Update on Osteoporosis and vitamin D

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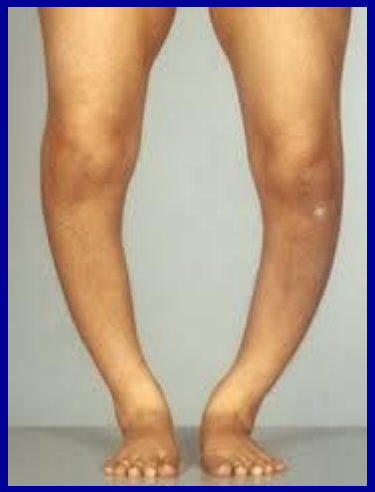
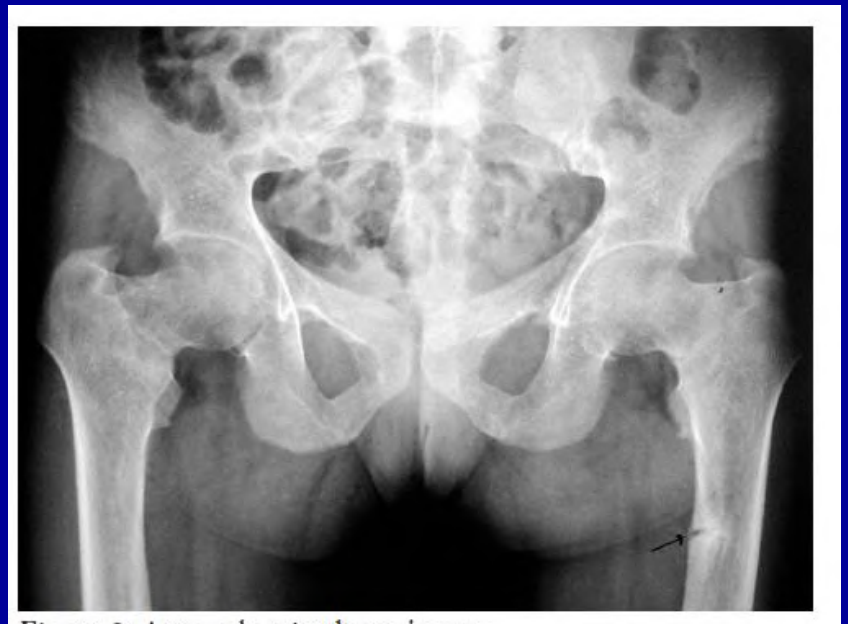
RSCH

Definitions: vitamin D deficiency

- Level <25 on lab testing
- Surrey PAD <30
- Clinical syndromes
  - Rickets
  - Osteomalacia
  - Proximal myopathy
  - Bony pain
  - Myalgia
  - Pathological fracures





What does the vitamin D level mean clinically?

- <25 = Deficient (<30 Surrey)
  - Will need Rx, with high dose vitamin D if symptomatic
- 25-50 = Insufficient
  - Needs vitamin D supplementation, may be cause of symptoms but less likely
- 50-75 = Adequate
  - Will not be causing symptoms. Lifestyle advice unless osteoporotic, in which case supplement
- >75 = Replete
  - No need for Rx

Who to screen for low vitamin D? Symptoms

- Anyone with established osteoporosis/ osteoporotic fractures
- Insidious onset of widespread or localised bone pain and tenderness
- Proximal muscle weakness i.e. in quadriceps and glutei.
- Swelling, tenderness and redness at pseudo-fracture sites
- Non-specific myalgia especially with a raised creatine kinase (CK)
- Myalgia on prescription of a statin

Who to screen for low vitamin D? Lifestyle risk factors

- Black and ethnic minority patients with darker skin
- Elderly patients in residential care or housebound
- Intestinal malabsorption, (eg. coeliac disease, crohn's disease, gastrectomy)
- Routine covering of face or body (eg. wearing a veil or sunscreen)
- Vegan or vegetarian diet
- Liver or renal disease
- Medications (eg. anticonvulsants, cholestyramine, rifampicin, glucocorticoids, anti-retrovirals)

Who should be supplemented with vitamin D? NICE:

- Infants and children aged under 4
- Pregnant and breastfeeding women, particularly teenagers and young women
- People over 65
- People who have low or no exposure to the sun, for example, those who cover their skin for cultural reasons, who are housebound or confined indoors for long periods (eg Nursing home)
- People with darker skin, for example, people of African, African-Caribbean or South Asian family origin.
- Suitable supplements should also be available for people with particular dietary needs (for example, people who avoid nuts, are vegan or have a halal or kosher diet).
- Anyone with a diagnosis of osteoporosis
- Anyone with a deficiency due to other disease process

What dose should I use? Local guidelines

- Maintenance

  800 – 1000 IU od

- Insufficient

  1000 – 2000 IU od for 12/52, then recheck

- Deficient

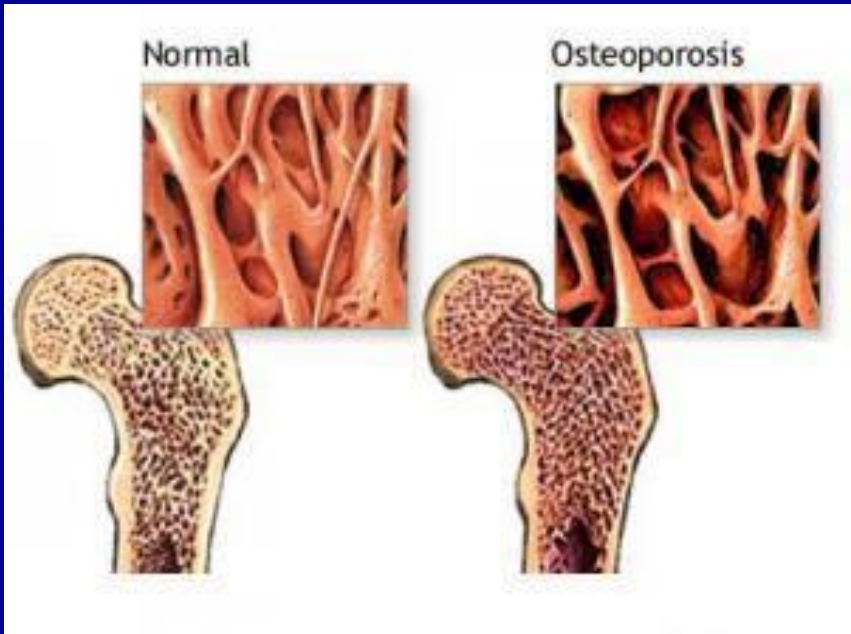
  3000 IU bd for 1/12

  60 000 IU once/week for 12/52

  Recheck Vitamin D no sooner than 12/52 after change

Definitions: osteoporosis

- ‘Porous bone’
- Disease of bone leading to an increased risk of fracture (‘fragile bones’)
- Low bone mineral density measured on DEXA: T score <-2.5
- Reduction in 20% vertebral body height



Who to screen for osteoporosis? NICE recommends

- All women aged ≥ 65 years and all men aged ≥75 years
- Women aged < 65 years and men aged < 75 years in the presence of risk factors:
  - previous fragility fracture
  - current use or frequent recent use of oral or systemic glucocorticoids
  - history of falls
  - family history of hip fracture
  - other causes of secondary osteoporosis
  - low body mass index (BMI) (less than 18.5 kg/m^2)
  - smoking
  - alcohol intake of more than 14 units per week for women and more than 21 units per week for men

Who NOT to screen

- Do not routinely assess fracture risk in people aged under 50 years, because they are unlikely to be at high risk
- UNLESS significant risk factors

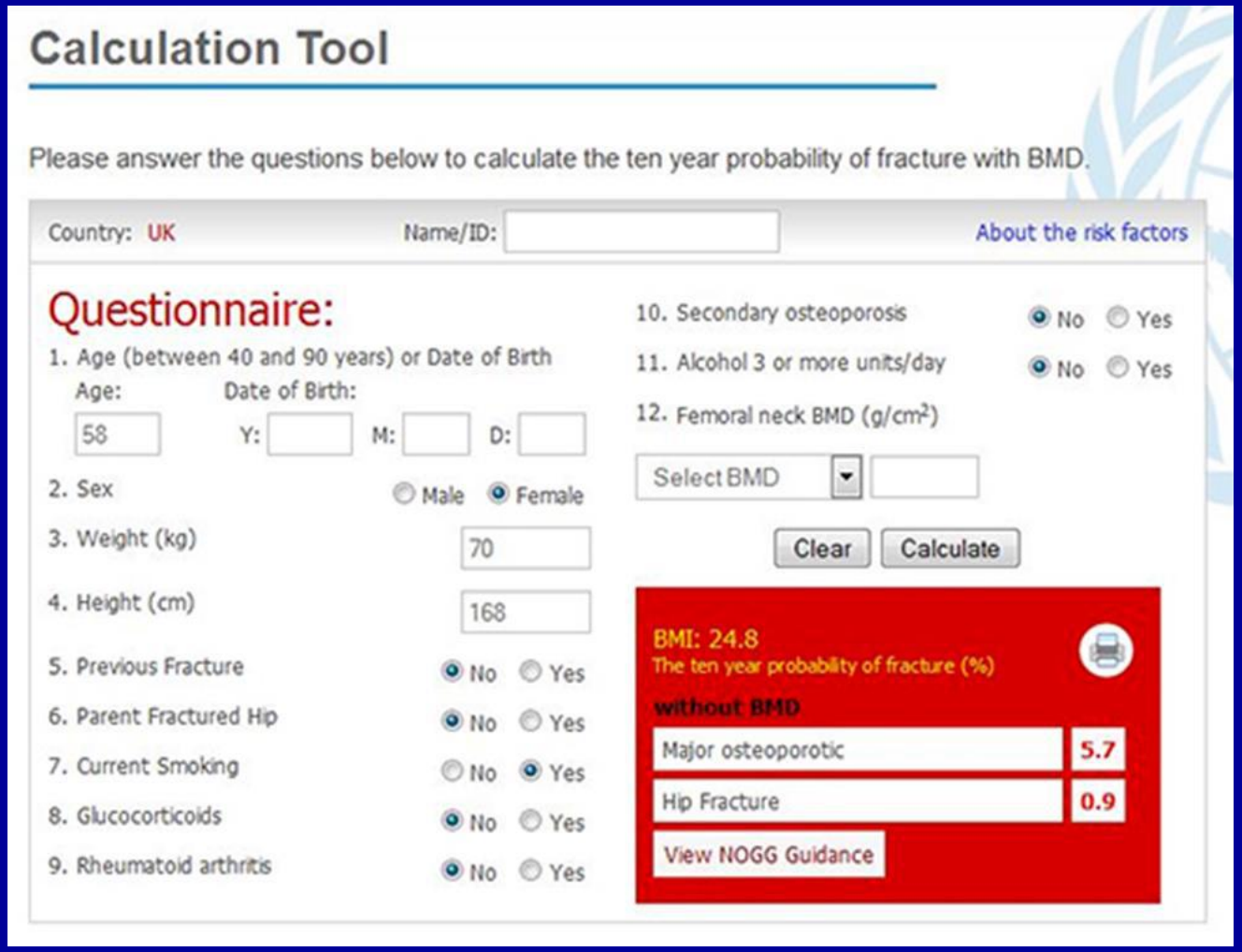
  - current or frequent recent use of oral or systemic glucocorticoids
  - untreated premature menopause
  - previous fragility fracture

Tools to help osteoporosis screening

- Helps convince the worried well they don't need treatment
- Helps convince the 'no medicine' brigade that they do need treatment

- FRAX
  - http://www.sheffield.ac.uk/FRAX/
- Qfracture
  - www.qfracture.org

FRAX



Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: UK Name/ID: About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 58 Date of Birth: Y: M: D:
2. Sex — Male / Female
3. Weight (kg) — 70
4. Height (cm) — 168
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/day — No / Yes
12. Femoral neck BMD (g/cm^2) — Select BMD

Clear Calculate

BMI: 24.8

The ten year probability of fracture (%)

without BMD

Major osteoporotic	5.7
Hip Fracture	0.9

View NOGG Guidance

NOGG guidelines

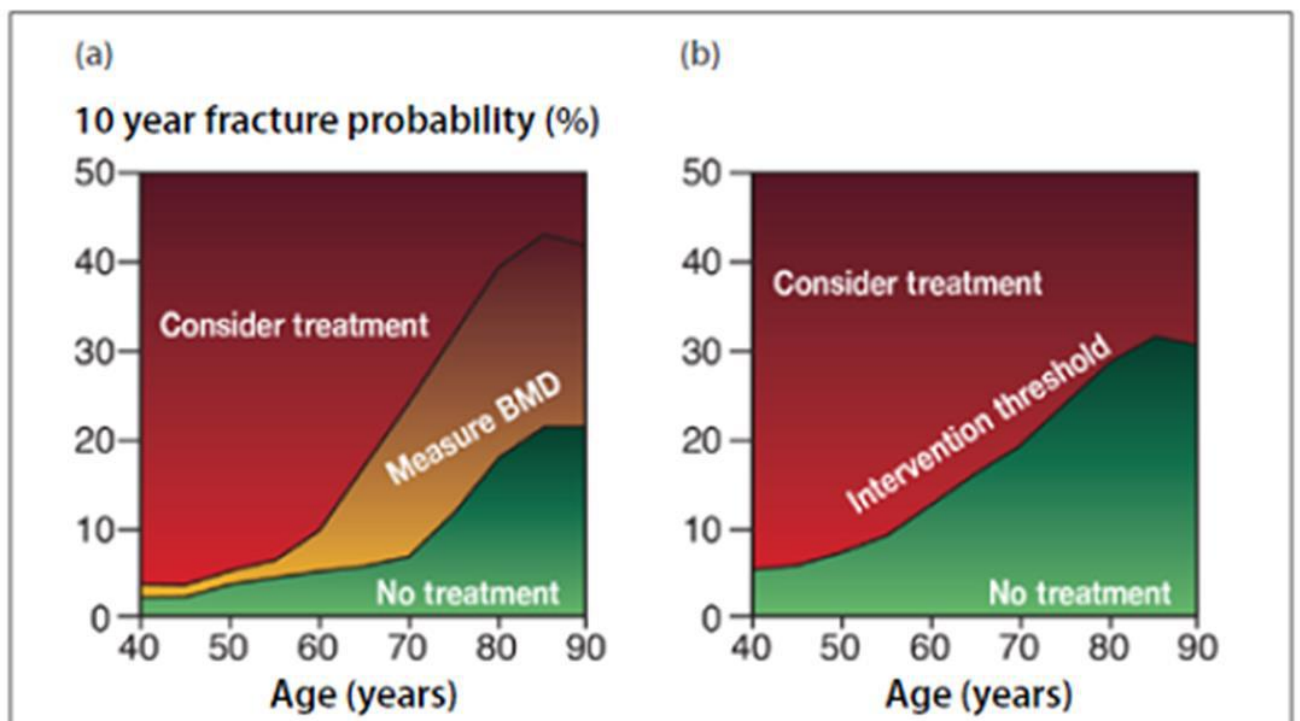


FIGURE 1. NOGG intervention thresholds: assessment (a) without BMD, (b) with BMD.[19] (Reproduced with permission from: National Osteoporosis Guideline Group, Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK; 2010 July.)

FRAX + NOGG

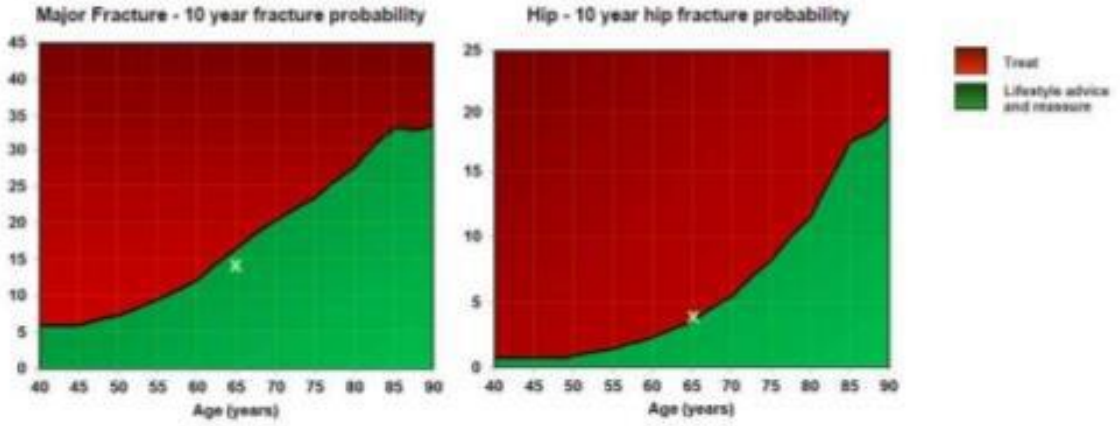
nogg NATIONAL OSTEOPOROSIS GUIDELINE GROUP

Updated May 2013

Graphs

Back to FRAX Home Back to NOGG Home Manual Data Entry FAQ Download Documents

Intervention Threshold



QFracture

About you

Age (30-99): 65

Sex: ○ Male ◉ Female

Ethnicity: White or not stated

Clinical information

Smoking status: non-smoker

Alcohol status: none

diabetes: type 2

Do either of your parents have osteoporosis/hip fracture? ☐

Do you live in a nursing or care home? ☐

Have you had a wrist spine hip or shoulder fracture? ☑

History of falls? ☑

Dementia? ☐

Cancer? ☐

Asthma or COPD? ☐

Heart attack, angina, stroke or TIA ☐

Chronic liver disease? ☐

Chronic kidney disease? ☐

Parkinson's disease? ☐

Rheumatoid arthritis or SLE? ☐

Malabsorption eg Crohn's disease, ulcerative colitis, coeliac disease, steatorrhea or blind loop syndrome? ☐

Endocrine problems eg thyrotoxocosis, hyperparathyroidism, Cushing's syndrome? ☐

Epilepsy or taking anticonvulsants? ☐

Taking antidepressants? ☐

Taking steroid tablets regularly? ☐

Taking oestrogen only HRT? ☐

Leave blank if unknown

Body mass index

Height (cm): 165

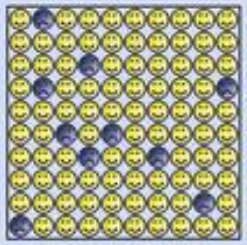
Weight (kg): 65

Your results

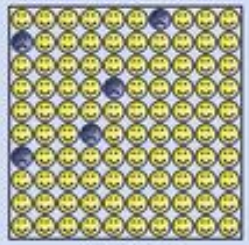
Your risk of having any osteoporotic (i.e. hip, wrist, shoulder or spine) fracture or hip fracture alone within the next 10 years is:

Hip, wrist, shoulder or spine fracture	10%
Hip fracture	5.3%

In other words, in a crowd of 100 people like you, 10 will develop osteoporotic fracture of hip, wrist, shoulder or spine within the next 10 years. Similarly, 5 will develop hip fracture within the next 10 years. This is represented by the smileys below.



fracture of hip, wrist, shoulder or spine



hip fracture

Guidelines for Rx of osteoporosis

- NICE
  - Quality measures
  - Primary prevention
  - Secondary prevention
- RCP
  - Corticosteroid induced

NICE Quality standard for osteoporosis

- Statement 1 Adults who have had a fragility fracture or use systemic glucocorticoids or have a history of falls have an assessment of their fracture risk.
- Statement 2 Adults at high risk of fragility fracture are offered drug treatment to reduce fracture risk.
- Statement 3 Adults prescribed drug treatment to reduce fracture risk are asked about adverse effects and adherence to treatment at each medication review.
- Statement 4 Adults having long-term bisphosphonate therapy have a review of the need for continuing treatment.

NICE Primary prevention

- Treatment group T score <-2.5
- >75 women: don't have to have DEXA if have 2 RF
- >65: T score <-2.5 plus RF
- <65: T score <-2.5 plus 2 RF

- ALL should have 'adequate calcium intake and are vitamin D replete'
- In real life, the evidence suggests calcium 1g od and vitamin D 800 IU od

- First line alendronate
- If fails…
  - Risedronate (company claim less GI side effects)
  - Ibandronate (only once a month, not advised by NICE)
  - Iv bisphosphonates (Rheumatologist only, not covered by NICE)
  - (Raloxifene not included in NICE)
  - Strontium is still included in NICE guidelines, but has been withdrawn
  - Denosumab only recommended with T score -4 or worse

Risk factors for osteoporosis

- FH
- Malabsorption/ Diarrhoea
- XS EtOH (3Units/day or more)
- Liver disease
- Smoker
- Long term immobility
- Anorexia
- Premature menopause/amenorrhoea
- Post menopausal
- Elderly
- Hyperthyroid
- DM
- Drugs; steroids, PPIs, SSRIs aromatase inhibitors, heparin

Lots of complicated rules…

Treat with risedronate only if alendronate is contraindicated/ pt intolerant

	Number of independent clinical risk factors for fracture (section 5)		
Age (years)	**0**	**1**	**2**
65–69	– [a]	– 3.5	– 3.0
70–74	– 3.5	– 3.0	– 2.5
75 or older	– 3.0	– 3.0	– 2.5

[a] Treatment with risedronate or etidronate is not recommended.

Although NICE still recommend treating with strontium when alendronate, risedronate, etidronate are contraindicated/ pt intolerant, this is no longer available

	Number of independent clinical risk factors for fracture (section 5)		
Age (years)	**0**	**1**	**2**
65–69	– [a]	– 4.5	– 4.0
70–74	– 4.5	– 4.0	– 3.5
75 or older	– 4.0	– 4.0	– 3.0

[a] Treatment with strontium ranelate is not recommended.

NICE Denosumab: Primary prevention in postmenopausal women

- Intolerant/contraindication /non-compliance with alendronate, risedronate, etidronate

- RF: parental history of hip fracture, alcohol intake of 4 or more units per day, and rheumatoid arthritis

	Number of independent clinical risk factors for fracture		
Age	**0**	**1**	**2**
65–69	Not recomme-nded	−4.5	−4.0
70–74	−4.5	−4.0	−3.5
75 or older	−4.0	−4.0	−3.0

NICE defined risk factors

- Parental hx hip fracture
- EtOH 4+ units/day
- Rheumatoid arthritis
- BMI <22 kg/m^2
- Ankylosing spondylitis
- Crohn's
- Untreated premature menopause
- Conditions that result in prolonged immobility

NICE secondary prevention

- Previous low trauma fracture and a T score on DEXA <-2.5
- If woman >75yrs, no need for DEXA
- Same array of medications
- Includes raloxifene and teriparatide (PTH analogue)

- ALL should receive ‘adequate calcium and be vitamin D replete’ (1g od calcium, 800 IU od vitamin D)
- Alendronate/risedronate first line
- Denosumab second line
- Teriparatide for severe osteoporosis (T<-3.5)

Even more complicated rules…

Treatment with risedronate/ etidronate if alendronate not tolerated/ contraindicated

	Number of independent clinical risk factors for fracture (section 5)		
Age (years)	0	1	2
50–54	– [a]	– 3.0	– 2.5
55–59	– 3.0	– 3.0	– 2.5
60–64	– 3.0	– 3.0	– 2.5
65–69	– 3.0	– 2.5	– 2.5
70 or older	– 2.5	– 2.5	– 2.5

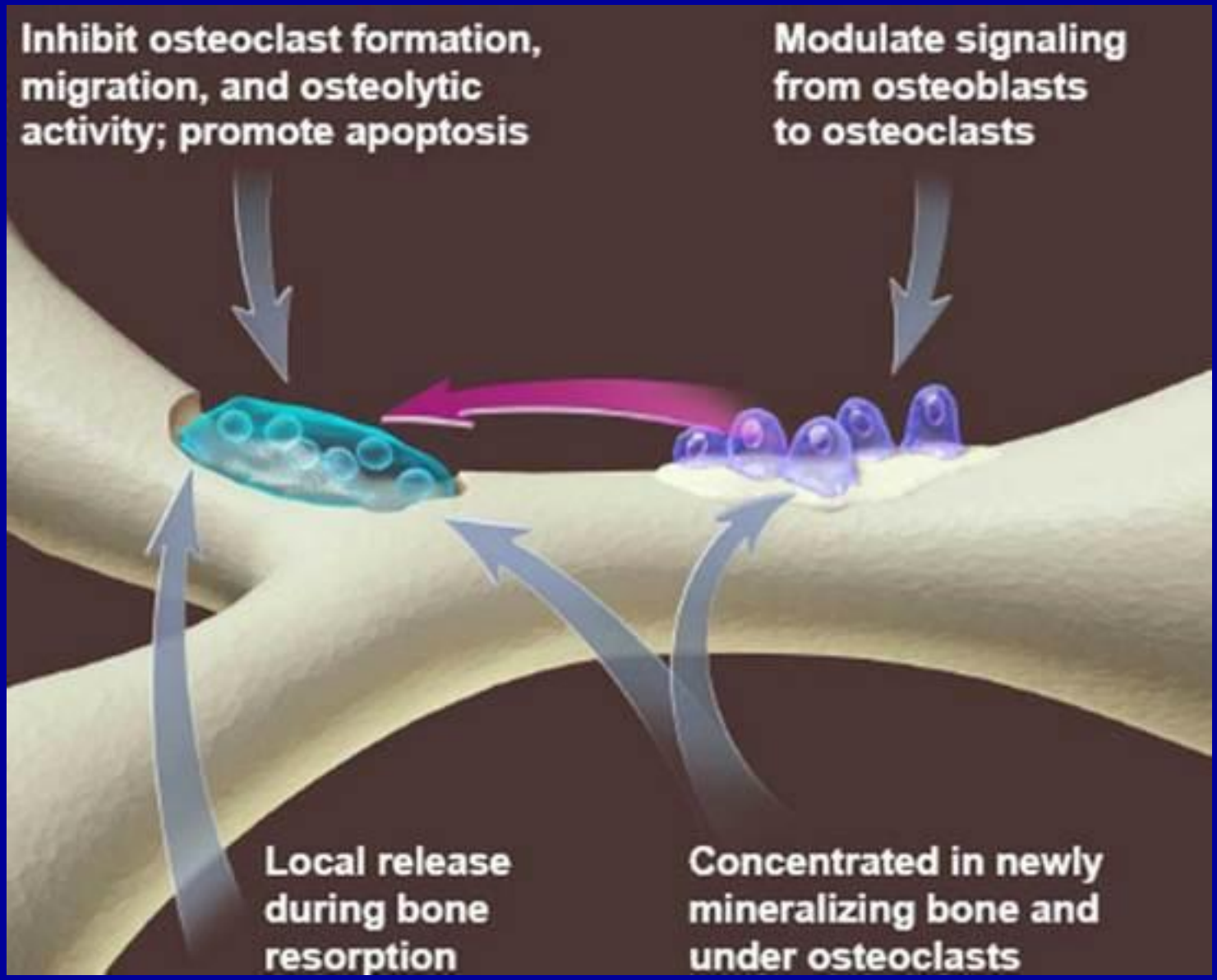
[a] Treatment with risedronate or etidronate is not recommended.

Treatment with raloxifene when alendronate/ risedronate/ etidronate not tolerated/ contraindicated

	Number of independent clinical risk factors for fracture (section 5)		
Age (years)	0	1	2
50–54	– [a]	– 3.5	– 3.5
55–59	– 4.0	– 3.5	– 3.5
60–64	– 4.0	– 3.5	– 3.5
65–69	– 4.0	– 3.5	– 3.0
70–74	– 3.0	– 3.0	– 2.5
75 or older	– 3.0	– 2.5	– 2.5

[a] Treatment with raloxifene or strontium ranelate is not recommended.

Bisphosphonates



Side effects of bisphosphonates

- Main side effect is ulceration/inflammation of oesophagus

- Osteonecrosis of jaw is reported in all bisphosphonates, but extremely rare in oral forms
- Risk factors
  - Iv bisphosphonates (zoledronate)
  - Cancer (may be also related to dose given)
  - Steroids
  - Dental infection/procedures
  - Diabetes

- Iv is an excellent option for patients with absorption problems
- BUT vitamin D must be replete first, or risk of prolonged hypocalcaemia

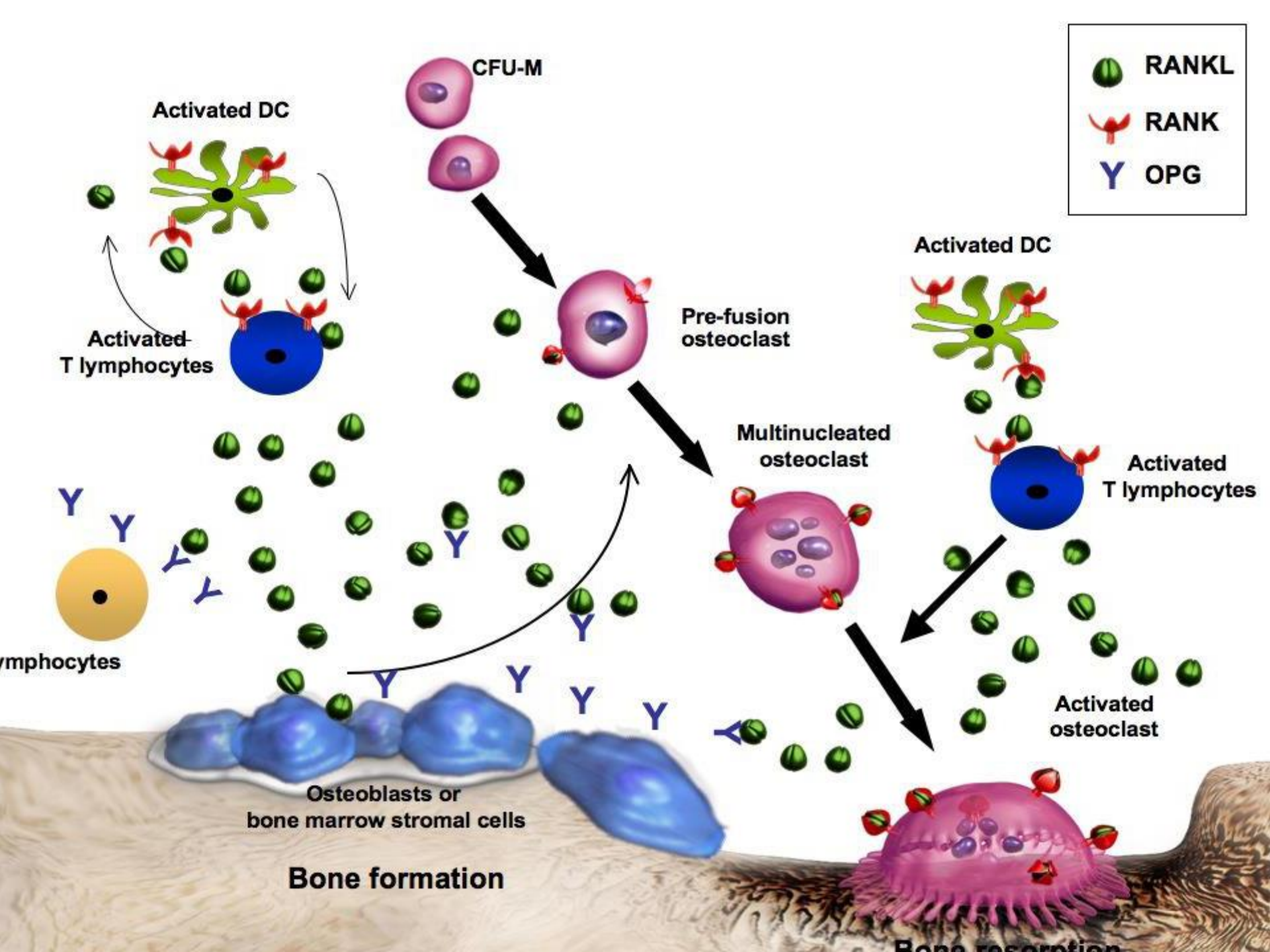
Teriparatide (PTH analogue)

- Anabolic agent, directly building bone
- NICE guidelines only for postmenopausal women
  - >65yr
  - Failed bisphosphonates (alendronate, risedronate, etidronate) and strontium
  - T score <-4.0
  - T scores <-3.5 + 2 fragility fractures
  - >55yr; T score <-4.0 plus 2 fragility fractures
- Sarcomas in rats
- Not currently available for men

Denosumab (Prolia)

- Fully humanised monoclonal antibody targeting RANK ligand
- Licensed in UK

- Subcutaneous injection every 6 months
- Dose 60mg (~£366/year)
- Prescribed with daily calcium and vitamin D

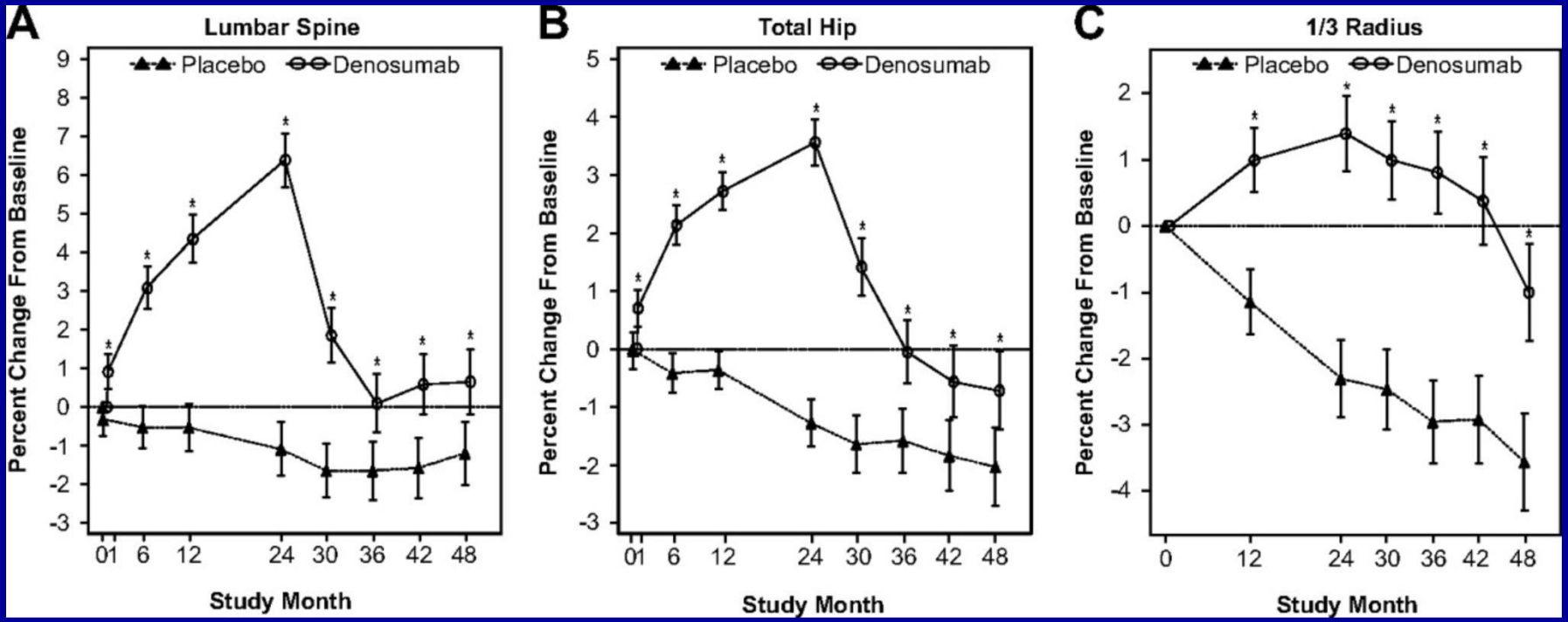

RANKL
RANK
OPG
CFU-M
Activated DC
Activated
T lymphocytes
Pre-fusion
osteoclast
Multinucleated
osteoclast
Activated DC
Activated
T lymphocytes
ymphocytes
Activated
osteoclast
Osteoblasts or
bone marrow stromal cells
Bone formation

Denosumab side effects

- Increased risk of skin and urine infections
- Myalgia and arthralgia
- Hypocalcaemia; ensure vitamin D is >50, and patient is on calcium and vitamin D
- ONJ
- Atypical femoral fracture

- Rebound multiple vertebral fractures if stopped; within 9-16 months after last injection

- Lamy O, Gonzalez-Rodriguez E, Stoll D, et al. **Severe rebound-associated vertebral fractures after denosumab discontinuation: nine clinical cases report**. *J Clin Endocrinol Metab*. 2016 Oct 12:jc20163170.



From: Effects of Denosumab Treatment and Discontinuation on Bone Mineral Density and Bone Turnover Markers in Postmenopausal Women with Low Bone Mass

J Clin Endocrinol Metab. 2011;96(4):972-980. doi:10.1210/jc.2010-1502

The dark art of drug holidays

Drug holidays

- Denosumab – don't. Just don't
- Bisphosphonates
  - Contentious
  - There is no evidence that drug holidays reduce the risk of atypical femoral fracture
  - There is wide variety in practice
  - Always consider a patient's risk of fracture; if this significantly outweighs the risk of side effects, then it may be worth continuing

Drug holidays; what to consider

- Any patient who has been on bisphosphonate for 10 or more years
- Think about it at 5 years, definitely if T score is no longer osteoporotic
- You need a baseline DEXA to guide your treatment
- Be pragmatic, use common sense; a low trauma fracture must weigh heavier in the balance than the T score
- Weigh up the current fracture risk

Drug holidays; how long?

- If you are stopping alendronate, probably need to think about restarting after 2 years
- Risedronate; 18 months
- Zoledronate; 3-5 years

Who should I refer?

- Men
- Anyone premenopausal including children
- Difficulties with treatment
  - Eg. Malabsorption
- Failures of treatment
- Complex treatment decisions

Questions?