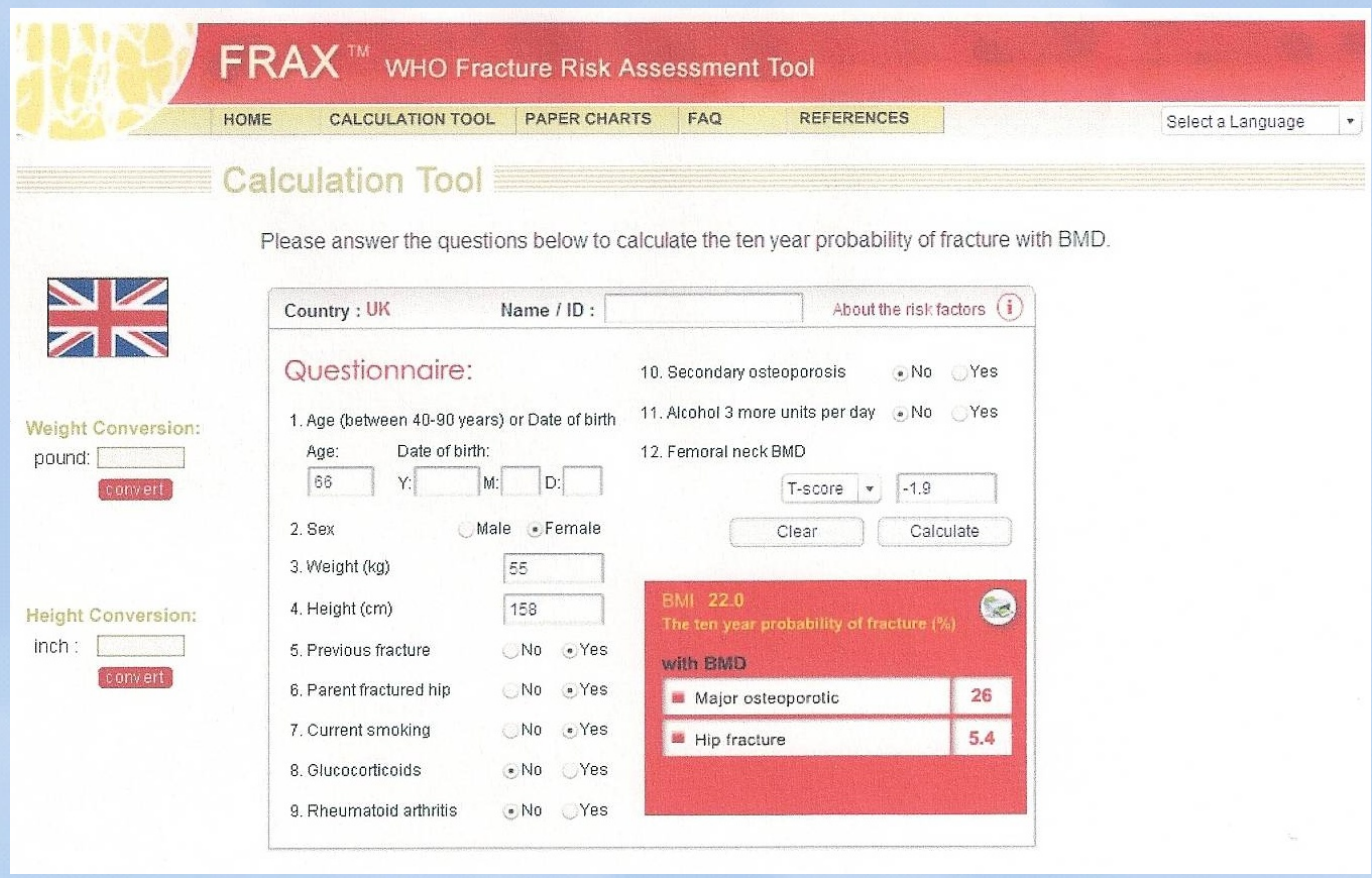
WHO Fracture Risk Assessment Tool

- 10-year probability of fracture based on
  - age, sex, BMI (height and weight), prior fragility fractures, parental history of hip fracture, long-term oral glucocorticoids, cigarette smoking, alcohol (3 units daily) and rheumatoid arthritis
- Validated in 11 Countries (in women)
- Now published and available on-line
  - http://www.shef.ac.uk/FRAX/index.htm

FRAX Online Fracture Risk Assessment Tool



Who To Treat


FRAX™ WHO Fracture Risk Assessment Tool
HOME
CALCULATION TOOL
PAPER CHARTS
FAQ
REFERENCES
Select a Language
Calculation Tool
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Weight Conversion:
pound:
convert
Height Conversion:
inch :
convert
Country : UK
Name / ID :
About the risk factors
Questionnaire:
1. Age (between 40-90 years) or Date of birth
Age:
Date of birth:
66
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
55
4. Height (cm)
158
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 more units per day
No
Yes
12. Femoral neck BMD
T-score
-1.9
Clear
Calculate
BMI 22.0
The ten year probability of fracture (%)
with BMD
Major osteoporotic
26
Hip fracture
5.4

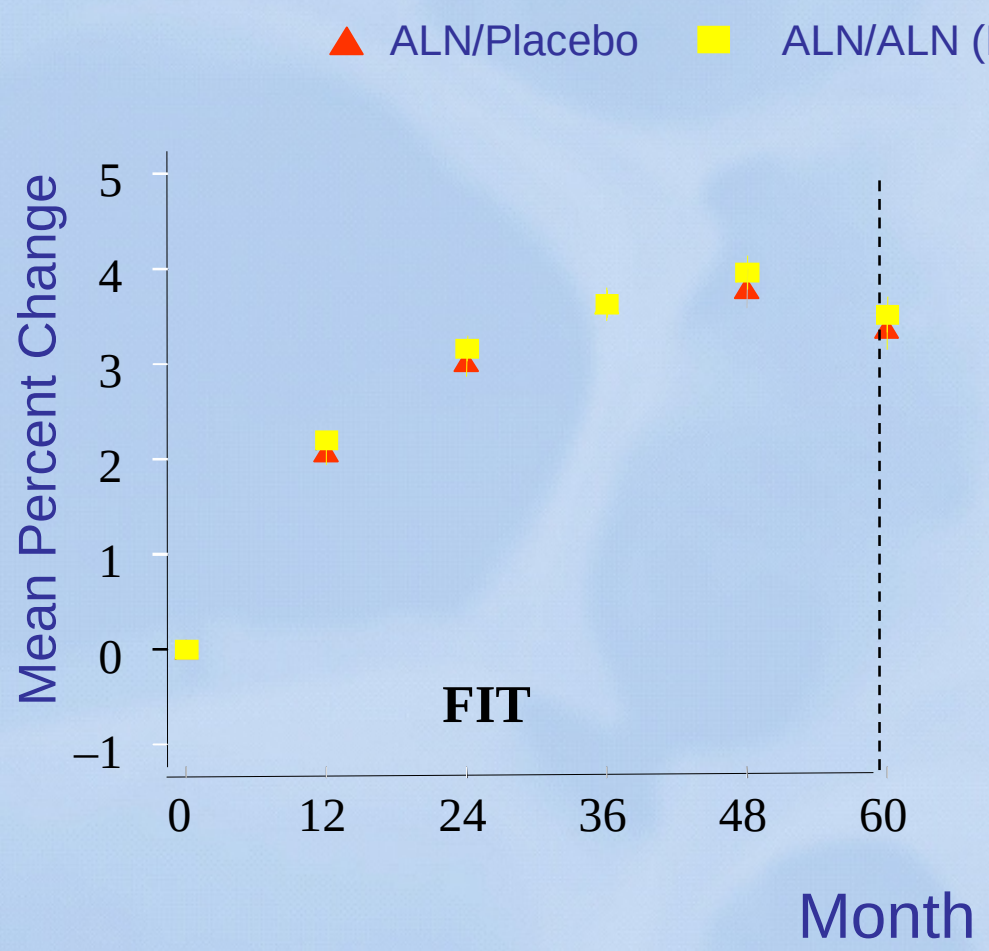
Who To Treat

- Compared with treatment based on T scores
  - some patients do not need treatment even if T<-3 (eg younger patients, absence of risk indicators for fracture)
  - some patients with T>-3 have a high risk of fracture (other risk indicators for fracture are present)
- Treatment thresholds based on cost-utility analysis: UK
  - 20% 10 yr risk of osteoporotic fracture
  - 5% 10 yr risk of hip fracture
- Caveats
  - Risk assessment tool is a guide only, risk cutoffs are abitrary
  - Not applicable to those who have been treated

Fracture Risk Reduction in Osteoporosis

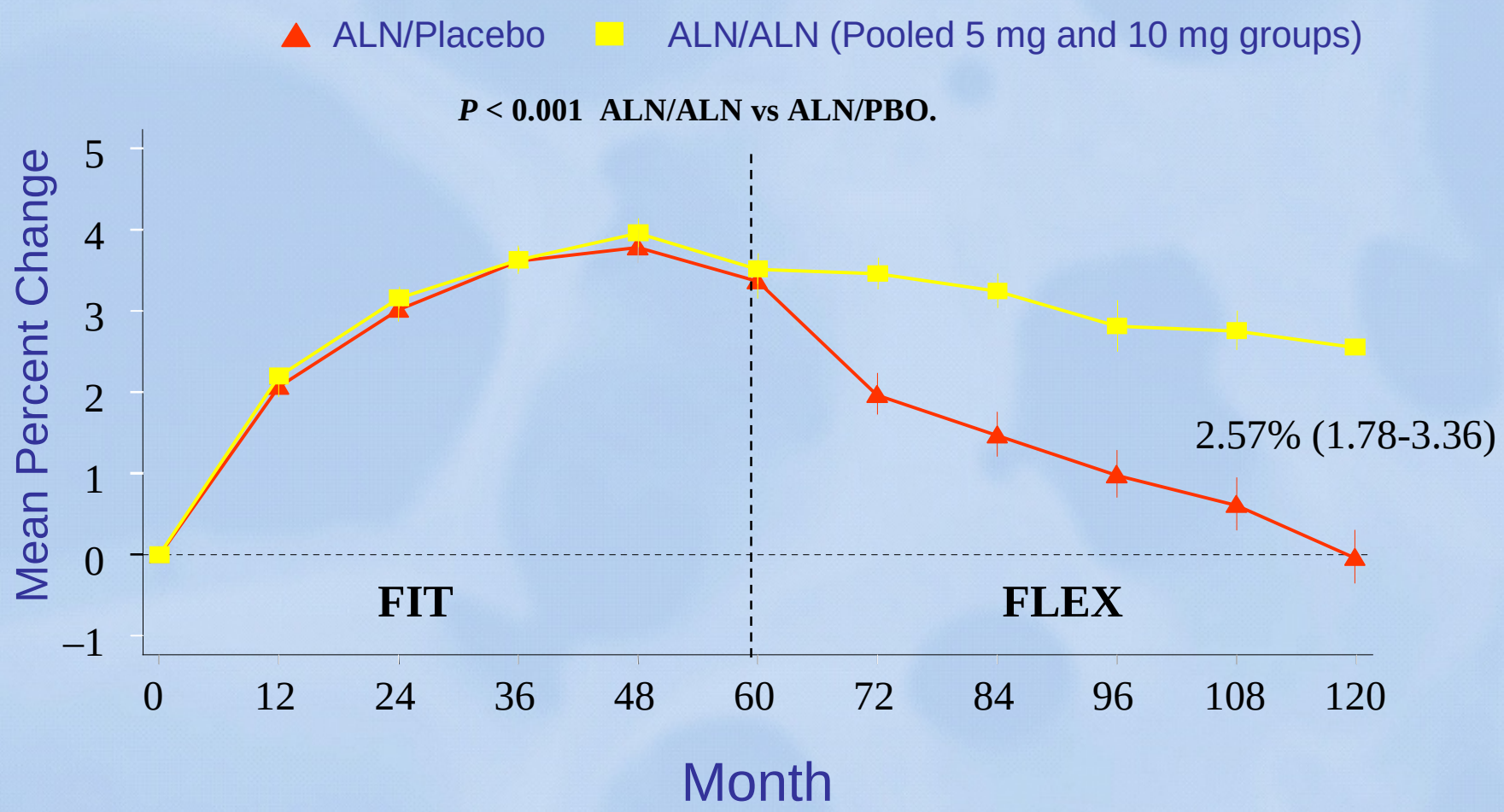
Risk Factors	Therapies
• Bone loss/low BMD Calcium/D deficiency Estrogen deficiency	• Preserve/increase BMD Calcium/D supplementation Drug therapy
• Tendency to fall Muscle weakness Poor balance	• Fall prevention Strengthening exercises, vit D Balance exercise

Effect of Alendronate on Hip BMD over 5 years
The FIT Study



Black, et al. JAMA 2006;296:2927-2938

Effect of Stopping Alendronate on Total Hip BMD
The FLEX Study



Black, et al. JAMA 2006;296:2927-2938

Duration of Bisphosphonate Therapy

- "Drug holiday" after 5 years treatment if good response:
  - + 3-5% increase in hip BMD, 8-10% at lumbar spine
  - T Score above -2.5
  - Not at increased risk of vertebral fractures
  - Resume if rapid bone loss
    - (-8% at 1yr, -10% at 2yr, -5% Pre-treatment)

- Continue treatment
  - High risk of vertebral fractures
    - (prevalent vertebral fractures, T Score <2.5)

Colon-Emeric JAMA 2006;296:2968-2969

Summary

- Osteoporosis is an important issue in men
  - Investigate as causes often present
- Vitamin D is important
  - Effect on falls as well as fractures
- Calcium supplements are still important
  - Consider CV risk
- Fracture Risk Assessment should guide treatment decisions not just T scores
- Long term use of bisphosphonates
  - Consider a drug holiday after 5 years