Osteoporosis Update
GP presentation
2nd March 2023

Prof David J Armstrong MD FRCP(UK)

Disclosures

Professor David Armstrong discloses:

- Advisory work, honoraria for presentations and chairing, and conference support from UCB Pharma
- Honoraria for chairing symposia from the European Milk Forum
- Honoraria for video work for the Dairy Council Northern Ireland

- Member of the Expert Advisory Group for NOGG, including work on the latest NOGG 2021 guidance
- Vice Chair, Clinical and Research Committee, Royal Osteoporosis Society
- Co-host, 'BoneUp' podcast, including expression of opinion on osteoporosis drugs and management
  - Podcast is not sponsored and does not carry advertising

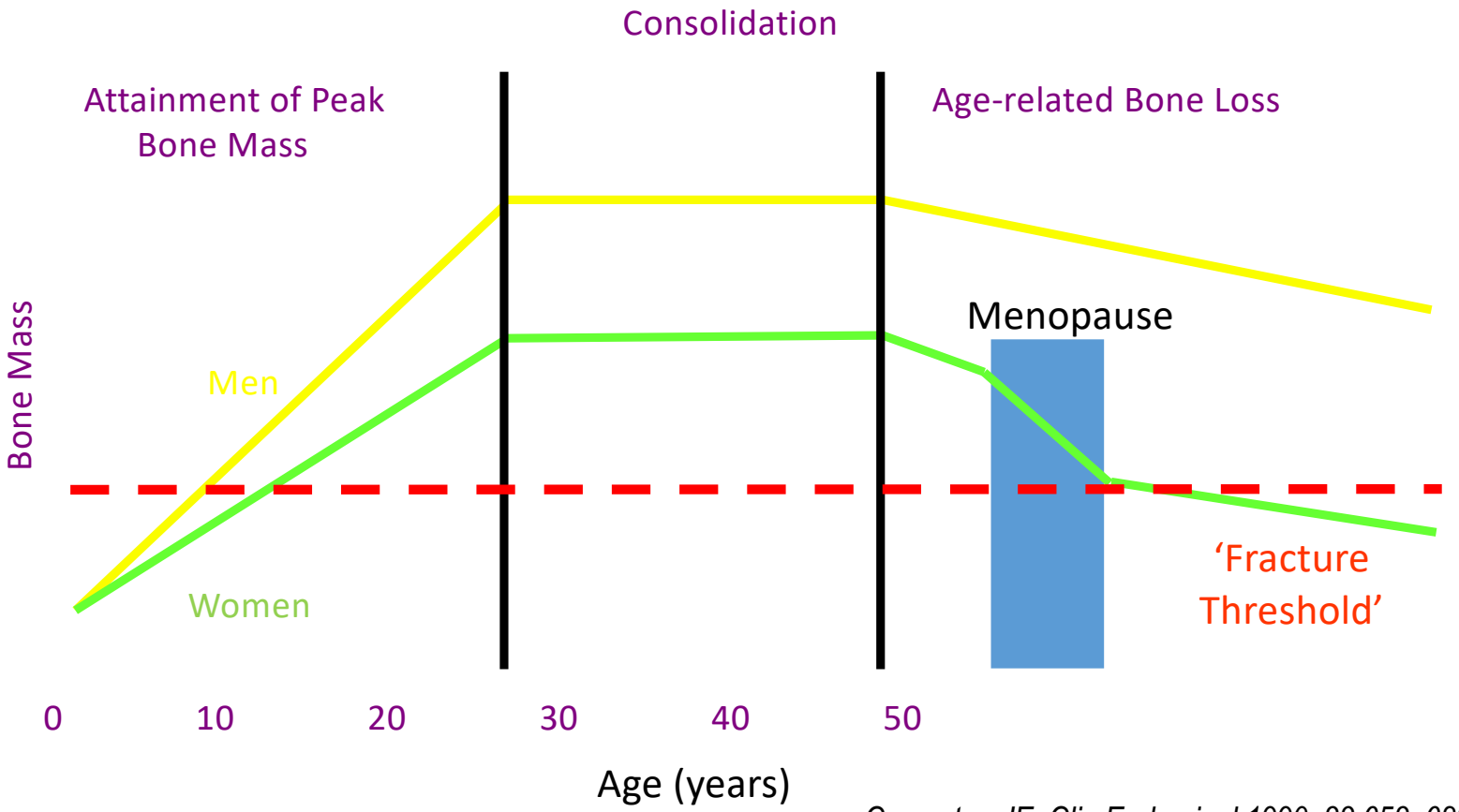
NOGG, National Osteoporosis Guideline Group.

Osteoporosis - Fracture Prevention

- Aim of treatment of osteoporosis is to prevent fracture
- Osteoporosis is asymptomatic unless a fracture occurs
- Hip fracture has 26-29% 1 year mortality (1,2)
- More than 50% of patients with hip fracture have already had one fragility fracture (3)
- Osteoporosis management is typical PREVENTATIVE medicine

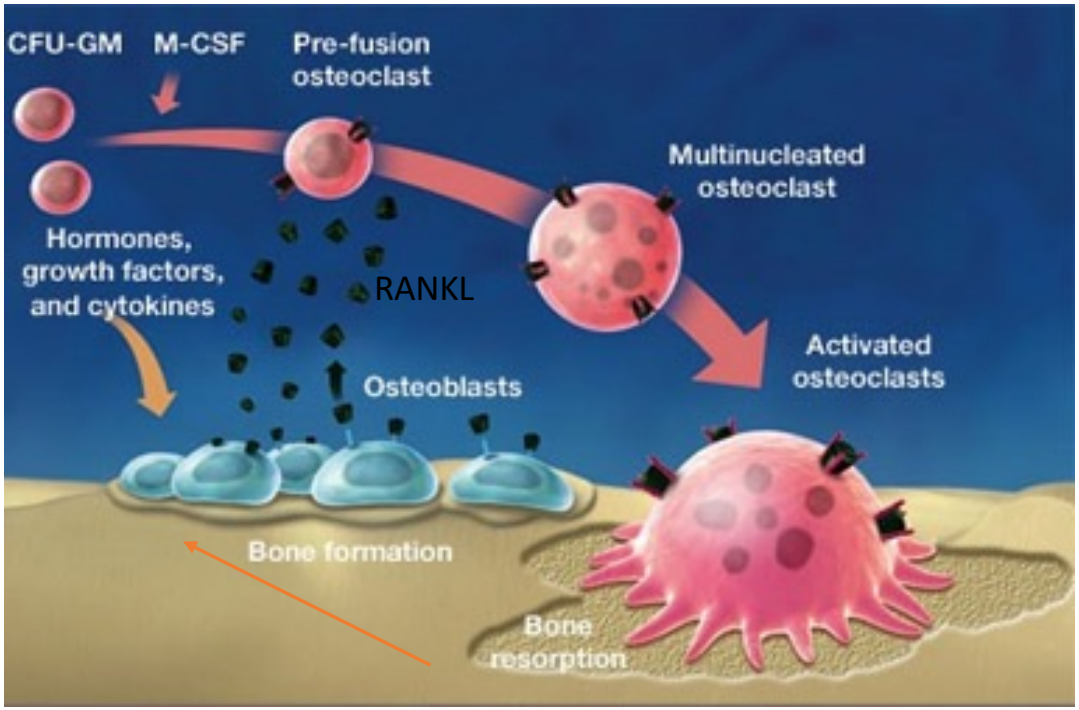
- Neuburger J, *et al. Med Care* 2015;53:686–91;
- 2. Mattisson L, *et al. BMC Musculoskelet Disord* 2018;19:369;
- 3. Ahmed LA, *et al. J Bone Miner Re*s 2013;28:2214–21

Age related changes in bone mass



Compston JE. Clin Endocrinol 1990; 33:653–682 (modified DJA).

Osteoblasts v Osteoclasts – bone turnover



Bianco P, Sacchetti B, Riminucci M .Best Practice & Research Clinical Haematology, March 2011 (modified DJA)

What is Osteoporosis?

- **DIAGNOSTIC THRESHOLD v THERAPEUTIC THRESHOLD**
- **Who has osteoporosis v who needs treatment?**

- **World Health Organisation**
- Disease characterized by
- **low bone mass** and **microarchitectural deterioration** of bone tissue, leading to enhanced bone fragility and a consequent increase in **fracture risk**

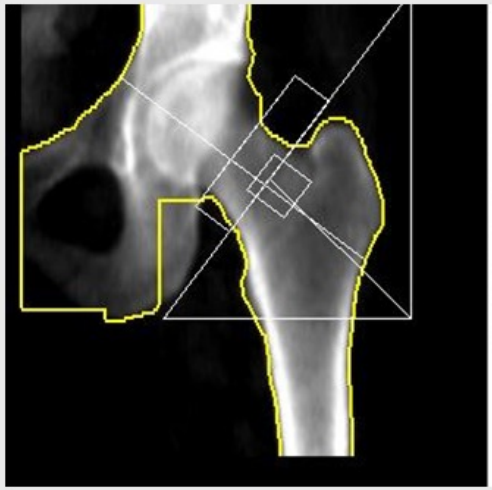
What is Osteoporosis?

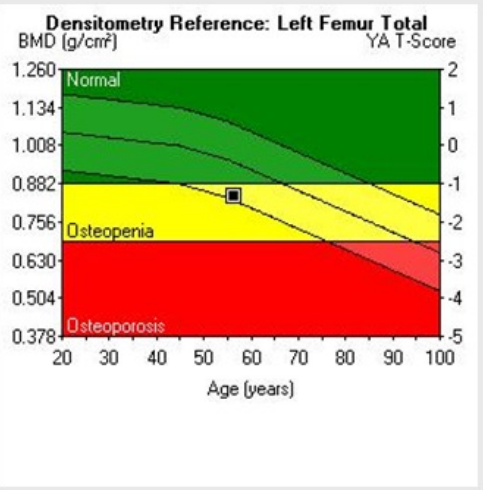
- **DIAGNOSTIC THRESHOLD**
- T score of <-2.5 on DEXA

- **THERAPEUTIC THRESHOLD**
- FRAX score – ‘who needs treatment?’
- NOGG guidance 2021

- Not everyone with T<-2.5 needs pharmacological treatment
- MANY patients with T>-2.5 DO need treatment

DEXA scan




Densitometry Reference: Left Femur Total
BMD (g/cm²)
YA T-Score
1.260
1.134
1.008
0.882
0.756
0.630
0.504
0.378
2
1
0
-1
-2
-3
-4
-5
Normal
Osteopenia
Osteoporosis
20
30
40
50
60
70
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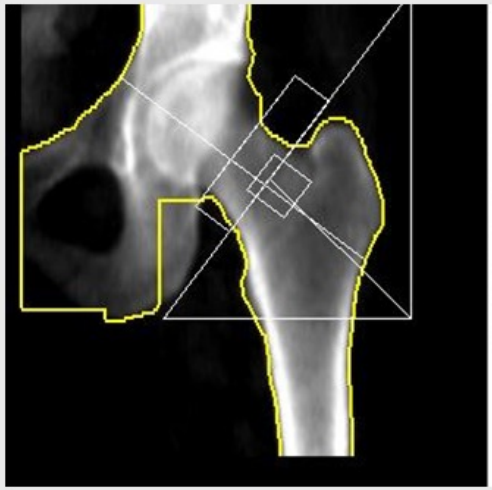
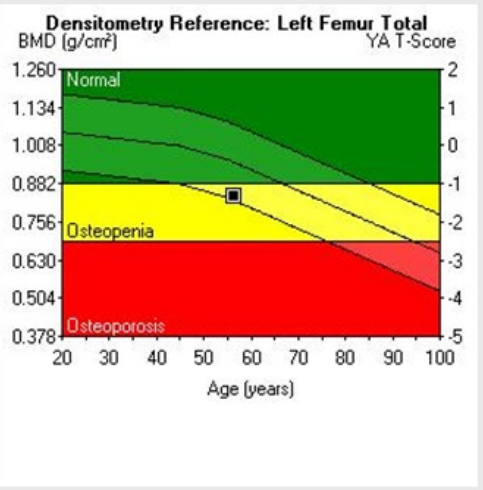
90
100
Age (years)

DEXA scan

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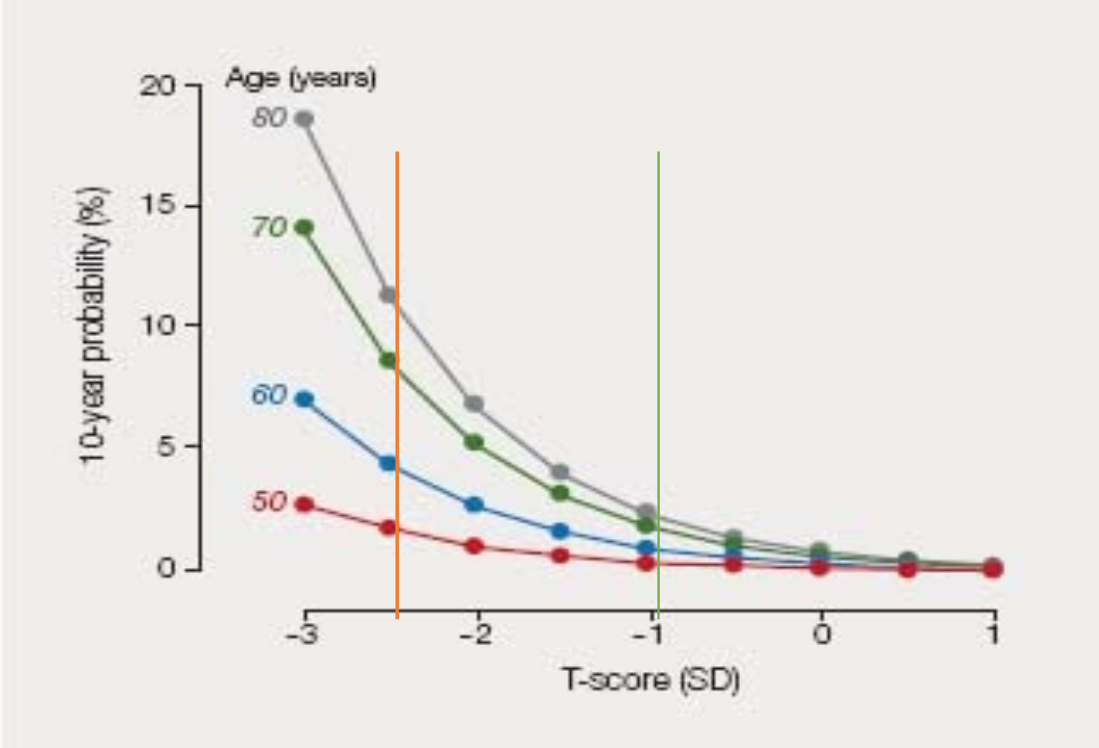
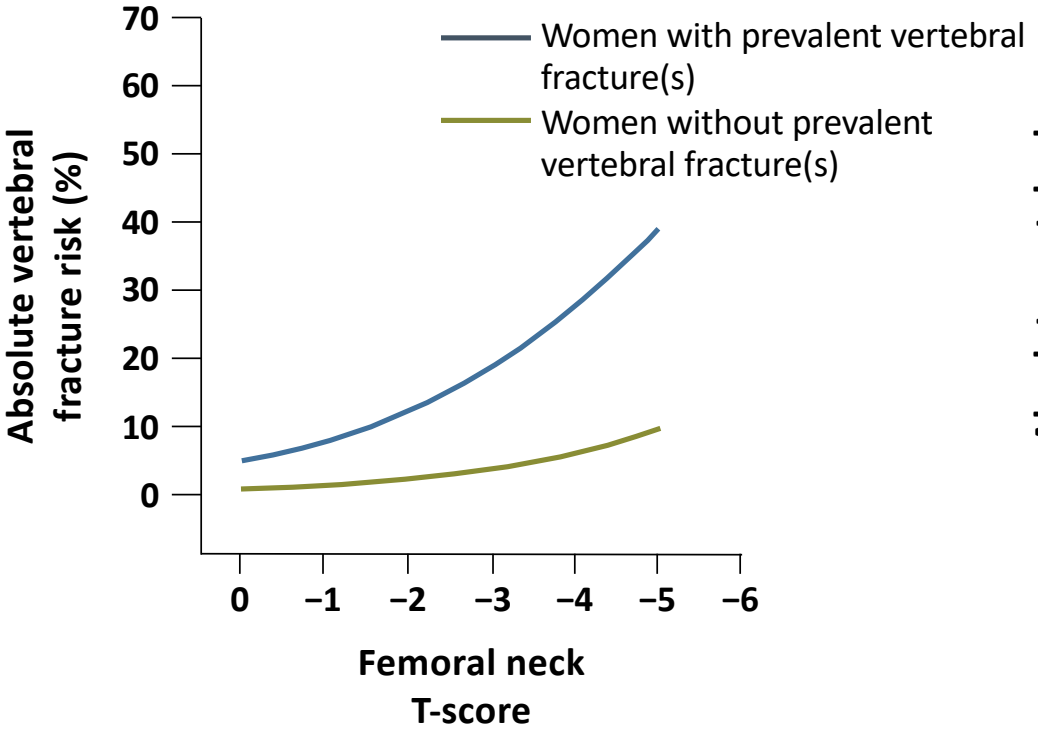
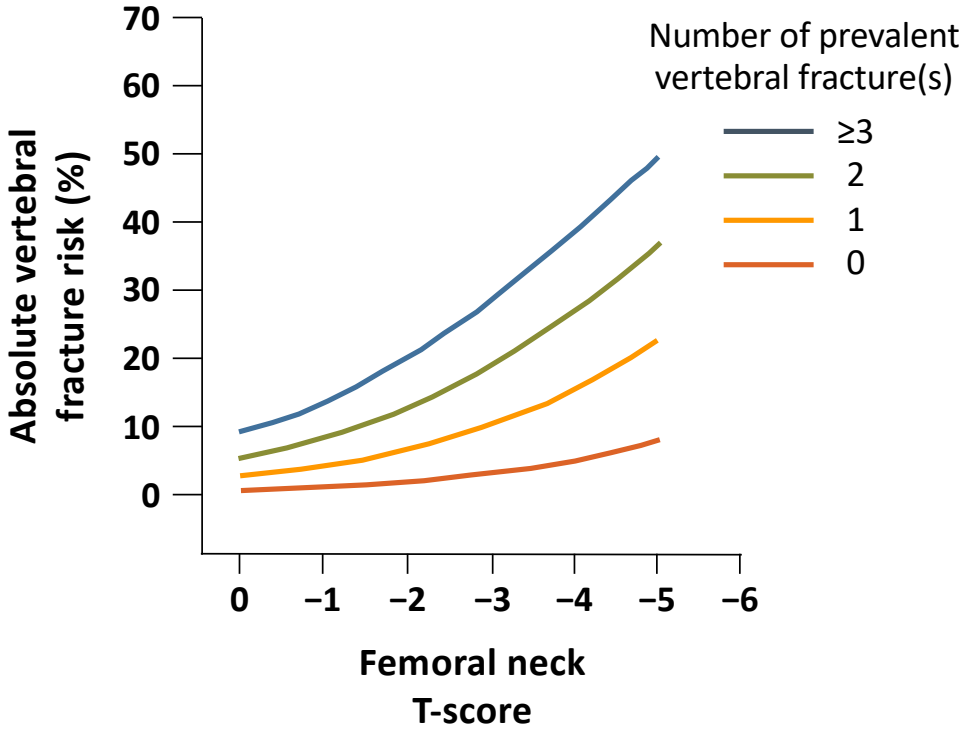
BIG QUESTION - How likely am I to fracture?



Ten-year probability of hip facture by age and femoral neck bone mineral density
in women from Sweden. Modified from reference 29: Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Johnson B. Osteoporos Int. 2001;12:989-995. Copyright © 2001, Springer

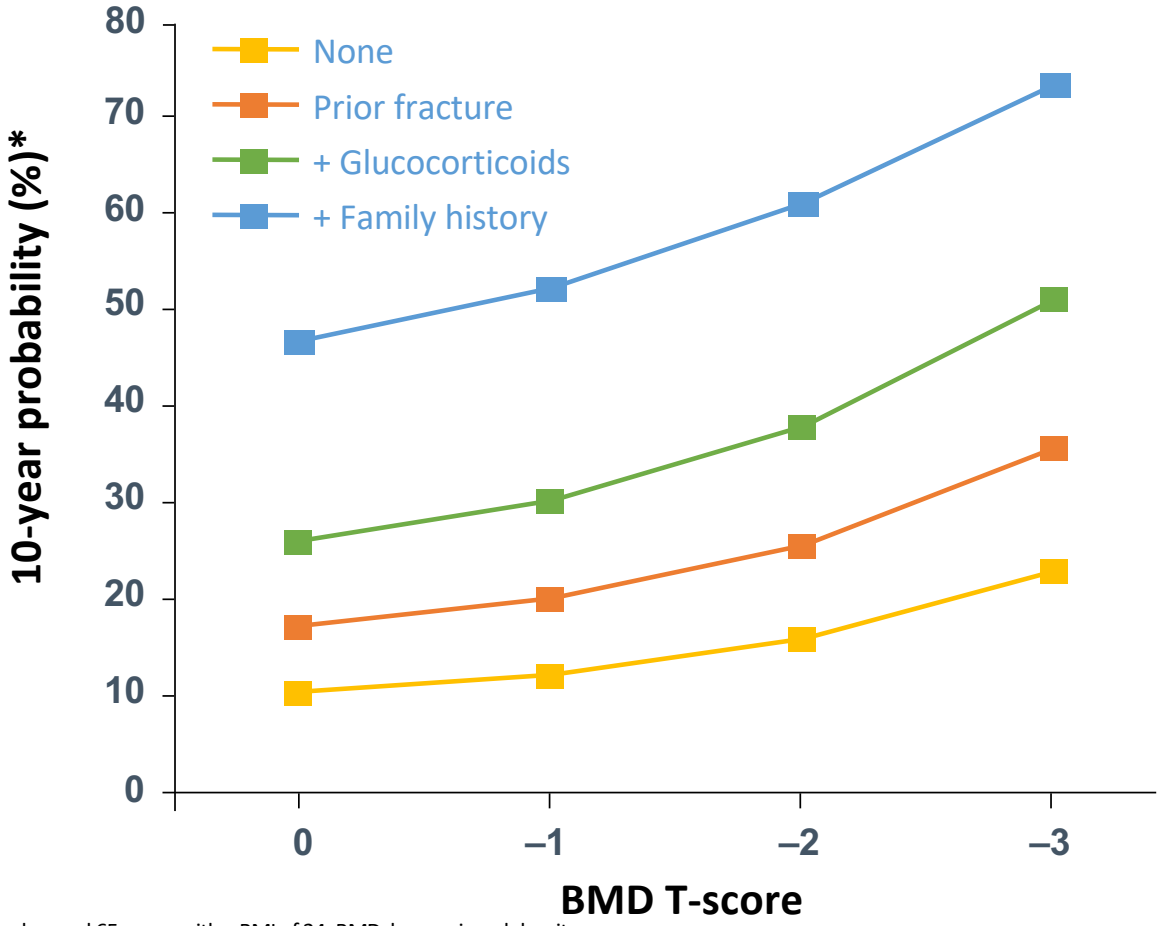
BMD and existing fractures as predictors of new vertebral fracture risk





BMD, bone mineral density
Siris ES, *et al. Osteoporos Int* 2007;18:761–770.

Combining risk factors to evaluate fracture risk



*US Caucasian female, aged 65 years, with a BMI of 24. BMD, bone mineral density.
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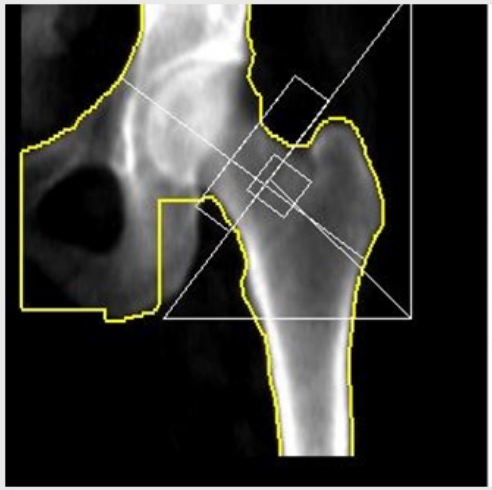

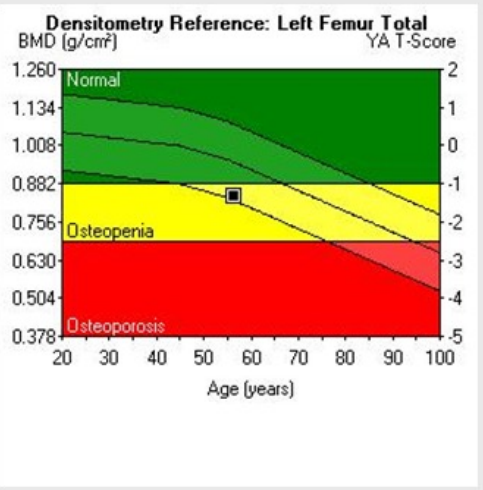
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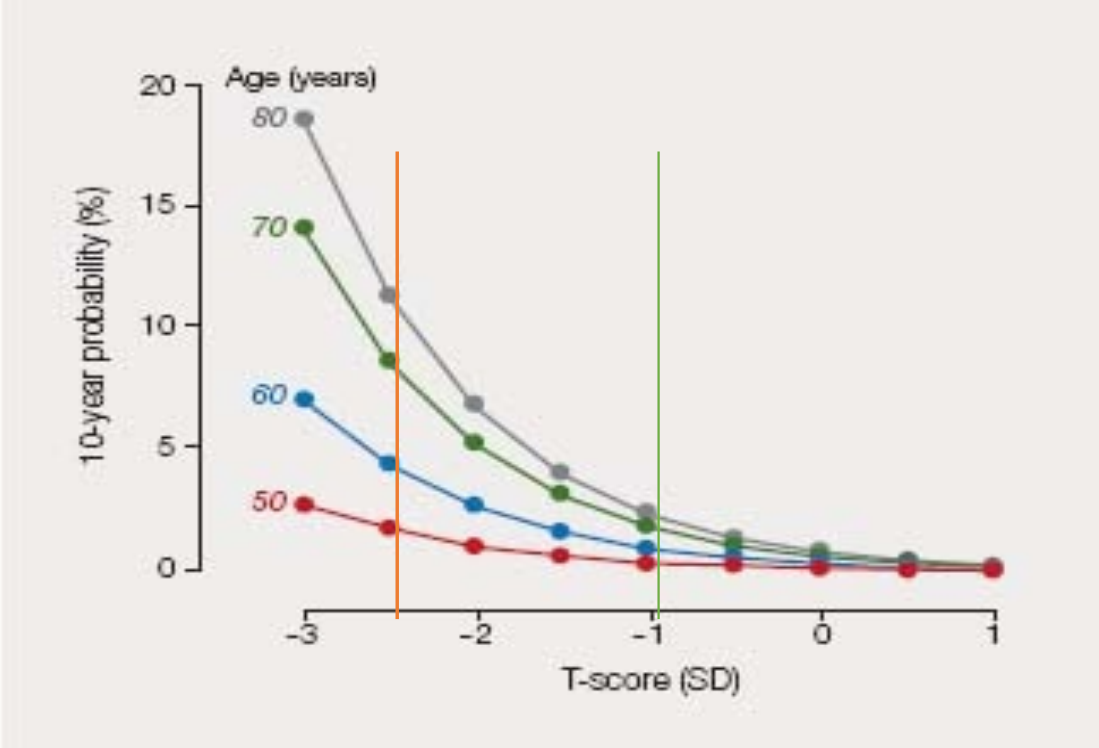

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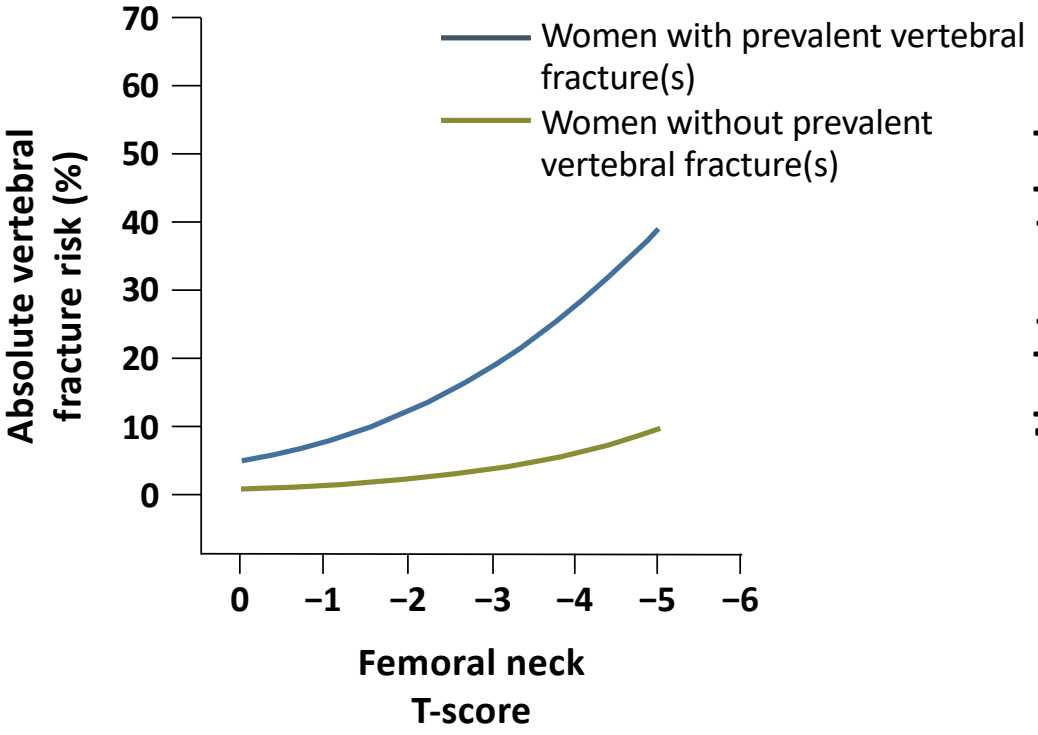

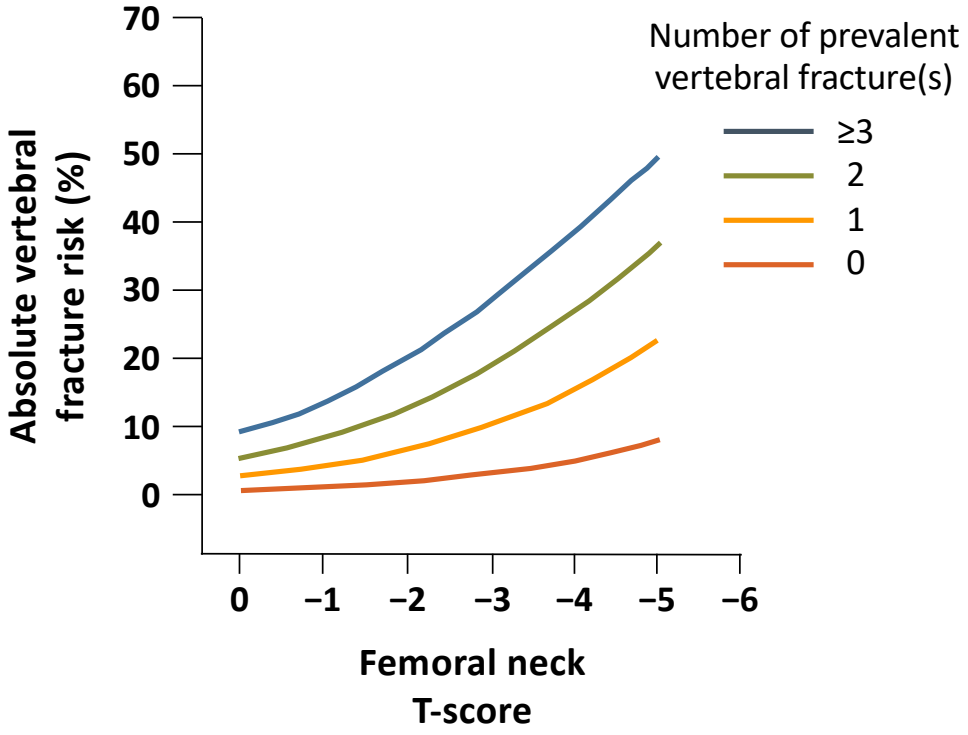

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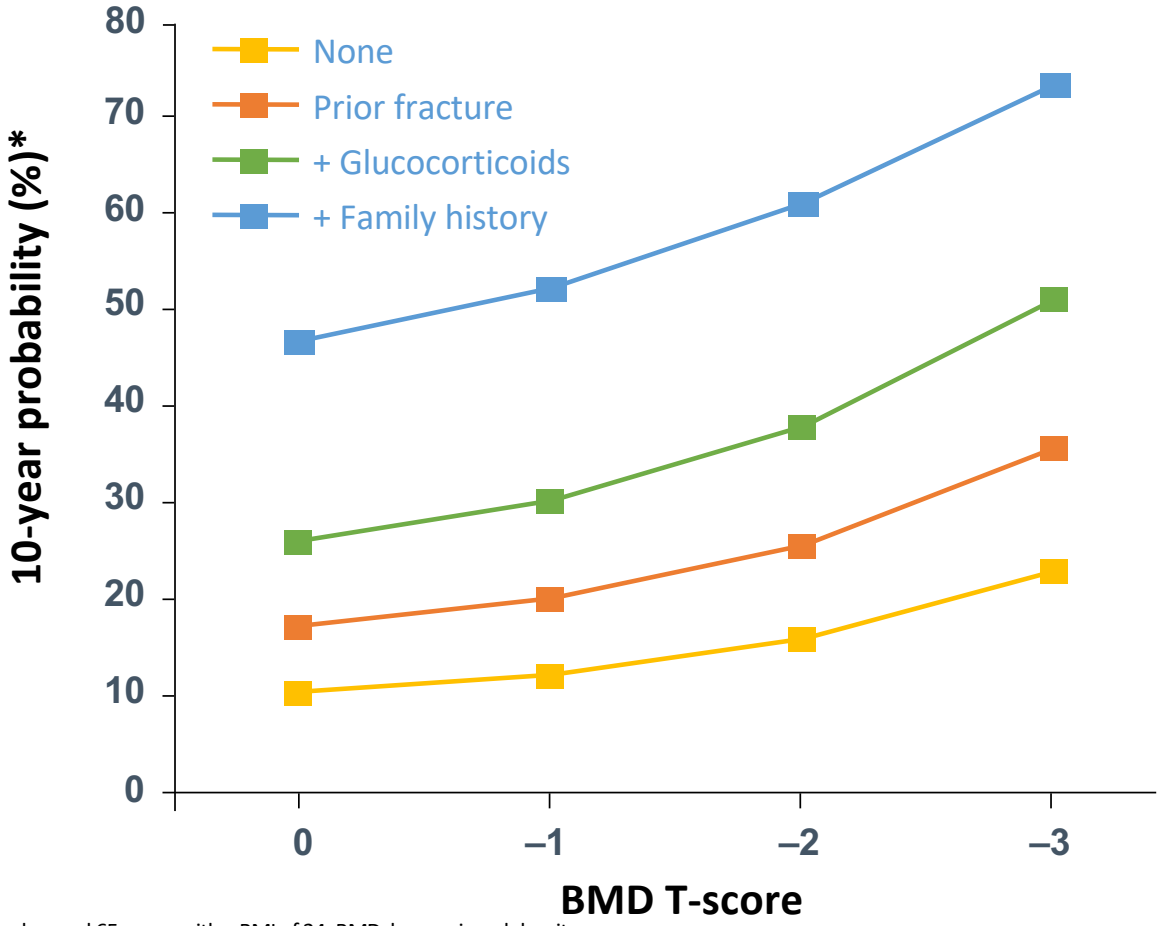

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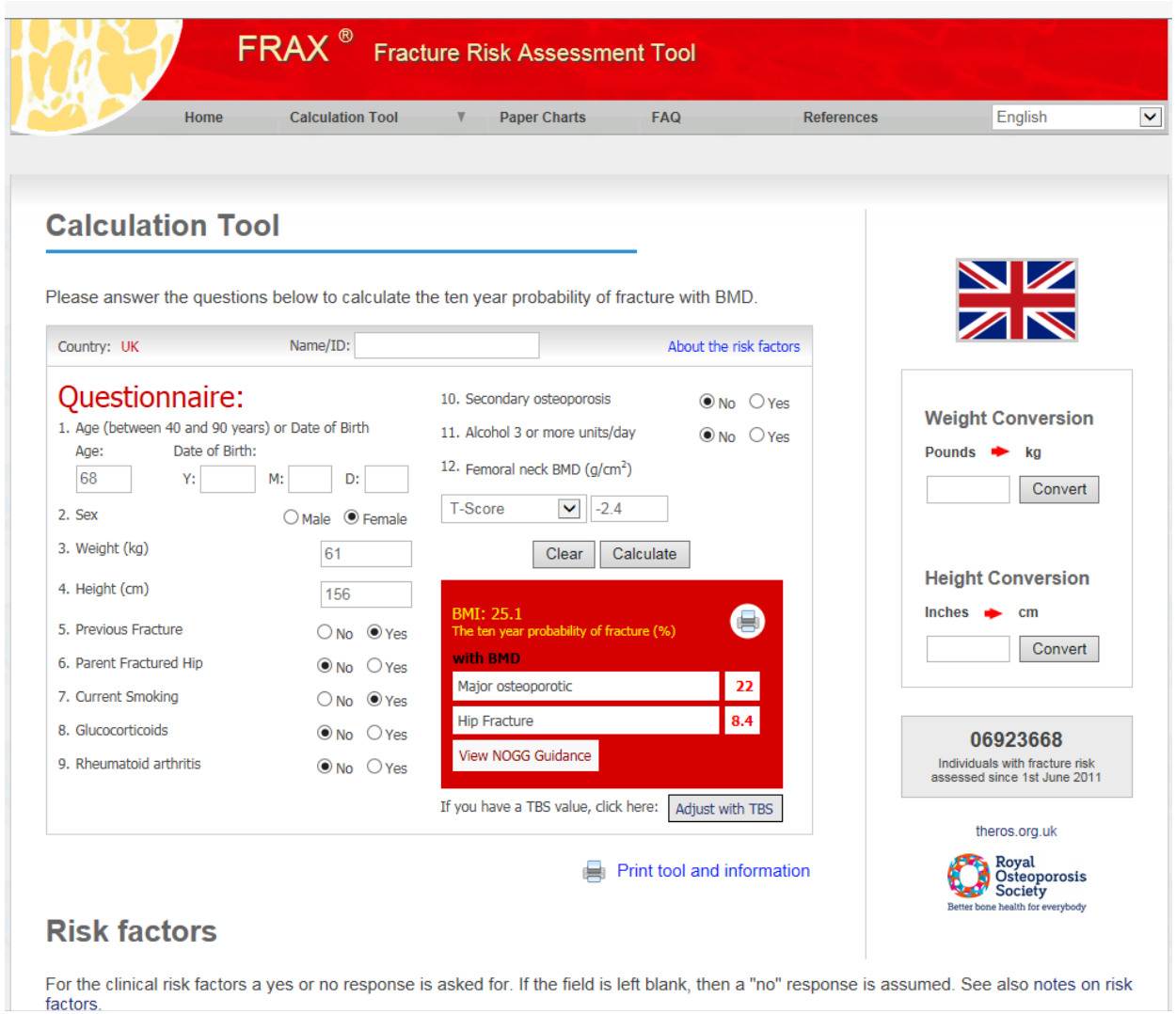
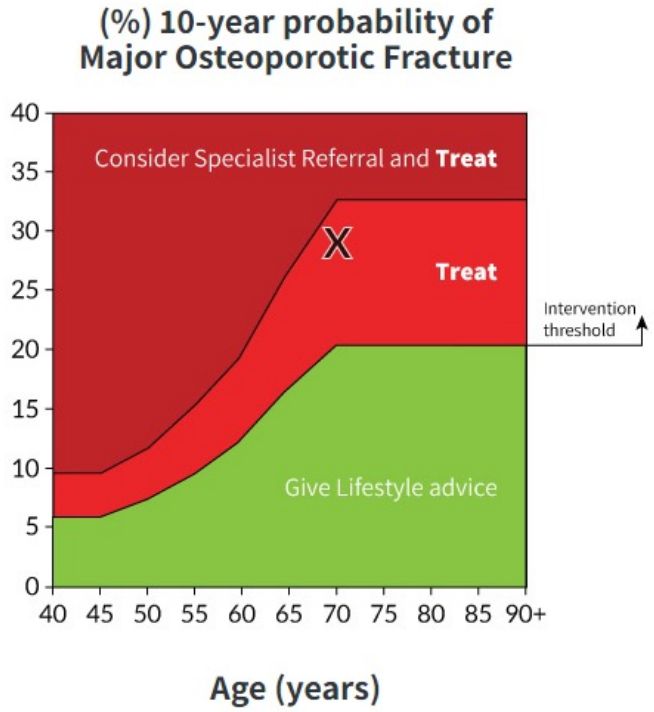
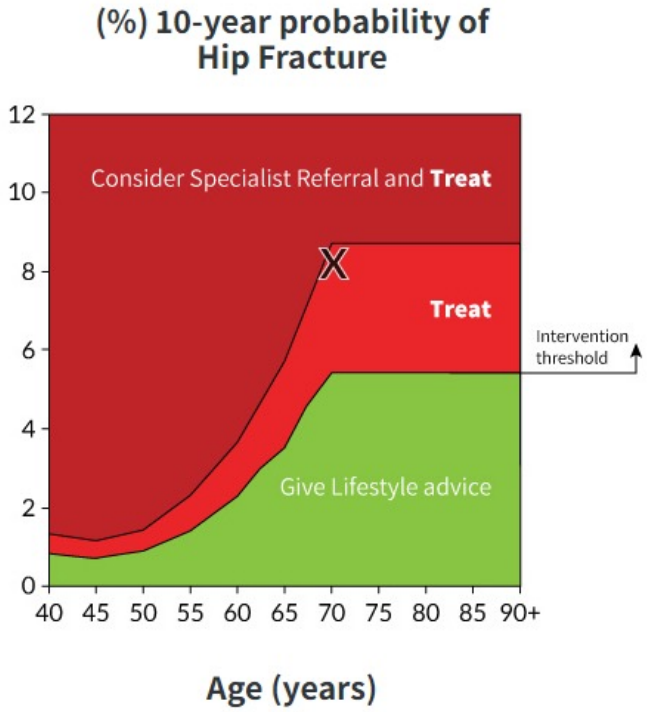
10 year fracture risk - FRAX

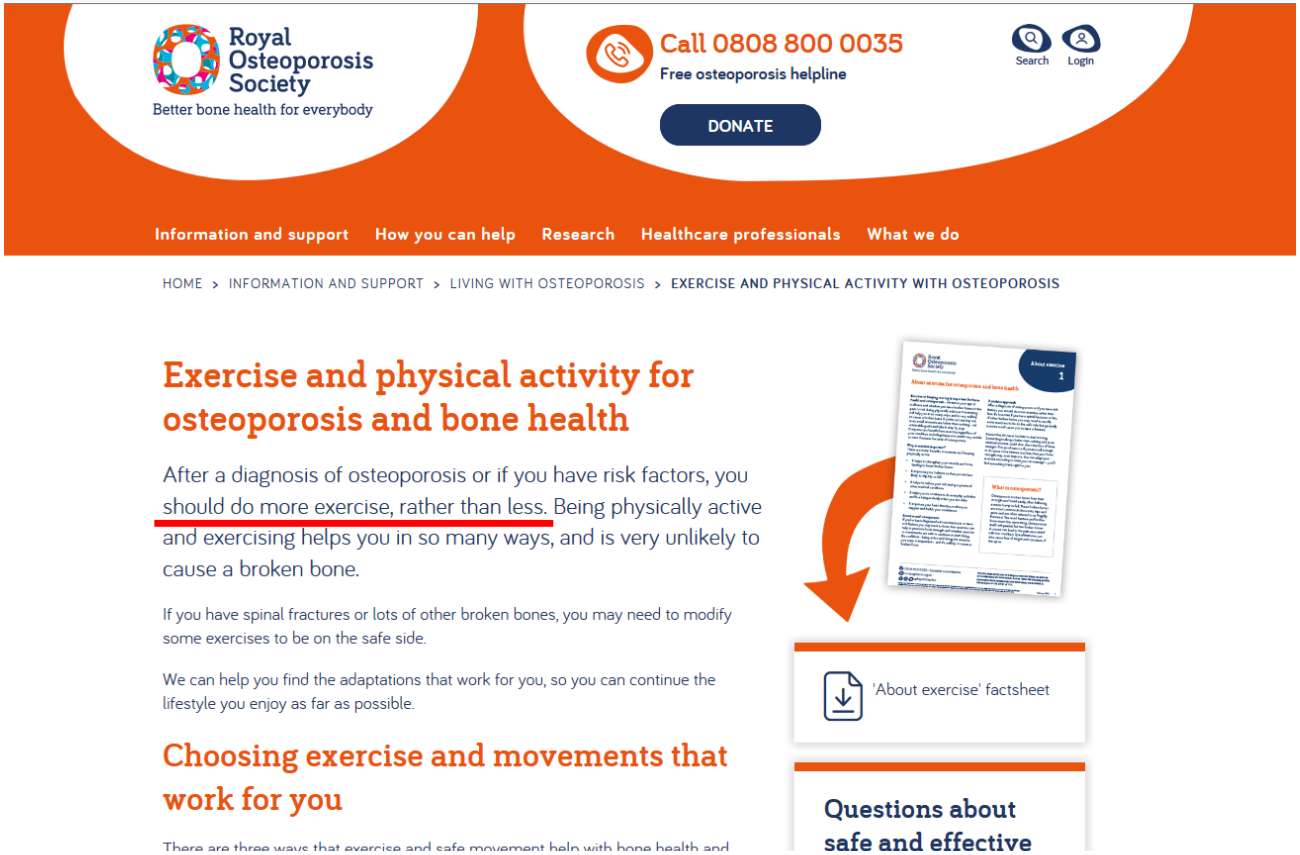


‘VIEW NOGG GUIDANCE’ - TREATMENT THRESHOLD





Royal Osteoporosis Society
www.theros.org.uk

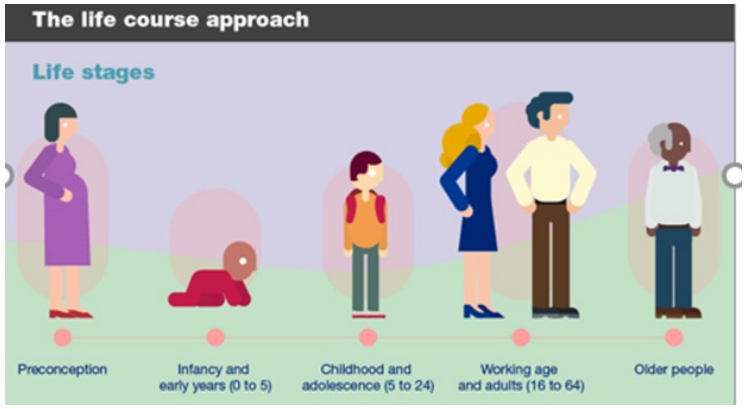


Life course approach

We are taking a life course approach recognising benefits of lifestyle changes at all ages.

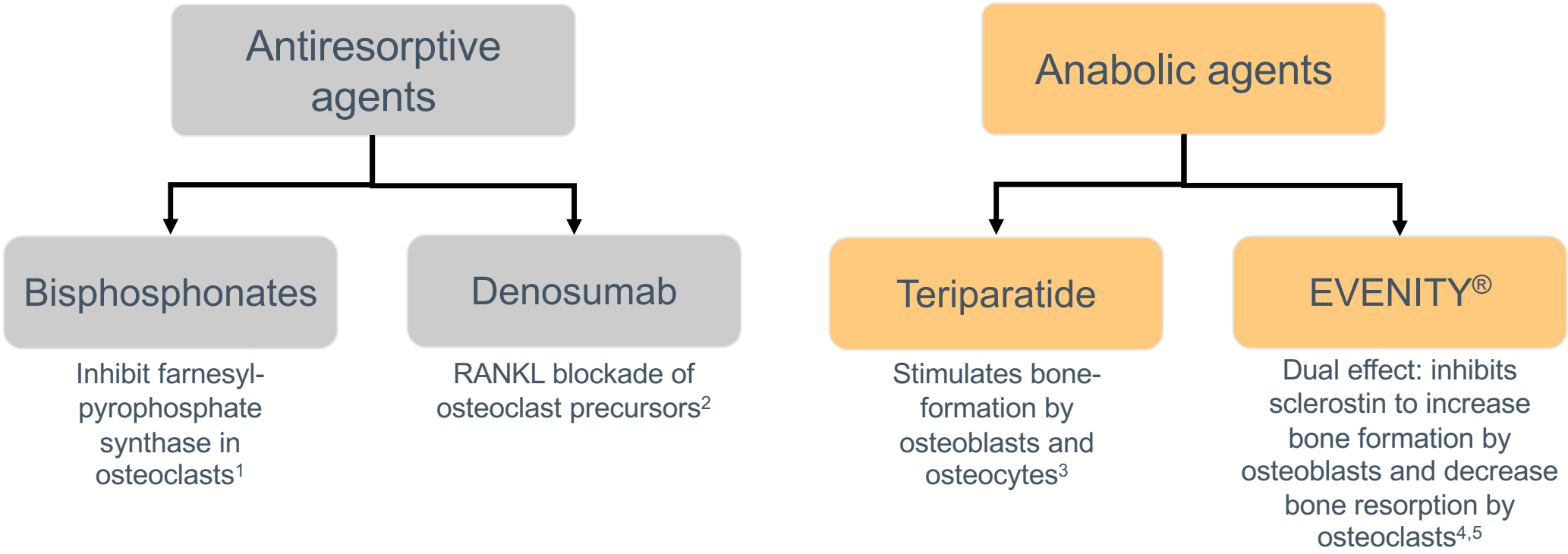
- We especially want action early in life, among children and young people.

- **“It’s estimated a 10% increase of peak bone mass in children reduces the risk of an osteoporotic fracture during adult life by 50%”** (source IOF)



Royal Osteoporosis Society
Better bone health for everybody

Common therapeutic options for patients with osteoporosis at high risk of fracture



RANKL, receptor activator of nuclear factor kappa-B ligand.

1. Rogers MJ, *et al. Bone* 2011;49:34–41; 2. Ming J, *et al. Front Oncol* 2020;10:1283; 3. Canalis E, *et al. N Engl J Med* 2007; 357:905–16; 4. Baron R, Gori F. *Curr Opin Pharmacol* 2018;40:134–41; 5. EVENITY®. Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/10956 (accessed August 2021).

Bisphosphonates

Bisphosphonates

- Drugs which prevent bone loss
- Act on osteoclasts
- By mouth x1/week or x1/month, or iv x1/year
- GFR >30 ml/min; upper GI adverse effects
- Must be taken on empty stomach with tap water and not lie down afterwards
- Adhere to and become incorporated into bone
- Therefore build up and continue to act for years after stopping
- Relatively slow onset of action

- FIT study

- Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group.
- **Lancet. 1996;348:1535–1541**
- Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial.
- **JAMA. 1998;280:2077–2082**

Too much of a good thing?

- Bisphosphonates ‘work well’ up to 5 years
- 5-10 years – ‘work’ for some patients
- **Patients should generally stay on Rx >5 years if**
- previous vertebral #
- age>75
- T score <-3.0 or HIGH FRAX

- After 10 years, **no evidence** that they continue to increase BMD or reduce fractures further at that point
- BUT increased risk of rare adverse events –
- AFF and ONJ
- Usually osteoclast activity very low
- Stop – ‘holiday’

AFF and ONJ

- Osteoclast function important in healing ‘micro-cracks’ in bone
- Over many years, micro-cracks can turn into fault lines with sudden catastrophic fracture of mid shaft femur
- Osteoclasts important in healing sockets in jaw
- Long term use of bisphosphonates increases risk of both
- More common in smokers (both ONJ and AFF)
- Steroids not protective – might increase risk

AFF and ONJ

- ‘Drug holiday’ – stopping the bisphosphonate
- 70% reduction in AFF after 1 year of holiday
- BMD maintained and no increase in fracture at least 2 years
- **Important to remember to restart the drugs again!**
- **10 years is NOT a lifetime limit!!**

Denosumab (Prolia)

- S/C Injection every 6 months
- Biological drug (antibody and not a chemical)
- ‘Targeted’ – design based on osteoprotegerin
- Denosumab (and osteoprotegerin) bind RANKL
- Stops communication between cells
- Switches off maturation of osteoclasts
- Does not build up in bones

Does Denosumab work?

- Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis
- Steven R. Cummings, M.D. et al 2009

- 3933 woman in the denosumab group and 3935 in the placebo group.
- 68% relative reduction in **vertebral** fracture after 3 years
- 40% reduction in **hip** fracture after 3 years
- No cases of AFF or ONJ (only 3 years)

Rebound Fractures

- Denosumab does not accumulate in bone (unlike bisphosphonate)
- (There remains a risk of AFF and ONJ)
- If denosumab is stopped, **rapid loss of BMD** and increase fractures within 12 months
- Fracture risk may actually increase ABOVE previous for a short period
- No clear guidance about drug holidays, but **should not be stopped** without replacement by other meds eg IV bisphosphonate
- Consensus that pause needed between 5-10 years
- Should not be started in Primary Care (and without 'exit plan')

What about HRT?

Evorel Conti
jansse
Evorel® Conti
Evorel Conti
Evorel Conti
Evorel

Mechanisms of Oestrogen Action on Bone

- Complex
- 1. Direct effect of oestrogen on osteoclast and osteoblast function
- 2. Peripheral effects eg PTH, vitamin D metabolism, IGF

- First 10 years post menopause – direct effects more important
- Initially loss of cancellous/trabecular bone (direct action on osteoclasts)

- After 10 years more general loss of both cortical and cancellous bone
- Other long term effects of oestrogen loss involved

HRT efficacy for fracture

- HRT effectively increases BMD across sites (1)
- HRT effectively reduces fracture risk at vert and non-vert sites (2)
- Especially in under 60s

1. Wells G et al. Endocr Rev. 2002 Aug;23(4):529-39
2. Torgerson DJ, Bell-Syer SE. JAMA.2001;285:2891-7.

Controversy

- Women's Health Initiative (2002) Million Woman Study (2003)
- Suggested substantially increased risk of breast cancer and no protection against stroke and CVS disease
- 50% fall in global HRT use
- Re-evaluated in last 5-7 years
- Risk of breast cancer over-estimated but present
- HRT now viewed by many as good choice for patients under 60 with osteoporosis and menopausal symptoms

British Menopause Society

- Cochrane analysis in 2015 showed that HRT was associated with a **significant reduction in cardiovascular disease, cardiovascular mortality and all-cause mortality in women under the age of 60.**
- Large randomised data (eg WHI, MWS) have shown a significant beneficial effect of HRT on bone health and a protective effect against osteoporosis

How Big is the Risk?

- **Six** in every 100 women not taking menopausal hormone therapy would develop breast cancer between the ages of 50 and 69.
- If they took oestrogen and progestagen every day for five years, **eight** of the women would develop breast cancer.

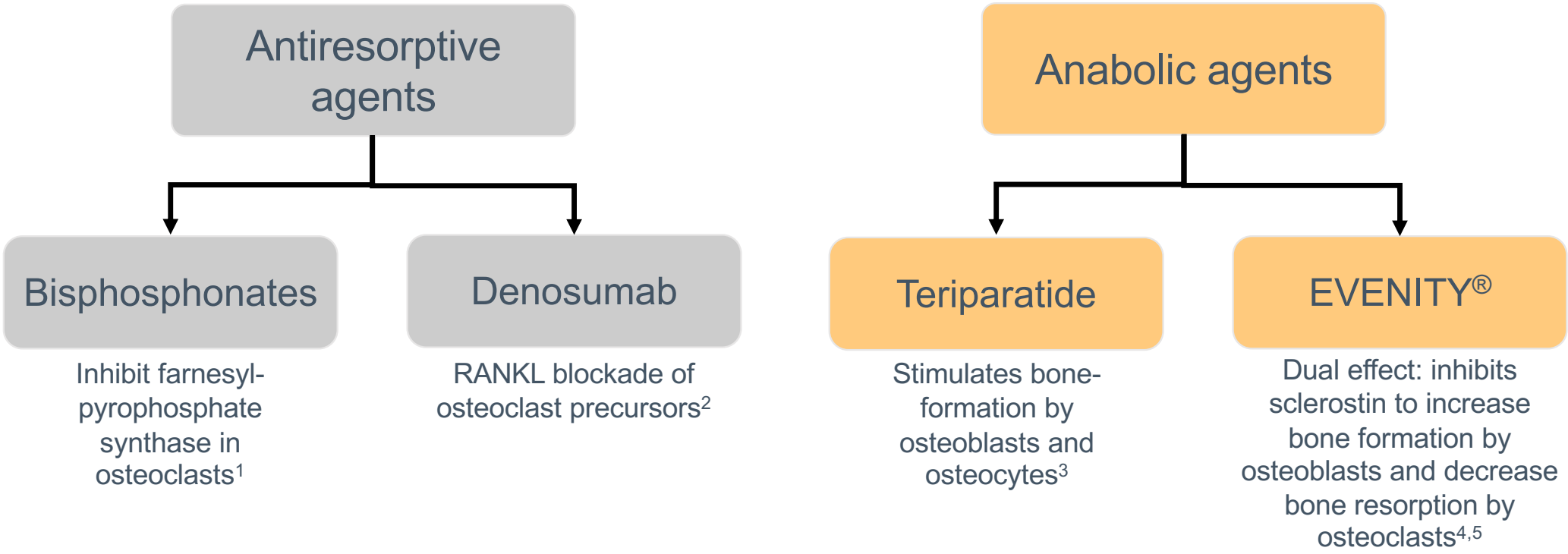
How Big is the Risk?

- **How does the hormone risk compare?**
- Cancer Research UK
- 2% of breast cancer cases in the UK are caused by HRT
- 8% of breast cancer cases in the UK are caused by overweight and obesity.
- 8% of breast cancer cases in the UK are caused by alcohol drinking.
- 5% of breast cancer cases in the UK are caused by not breastfeeding.

New forms of HRT

- New methods of delivery eg pessaries, rings, patches, coils, gels
- New forms of hormone – ‘progesterones’
- Progesterone = body’s natural hormone
- Progestogen = manufactured synthetic equivalent
- Micronised progesterone – may be safer and have fewer side effects

Common therapeutic options for patients with osteoporosis at high risk of fracture



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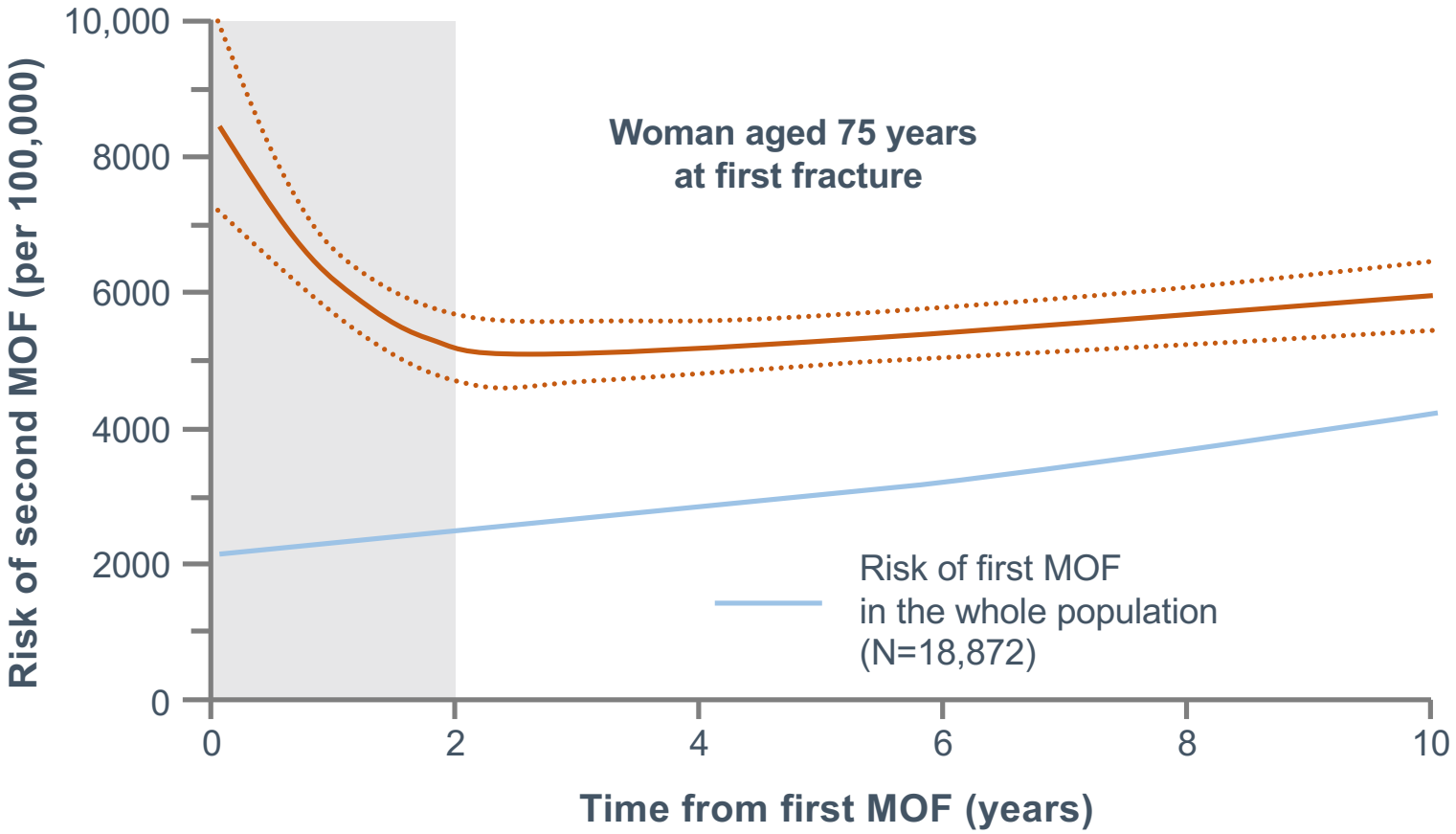
Teriparatide

- Daily hormone injection (PTH) for 2 years
- Previously reserved for ‘most severe’ cases of osteoporosis
- t score <-4
- t score <-3.5 with 2 fractures
- Stimulates OSTEOBLASTS
- Fracture reduction –
- 70% in vertebral fracture
- 40% in non-vertebral fracture

NOGG 2021 GUIDANCE

- **NOGG 2021 Section 11**
- 'Consider referral of Very High Risk patients to an Osteoporosis Specialist for consideration of parenteral or anabolic treatment'
- VERY HIGH RISK?
- **Recent vertebral fracture** (2 years) **or**
- More than 2 vertebral fractures **or**
- BMD T score <-3.5 **or**
- High dose glucocorticoids (7.5mg for 3 months) **or**
- Multiple clinical risk factors/high FRAX
- FAST TRACK CLINIC for NEW VERTEBRAL FRACTURES

Fracture risk is highest in the first 2 years following fracture



MOF, major osteoporotic fracture (vertebral, proximal humerus, distal radius, hip).
Johansson H, *et al. Osteoporos Int* 2017;28:775–80.

Romosozumab

- Anti-sclerostin antibody
- Single action, dual effect
- Two injections per month for 12 months
- Immediate increase in BMD at both hip and spine
- Can be seen from 6 months
- Unlike teriparatide which may cause initial fall in hip BMD
- Romosozumab best given FIRST line (attenuated by prior antiresorptive)
- Cardiovascular risk profile assessment
- Available as CPC drug in NI from Sept 2022

SUMMARY OF MAIN RECOMMENDATIONS

Updated September 2021

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Summary of main recommendations
Scope of this guideline
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Intervention thresholds
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Pharmacological treatment options
Strategies for management
Management of vertebral fractures
Models of care for fracture prevention
Recommendations for training
Recommendations for commissioners
Criteria for audit & quality improvement

NOGG members
Stakeholders
Grading of evidence
AMSTAR2 grading
References

Download Full Guideline
Download Summary Recommendations

This guideline summary addresses the assessment, diagnosis and current treatments for osteoporosis, including recommendations to prevent fragility fractures. It applies to postmenopausal women, and to men age 50 years or older.

Concerning assessment of fracture risk in postmenopausal women, and men age ≥50:

1. **Conduct a FRAX assessment in people with a clinical risk factor for fragility fracture.**
2. **Measure BMD in people with intermediate fracture risk by FRAX** (amber) to refine the estimate of 10-year risk.
3. **Measure BMD in people with high and very high fracture risk by FRAX** (red) to guide drug choice and provide a baseline for BMD monitoring.
4. **Consider imaging to look for a vertebral fracture in people with acute onset back pain who have risk factors for osteoporosis** , and/or in people with a history of ≥4cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, or a BMD T-score ≤-2.5.
5. **Assess falls risk in patients with osteoporosis and/or fragility fractures and offer those at risk an exercise programme** to improve balance and muscle strength.

Regarding drug treatment to prevent fractures in postmenopausal women, and men age ≥50:

6. **Offer drug treatment to people at high and very high risk of fracture.**
7. **If BMD measurement is not practical (e.g. due to frailty), use the online NOGG intervention thresholds based on FRAX, to guide treatment decisions.**
8. **Consider, particularly in older people, drug treatment in those with a prior and/or recent fragility fracture.**

When selecting drug treatments to prevent fractures in postmenopausal women, and men age ≥50:

9. **Consider the level of fracture risk, any additional clinical risk factors, patient choice, and the cost-effectiveness of treatment**, when deciding on a particular drug treatment.
10. **Start treatment promptly following a fragility fracture**, because risk of re-fracture is highest immediately after a

Pregnancy Associated Osteoporosis

- Study led by University of Edinburgh
- Sponsored by ROS
- Altnagelvin NI recruitment centre
- Usually new vertebral fractures during third trimester or lactation
- Usually very low T scores

Questions?

- NHS: David.Armstrong@westerntrust.hscni.net
- Twitter: @osteoporosisNI
- Research: d.armstrong@ulster.ac.uk
- BoneUp podcast